

Pediatric Overweight and Obesity

Comorbidities, Trajectories,
Prevention and Treatments

Manuel Moya

 Springer

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and Treatments



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Foreword

I have great pleasure in writing this prologue for Dr. Manuel Moya's book *Pediatric Overweight and Obesity-Comorbidities, Trajectories, Prevention and Treatments*. I have known Dr. Moya for a long time and he is an accomplished academician and a world-renowned authority in field of nutrition.

He joined the International Pediatric Association (IPA) in 1990 as a member of the then so-called Expert Committee on Nutrition and was consolidated as Standing Committee (SC) member during the period of 2001–2007. This allowed him to work as member of the Nutrition Panel, then at the Global Alliance Policy Group for Obesity Prevention under the auspices of WHO, and finally as Chair of the Technical Advisory Group on Nutrition. Besides these IPA activities, he is a member of the WHO Food Security and Nutrition Forum since 2016.

Childhood obesity is a burden in developed and developing countries. It is a serious medical condition that affects children and adolescents. Overweight and obesity are caused by numerous social and environmental factors that influence people's food habits and physical activities. Childhood obesity is particularly troubling because the extra pounds often start children on the path to health problems that were once considered adult problems like diabetes, high blood pressure, and high cholesterol.

This new book edition aims to provide readers with a general as well as an advanced overview of the key trends in childhood obesity and also provide the highlight of best practices and potential interventions to reduce the burden of obesity in children and youth.

Dr. Moya has done a laudable job in writing this book, and he deserves all praise and admiration from global medical community. I am sure all will find this book useful for their day-to-day learning, teaching, and practice. I wish the publication large acceptance and huge readership.

I once again congratulate and wish Dr. Moya all the best.

President at The International Pediatric Association
Webster Groves, Missouri, USA

Naveen Thacker

Foreword (1)

It is still necessary to write to teach and also to read to learn. This will be demonstrated in this excellent work by Professor Manuel Moya on childhood obesity, that this clinical and social issue that the Pediatrics of the last century has transferred to the twenty-first century. In it, all preventive and therapeutic work will be of little importance, and it should be remembered in an elementary way that obesity is an excess of body fat, a harmful excess, and very far from the protective role that was attributed in distant times to the abundance of body fat in infants and children in general, when there was no shame in proclaiming the satisfactory roundness of the healthy child. Now its epidemiological progress is accepted, with 23% of children being overweight and 18% suffering from obesity, both in high-income countries and in developing countries, and what is more worrying: the intervention of this abundance of fat in the triggering of the main non-communicable diseases such as cardiovascular pathology, diabetes and even neoplasms, among others, such as some psychological and respiratory problems. In principle, this excess of body fat would be conditioned by an imbalance between the increased calorie intake and the decreased energy expenditure.

The definition seems simple, but the diagnosis has its nuances and the etiological orientation can be delicate, as there are numerous genetic, epigenetic, and environmental factors involved in its production. And there are therefore many reasons that have induced the much-appreciated author to this new task of maturity: the writing of a work on childhood obesity with an uncompromising scientific foundation, as opposed to the known tendency in this time to disseminate pseudo-books called to capture the attention of readers dazzled by the originality, speed of or spectacularity of the proposed procedures, without scientific or even logical foundations. On the contrary, Professor Moya dissects through his book the etiopathogenesis, clinical, diagnosis, prevention, and treatment of childhood obesity, based on his extensive experience in health care and prolonged laboratory work, as well as on a well-selected bibliography. Thus, in just 10 chapters he shows the advances but also the controversies, and without letting the dominant technology hide the importance of the environmental and psychosocial aspects as well.

By subtitling the book as *Comorbidities, Trajectories, Prevention and Treatments*, the Author warns that its objective is not only didactic and scientific, in a context of great actuality, but also practical, since it is providing a very useful tool for all those interested in preventing or eradicating the problem. The beneficiaries of his reading should be not only specialists in endocrinology and nutrition, but also pediatricians and doctors who take care of children and young people, patients in the age of development, with the known high risk of suffering from overweight or established obesity, and its close and distant consequences, with which it is possible to begin to master by modifying lifestyle and eating habits.

The book that I am pleased to present and that comes to us from the careful editorial hands of Springer (Ergon) was to be expected, given that the new fruit of the scientific-teaching activity of Professor Moya is backed by his career as a scholar and researcher of this new branch of pediatrics, to which he has dedicated his main efforts with the greatest tenacity, contributing to a better knowledge of growth and nutrition. This orientation always stood out, as his extensive curriculum shows, from his initial stage at the University of Valencia, where he became Associate Professor, to the culmination as Professor, first at the University of La Laguna (Canary Islands) and finally at the University of Miguel Hernández in Alicante. Each step has been marked by the logical fruits of his numerous publications, with participation in 85 books and almost three hundred scientific papers in both international and Spanish journals, his repeated stays in centers of great international prestige and activity in numerous scientific societies. He has been president of several of them, such as the Spanish Association of Paediatrics, the European Society for Paediatric Research (ESPR), and the Spanish Society for Research in Paediatric Nutrition and Food, always as a true reflection of his talent and his continuous effort, without the obsession to succeed, only to be useful to others.

The author is accustomed to participating in transversal study projects; this book takes us at the same time to the new scenarios where medicine is developing. From the references to empirical medical science, still latent in his first teachers, he went on to participate as a protagonist in the scientific pediatrics of the second half of the twentieth century, to leave the windows open to evidence-based pediatrics and now to precision pediatrics. In the latter, the boundaries between specialties will be blurred and the enormous amount of data can be obtained from each patient, thanks to progress in computer science and multiple techniques, increasingly affordable, will be shared by a great common science, human ontology.

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Manuel Cruz Hernandez

Preface

The idea of this publication was born many years ago and in my insular stage in Atlantic waters when in a child we confirmed our first case of fatty liver (non-alcoholic) and that then was labeled idiopathic hepatic steatosis. Those were times when obesity was not perceived as a health problem and there were no systematic measurements of its prevalence. The idea grew slowly as the nutrition and metabolism units of our clinical work developed. From the 1990s onwards and due to this contingent of affected children, a collection and classification of the literature on pediatric obesity was produced, which, although it had the proximate goal of patient care and study, became the dynamic basis of this publication. Its content has been influenced by the global (and local) evolution of obesity and the minor effectiveness of the plans against its prevalence. As a consequence, a preventive spirit permeates all the chapters of the book, not only those with clinical connotations but also those dealing with the necessary biochemical, genetic, morphological, or even evidence bases.

The first part of this publication refers to the present bases that generate obesity and specifically the first chapter in addition to the concept includes the most recommended assessment of overweight and some milestones in the history of obesity, especially pediatric obesity.

The second chapter (Epidemiology) analyzes the evolution and projection of global obesity and especially its evolutionary and numerical reflection in the pediatric field. It also analyzes the situation of malnutrition (including over- and under-nutrition) due to its coexistence and also assesses the evolution in our country.

The third chapter shows the etiological factors but under a pragmatic prism going from those that positively affect the energy balance to the genetic predisposing factors, especially the genetic variants, without forgetting the residual syndromic obesities.

Finally and in this first part, the fourth chapter (Pathogenesis) deals with the basis of bioenergetic balance and appetite regulation. Special coverage is given to adipose tissues as well as a possible regulatory role unrelated to hypothalamic neuronal circuits. The second part of the publication deals with clinical aspects and is

aimed at diagnosis, prevention, and treatment as well as some ideas for clinical research.

The fifth chapter (Clinical) covers the classic aspects of overweight and obesity but also considers the pubertal modifications, the role of sleep, the important psychosocial problems, or the musculoskeletal ones. The complementary determinations are well defined and separated from those motivated by research purposes.

Chapter 6 (Comorbid States) points out their subtle presence as early as pediatric ages and how their discrete initial manifestations are often accompanied or preceded by insulin resistance or metabolic syndrome. It has specific descriptions of non-alcoholic fatty liver disease, elevated blood pressure, and type 2 diabetes.

Chapter 7 (Evolution and Prognosis) introduces the concept of trajectories and their consequences. The serious problem of weight maintenance and the complex prognosis of pediatric obesity today is addressed.

In Chapter 8 (Prevention), the types of prevention are analyzed but with the aim of facilitating the arrival of the knowledge and recommendations of the general preventive approach to the family environment of the child at risk, in short, to contribute to the individual application of the actions programmed at higher health levels. Early preventive actions are highlighted and with the methods which have so far proved to be the most appropriate.

Chapter 9 (Treatment) indicates that from the beginning this should coexist with all the principles expressed for prevention. It is specified in an initial and continuous clinical assessment, the change of lifestyle with specific recommendations to improve the energy balance and especially family support. In the pediatric context, pharmacological treatment and bariatric surgery are evaluated.

Finally, Chapter 10 *Where are we now?* is nothing more than a reflection on what can be done at this moment and perhaps what can be expected.

In relation to the content, I would like to say that the methodological theory of criticism must begin with oneself. In this way, one finds repetitions of scientific information in different chapters, but always supported by different studies. This shows that not everything that is new is new, and that not everything is clearly clear or clearly obscure. On the other hand, the predominance of references in the now scientific lingua franca is overwhelming, but it must be taken into account that good articles appear in the journals with the best impact index. Other criticisms will rightly exist, but my acceptance and recognition of these positive actions goes without saying.

San Juan, Alicante, Spain

Manuel Moya

Acknowledgements

My gratitude to the research institutions and especially to the four university hospitals and therefore the universities in which I have worked, for their support for research, modest as befits the economic environment in which we had moved, but which has been stable and has had an amazingly lasting stimulating effect.

But it is they, the children and adolescents with high body mass index to whom the greatest outpouring of my affection and appreciation is directed for the fortitude with which they have generally borne the cross of stigma during the long course of the disease. Not forgetting their parents for their cooperation and for the valuable feedback given. I also wish to apologize to some of them for not having been able to be as resolute as these children deserved and in some way expected, and if at the beginning, the language used may have reproachful tones.

It would be impossible not to mention the people with whom I have been fortunate to work daily, especially in the two Nutrition Units generated, to all these people so vivid in my mind without any exception I wish to give the most heartfelt thanks. There is also another nucleus of people who, having a high rank and scientific category, advised me and supported me or welcomed me and allowed me to work with them in areas of nutrition that were new to me. To them also my recognition and my respectful remembrance since some of them are no longer here.

Finally, to the beings of my closest past and present environment, to all of them my inexhaustible gratitude.

Manuel Moya

Utiel, February 2023

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Chapter 1

Pediatric Overweight and Obesity: Basis for an Early Modification of Their Development



Introduction

Before addressing the concept of obesity, it is reasonable to provide an overview of the problem in order to understand its complexity and the coordinated effort required for its improvement. The importance of childhood obesity has been recognized not only from the pediatric area but also and primarily from the general health point of view, especially from the clinical fields dealing with serious and chronic pathologies and all this as a consequence of the best results related to the precocity of preventive actions and in a context of a growing worldwide epidemic.

Thus, the World Health Organization (WHO) with a more recent and realistic criterion [1] in the report *It is time to act*, issued by the Commission for non-communicable diseases (NCDs), states that by 2030 premature mortality caused by these diseases should be reduced by a third. The main NCDs (cardiovascular disease, cancer, chronic respiratory disease, and diabetes) are related to obesity and are in turn covered by the Sustainable Development Goals (SDG 2 and 3) which refer, respectively, to the end of malnutrition in all its forms by default and excess and to health at any age.

Similar conclusions have been reached by the CDC, *Centers for Disease Control and Prevention* [2] with the spectacular figure of 86 million Americans suffering from prediabetes, 90% of whom are not diagnosed, or by European studies with a follow-up from 2 to 9 years of age [3].

It is a remarkable fact that in the developed world, the increase in the prevalence of obesity generally occurs in environments with no apparent excessive dietary energy load, which has led to an appropriate and fair assessment of changes in lifestyle or lifestyles. Moreover, the fact that not everyone in a given environment develops obesity suggests that there is a genetic mechanism that makes certain individuals able to manage more or less effectively the energy ingested. However, as Lustig [4] argues, it is not plausible that our jealously-guarded gene endowment

changed almost suddenly 50 years ago, which is when the spread of obesity began. Next-generation sequencing (NGS) and Mendelian randomization, and in the longer-term gene therapy, will define the role of genes in obesity, although part of this work has already been revealed as will be shown.

There is an urgent and global need to neutralize obesity due to the medical consequences it entails, given that in addition to the four NCDs mentioned, we must add non-alcoholic fatty liver disease, emotional disorders, risk of osteoarticular diseases, and, ultimately, the absolute and relative risk of premature death [5]. The American Heart Association (AHA) [6], after an analysis of 2018 data showing the estimated reductions in life expectancy according to the presence of five risk factors that may occur in obese patients and which can be in determined instances as high as two decades, reflects how the concept of life expectancy should be extended. This snapshot of their life deserves to be better known not only by this population but also by society as a whole. COVID-19, as being a cause of death itself, increases other leading causes (mainly cardiometabolic) linked to obesity [7].

Among the WHO's 2019 Ten Threats to Global Health, the second refers to non-communicable diseases where obesity is in the background. Almost all these situations have traditionally been considered as typical of the long-term obese adult; however, and as will be seen after a more detailed analysis and examination of obese children [3, 8], this pathology is present in its initial stages and in a more evident way in those already consolidated. However, since obesity is not among the ten most lethal pediatric causes, it contributes to the opinion that a robust child only needs to lose weight.

Why this increase? In high-income countries, the classic and widespread obesogenic environment (higher intake of higher energy foods and less physical activity), although basic, alone does not explain the variation in adiposity within the population. Therefore, in addition to general genetic predisposition, other factors must be considered such as changing eating behavior, less attention to pediatric obesity (including less research) [9], the more recent demonstrated relationship between obesity and low economic income [10], or the socioeconomic inequality that affects both adult and pediatric populations [8, 11]. This socioeconomic aspect is so important that it has given rise to a peculiar current of thought, that of reverse causality, which considers that obesity is not the result but the cause of lower economic income.

Faced with the increase in prevalence, which will be analyzed in the chapter on *Epidemiology*, the responses of the preventive approach have sought to be more concrete. Thus, at the state level, the design of actions against the obesogenic environment has been observed in almost all the countries of the westernized world and perhaps with greater interest once it has been demonstrated that the economic cost of obesity, when evaluated in terms of fewer hours worked and greater use of all levels of medical care, is significantly greater in obese people than in individuals with normal weight. Furthermore, it is necessary to factor in the cost of prevention programs [12, 13]. The number of life years lost due to disability caused by obesity (DALYs) is quantitatively important according to the extensive study carried out by the Global Burden of Disease Study of the Bill & Melinda Gates Foundation. On a *scientific* level, 6 of the 20 Key Clinical Guidelines published in 2017 [14] focus on

obesity, which could indicate an almost extreme (albeit disparate) responsiveness. The consolidation of bariatric surgery both in adult and, with specific restrictions, in pediatric patients [15] has meant a therapeutic advance not only in obesity but also in comorbidities but also a certain preventive relaxation. At the social level, the changes in attitude have not been sufficient, and consequently the overall therapeutic results have been lower. In addition, it should be mentioned that the counteroffensive of pseudoscience (slimming substances without lower food intake or increased exercise, etc.) in the media contributes to this stagnation.

Another peculiar circumstance of obesity is the lack of perception on the part of individuals, and in our case families, that obesity is a major health problem. Health authorities, national and supranational, have shown more awareness recently, but their general plans have often failed to catch on with the general public. It is enough to recall how simple, well-designed schemes such as the *Physical Activity and Nutrition (PAN) Program*, launched in 1966 by the prestigious International Life Sciences Institute (ISLI) and supported from the outset by the American Academy of Pediatrics [16], or *The Nutrition and Physical Activity Task Force* [17], launched in the United Kingdom for the general population in 1993, were unable to halt the ongoing increase in both countries and in both age groups, as in other countries with perhaps less ambitious programs.

The fact that there is no systematic record of the prevalence of obesity, especially simple at school age, contrasts with other health actions. Probably the lower awareness and less elementary knowledge at the individual level is a point to be taken into account for the better implementation of these major actions. Thus, 40% of American men and 20% of American women think that their weight is correct, when in fact they are overweight [18]. Moreover, the political decision to reduce the content of the *Affordable Care Act* [19] has led to a health regression in this same population. The fact that there is no *screening* program to assess overweight means that it surreptitiously leads to obesity at any age.

Another reason for this urgent neutralization is the fact that childhood-onset overweight and obesity will very often persist throughout life. Precisely for the pediatric and adolescent population and in order to increase understanding of the problem and adherence to the various programs, respectful language [20, 21] should be used by the pediatric healthcare community in relation to overweight based on body mass index and stigmatizing terms avoided [22]. There is even a recent opinion that the term obesity is outdated (and pejorative) and should be replaced by the term “chronic disease due to adiposity” [23], which makes some sense.

Concept

Obesity is defined as an abnormal accumulation or excess body fat that alters the health of the sufferer [24]. It is considered as a chronic disease and is recognized by the WHO in the International Classification of Diseases (ICD 11, 2018) under “Obesity due to energy imbalance (5B81.0)” along with a series of obesity-related

pathologies (comorbidities, syndromic obesity, etc.). However, neither the concept of obesity nor overweight (5C1Z) is usually properly coded because the numerical criteria that separate them are not stated. The problem is that a number of countries do not recognize obesity as a disease requiring treatment and prevention, although the criteria that would define it as a disease have been verified and recognized by the American Medical Association only in 2013. In 2021, the European Commission [25] defined obesity as a chronic relapsing disease, which in turn acts as a gateway to a range of other non-communicable diseases. This definition conceptualizes better the disease and should be extended. The age limit for pediatrics [26] with an upward trend almost everywhere in the world and with different limits, especially when adolescence is considered to end at 24 years of age, does not help either diagnostic or epidemiological accuracy. On the other hand, the term or terms like “metabolically healthy obesity”, whether in adults, children, or adolescents [27, 28] are neither clearly justified nor accepted (see below). Current definitions are too broad as they include the comorbidities initially studied in adults (cardiovascular disease, type 2 diabetes, and cancer) and later described also in pediatric obesity, as well as the causality of obesity (positive energy balance) and predisposing factors (especially those related to mitochondrial thermogenesis and its gene regulation of UCP1) or by abnormalities in the satiety hormone-CNS interplay [29]. This breadth together with the recent pathophysiological findings, which will be analyzed in this publication, has given obesity a doctrinal and care body.

How it is assessed and how the limits separating normality from overweight and obesity itself are established are more complex, although weight and external appearance may indicate that the limit of good nutrition has been crossed [30]. To the conventional anthropometric techniques, it is probably necessary to add other sociomedical aspects that the Canadian method of Edmonton (EOSS-Pediatrics) includes and that will be mentioned throughout this publication due to the pragmatic prognostic staging (from 0 to 4) that it contemplates for medical, mental, and functional areas. At present, the quantitative definition of obesity has not been standardized, making it difficult to compare accurately prevalence data from different parts of the world or even within one country. Methods for clinical use attempt to estimate the proportion of body fat responsible for weight gain: Of the two methods used, the first is based on weight-for-height ratio, and the second is based on body fat distribution. Both can be simple, inexpensive, accurate, and reproducible, and although the variants of these have made them scarcely comparable, the passage of time has led to a smaller series of comparative standards and methods of analysis that are clarifying this broad picture. Daily energy intake and particularly daily energy expenditure over long periods are scarcely obtained with sufficient accuracy and thus fail to clarify the conceptual and clinical course especially in childhood obesity.

The weight (kg)/height (m²) index or body mass index (BMI), which is an approximate measure of adiposity, was described by Quetelet in the nineteenth century and renamed BMI (*body mass index*) in the 1950s by Ancel Keys, as will be seen below, and applied to adult obesity with great success and effectiveness by defining overweight as above 25 kg/m² and obesity as above 30 kg/m². These limits have been amply demonstrated by the health-related risks that occur when these

figures are exceeded. The limit of 18.5 kg/m^2 indicates underweight also in adults [31]. The cut-off points of 30 kg/m^2 , 35 kg/m^2 , and 40 kg/m^2 which qualify adult obesity as grades 1, 2, and 3, respectively, are not applicable to the pediatric stage [32]. But given that the essence of obesity is the increase in adipose tissue, this kg/m^2 ratio can only be an indirect estimate of obesity, and this has generated some conceptual controversy. However, this anthropometric concept and through its good correlations with subcutaneous fat content in men and women ($r = 0.92$ and $r = 0.79$, respectively) although somewhat lower in relation to visceral fat has proven to be very useful in the day-to-day management of adult obesity [33]. The new description of the adult normal weight obesity syndrome is already of interest in pediatrics as it recognizes the predominance of abdominal fat even if the weight is normal. But we cannot overlook the need to redefine the term of metabolically healthy obesity [34] in the light of further evidence techniques [35].

Moreover, the term normal weight obesity [36] has nothing to do with the questionable concept of the normal obese child [37] because of the greater body fat content (DXA $> 25\%$ in boys or $>30\%$ in girls) association with cardiometabolic risk factors. Indeed, in adults insulin resistance and type 2 diabetes are present in the so-called healthy obesity phenotype [38]. New equations, such as the so-called relative fat mass (RFM) [39], are probably more accurate for estimating fat content and no more complex to carry out. Thus for ages 8–14 years, relative fat mass = $74 - 22 \times \text{height/waist} + 5 \times \text{gender}$ (0 for boys and 1 for girls), as can be seen in the Clinical Features chapter.

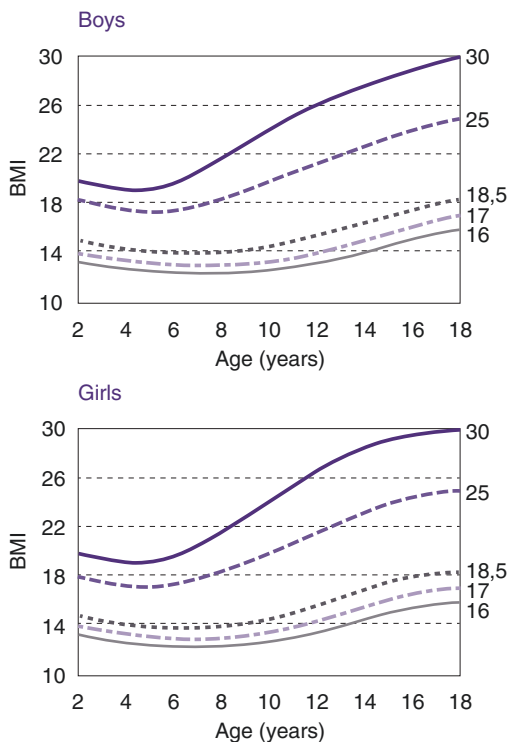
Assessment in Pediatric Ages

Raw and Percentile BMI

The crude BMI (kg/m^2), so practical for assessing adiposity in the adult population, should not be used in pediatrics as its medians change substantially with age: at birth it is 13 kg/m^2 ; at the age of 1 year, it rises to 17 kg/m^2 ; at 6 years it decreases to 15.5 kg/m^2 ; and at 20 years it is 21 kg/m^2 [40]. The commendable studies carried out on 200,000 children in 6 countries that are representative of the global population have established cut-off lines [41] for underweight, normal weight, overweight, and obesity according to age and gender, as shown in Fig. 1.1, which also reflects the less well-known cut-off points for undernutrition.

Thereafter, with adiposity estimated through BMI, as a result of the changes for gender or race, the logical idea arose of applying percentiles to this evolutionary series of averages, which makes it possible to compare a case with a normal population. Thus, in 1990, graphs were obtained in the United Kingdom using data from the growth charts known as “nine centile charts”. In the United States, the same type of graphs was generalized but with the data of the CDC 2000 for both genders from 2 to 20 years of age [42]. At the same time, the cut-off lines were established for

Fig. 1.1 Trajectories of absolute BMI (kg/m^2) for malnutrition between the ages of 2 and 18 years for both genders. The upper lines ending at the right ordinate of the BMI of 30 and 25 kg/m^2 coincide respectively with the 95th and 85th percentiles, demonstrating the continuity of the overweight and obesity criteria that will govern for adult ages. Note in the lower lines the inclusion of the cut-off points for the evaluation of underweight and malnutrition



underweight (< 5 centile), normal weight (5–85 centile), overweight (> 85 centile), and obesity (> 95 centile) which are so widely accepted. Figure 1.2 shows an example of the percentile chart for children. This new method was developed or adopted globally and in most westernized countries. Among the first, we can refer to the one mentioned by the CDC, the Euro Growth, and perhaps also the WHO, while taking into account its limitations [43]. In high-income countries with national BMI charts, the reference percentiles proposed by the CDC are generally accepted, although it is still possible to detect some variation. The Spanish Growth Study 2010 was based on representative national data and treated in accordance with international guidelines.

In general, these more global graphs for BMI have small differences with little clinical relevance, and therefore any choice may be appropriate, and their rigorous design and structure are always a guarantee. Ideally, these (frontier) percentile lines at 18 years of age would pass, respectively, through the 25 and 30 kg/m^2 points of the BMI that define overweight and obesity in adults. However, there are some circumstances that limit this classificatory quality of excess body fat or adiposity. The first problem is that the prevalence of overweight doubled in the final 20 years of the last century, when these graphs were drawn up. With data already referred to by Dietz [44] in relation to the careful study of the *National Health and Nutrition Examination Survey* (NHANES) and comparing the percentile lines of the 1980 study with those of the study carried out in 2000, we can see how the upper tail of

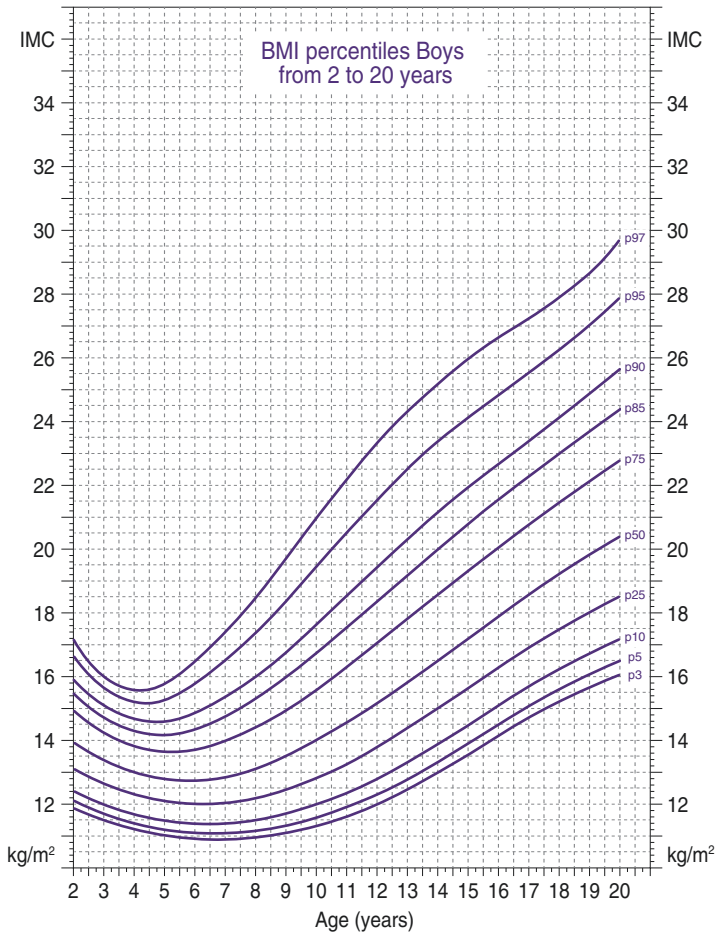


Fig. 1.2 Percentile body mass index (BMI) for children and youth from the Center for Diseases Control and Prevention. (Free access to the entire document through 2000 CDC Growth Charts for the United States: Methods and Development. Vital and Health Statistics. Series 11 number 246. May 2002 [42])

the BMI distribution has increased much more than the median. This means that children who are now close to, but below, the 85th percentile line will be considered normal when, if the 1980 standards are applied to them, in other words, before the explosion of weight gain, they are considered overweight and therefore candidates for preventive action. This trend was also demonstrated in Spain and specifically in Barcelona [45].

Furthermore, the attempt to internationalize standards of this type [40] using large masses of pediatric populations from six different countries has shown how the tails of the distributions at certain ages are somewhat different, which means that the cut-off points for obesity are less precise, a fact that is particularly striking in

adolescent boys. Thus, the percentiles for BMI are sensitive for the average range of adiposity but less so for the extremes (obesity, undernutrition). Therefore, and unlike what was previously thought and will be discussed later (in the chapter on *Epidemiology*), the use of national standards may not be the most appropriate way to define overweight or obesity in that population in a more global context. In the case of obesity, this method is not valid for accurately assessing the changes that occur during evolution, nor does it allow for a statistical assessment of groups. In summary, BMI percentiles are most useful for *screening* or for primary adiposity classification to indicate what percentage of the reference population is above a given percentile but not for quantifying changes in adiposity [46]. It is therefore desirable that both height and weight and abdominal circumference are measured, and once the z-score is obtained for their age and sex for at least these three parameters, the allocation of their nutritional status (underweight, normal weight, overweight, or obese) is made by comparing them with other series that use z-score (see below).

In order to increase the accuracy in the assessment of body fat, new procedures have appeared, one of the most important of which is the waist-to-height ratio (WHtR). When expressed in centimeters, this is a reliable indicator of central or visceral obesity and consequently of the risks involved. It was proposed in the mid-1990s in Japan and the United Kingdom, and since then its predictive capacity, when the ratio is greater than 0.5, has been widely proven in adults [47]. The same has been done in the pediatric age group [48], although on a smaller scale and where the normality interval is between 0.46 and 0.50. The Norwegian experience, which has even obtained percentiles, because of its interest and pragmatism deserves to be incorporated on a regular basis to anthropometry practiced in health examinations and would also require standardized graphs for age and gender. Its value in high-income countries has been noted especially in relation to the increase in obesity [49]. Relative fat mass pediatric [39] is a newer and informative index for trunk fat estimation that will be described below in the Assessment of Body Fat section. There are other procedures, such as the weight index, described by Rohrer in 1921 [50], which correlates better with fat content than BMI and, renamed tri-ponderal mass index [51], has the following cut-off points: figures above 16 kg/m^3 and 19 kg/m^3 would indicate overweight and obesity, respectively, in a population aged 7 to 17 years. Other methods, such as the study of mid-arm circumference or the ratio of arm circumference/height [52] or seated mass/height [53], or other less commonly used methods, have the advantage, like the tri-ponderal, of simplicity and validity at any age, but obviously require more representative and contrasted samples, for example, with DXA.

Apart from those mentioned above, BMI flaws continue to appear, for example, the poor relationship between BMI and health status after bariatric surgery [54], or the different thresholds (different from 30 kg/m^2) according to ethnicity in a cohort of nearly 1.5 million [55]. Therefore, other options such as WHtR or RFMp have shown a better capacity for prediction of body fat content and even distribution [56]. In this context, it is worth considering the present CDC recommendation for obesity screening in adults that it is neither more nor less than BMI and waist circumference [57].

BMI z-Score

Returning to the basic BMI, we must consider the existence of variants designed to identify more accurately excess weight attributable to body fat content. The first essential option in clinical research is the application of the *z-score* (or *Zs*), the basis of which is shown in Fig. 1.3. Technically, the *z-score* transformation, also called *standard score*, indicates for a given parameter, in this case the BMI, how much and in which direction it has departed from the mean of its distribution. The mathematical formula that allows its calculation (now computerized) gives the results, in the case like this of a normal distribution, in units that initially were from 0 to 3 standard deviations with positive or negative sign, indicating in this case overweight or underweight, respectively: normal weight between -1 and $+1$ SD and overweight between $+1$ and $+2$ SD and obesity >2 SD. The advantage of this transformation is that it allows a comparison of the various values of different distributions (populations) with different means and is particularly informative for other parameters, for example, waist circumference (WC), provided the distributions to which it is applied are of a normal type. When the *z-score* is adjusted for age and gender, then it reflects quantitatively the whole population (and not the percentage of overweight or obese), and, although it is also affected by the fact of the asymmetry of the distribution towards overweight, it is minimally so because this skew hardly modifies the mean (Fig. 1.3). This means detecting changes in BMI with greater precision the more obese the child is due to the asymmetry of the BMI distribution already intuited by the smaller distance between the lower percentiles than in the upper percentiles (Fig. 1.2). Nevertheless, and at a clinical level, it allows us to monitor even small changes in BMI (“adiposity”) either in a cross-sectional study of a given population or over time, both in an individual and in a group, under preventive or therapeutic

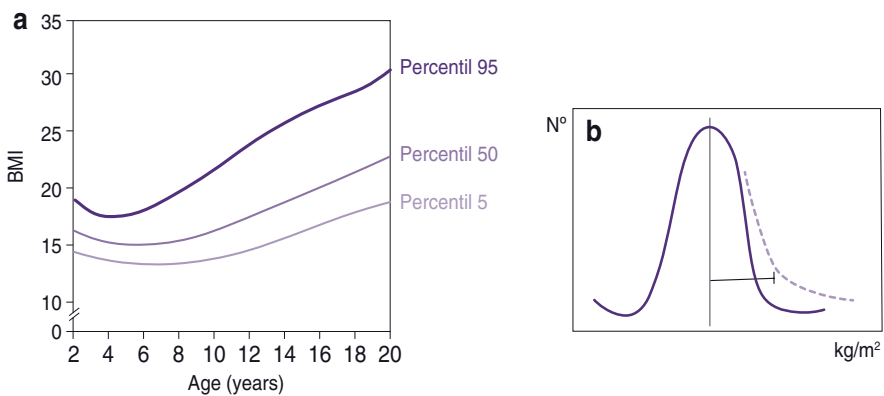


Fig. 1.3 Asymmetry in the current BMI percentiles. (a) The greater distance of the 95th percentile to the mean than that of the fifth percentile (Dietz, 35) is observed. (b) We can see how the bias towards overweight (dashed line) does not modify the mean BMI and the distance (–) is quantifiable by the *z-score*

action. The *z-score* is a good system for statistical calculations well-known from previous experience in the study of longitudinal growth and its deviations. Although there is still some controversy about the choice of cut-off points that would indicate overweight and obesity [58], if we start from a normal distribution, a *z-score* of +2 would correspond to a 98th percentile of the same distribution. Although there are tables for the evaluation of the *z-score*, it is advisable to calculate it for each patient with their current data.

Relative Body Mass Index (rBMI)

Although the idea of referring weight to the height of a population standard is an old one, it was Dr. E. Poskitt who materialized it [59] under the formula: $100 \times \text{kg/m}^2 \div \text{kg p50/m}^2 \text{ p50}$, and with an assessment of normality when the rBMI ranges between 90 and 110%, overweight if it is between 111 and 120%, and obesity when it exceeds 121%. It has the great advantage that the percentage of excess weight of a group of patients with respect to the average of their population can be compared with the excess weight of another group of patients of another ethnic or social group using their own standards.

Although the latter formula allows manual calculation, the ease of use of computer programs greatly simplifies its use. One, the auxological program Seinaptracker [60], with the introduction of the date of birth, gender, current and successive weight, and height of a given patient, calculates the BMI, the *z-score* of the same and the rBMI. The same is done for the various body circumferences. Considering that the data of each visit can be exported, subsequent statistical studies and their comparison can give reasonable information on the progress or otherwise of an action aimed at combating obesity. However, if the same problem is addressed from a local community, then it is more advisable to measure and weigh all children on two or three occasions during their school career, which would give the trend in that community. It should be remembered here how mistakes can be made, especially in measuring height, when several samplers are involved, and the uniformity and rigor of this simple practice should be ensured as far as possible [61].

BMI Percentage (% BMI)

This method of assessing adiposity through excess weight has undoubted advantages and uses the formula: $100 \log e (\text{BMI}/\text{average BMI})$. That is to say, it has the virtue of expressing as a percentage the deviation from the mean for a given age and sex, the results being comparable to those offered by the BMI *z-score* [58]. One of our first computer programs (TARGET) for the study of body mass index used this system and in its 15 years of existence showed excellent results although it applied Tanner's growth standards as a comparative basis.

Of these five ways of estimating adiposity through BMI, the one based on percentile estimation can be used for *screening* and only requires the appropriate graph for the country or a global projection. Those referred to as rBMI and *z-score* are more accurate but usually require a minimum level of computer support to be applied to each measurement.

Assessment of Body Fat and Its Distribution

If the physical substratum of obesity is adiposity, to quantitate it has proved a difficult objective. The commonly used rBMI or *z-score*, although the most advisable because of their correlation with total body fat, does not take into account skeletal size and especially muscularity [62]. Given that muscle is denser than fat, many young people who regularly play sport would give values that would place them in the overweight zone, a situation which is almost the opposite of sarcopenic obesity in adults. The opposite situation, in other words, sedentary children with lower mineral and/or muscle content, means that they might be identified as “underweight”. In addition, the body fat mass/fat-free mass ratio varies with age, race, and especially sex [63] without variations in weight and therefore BMI. The need then arises to assess body fat directly, as well as its distribution, because of the clinical implications. There are three types of methods for this: (1) anthropometric, especially the measurement of abdominal circumference (*z-score* and percentile) referred to above, and those based on the waist/height ratio, (2) physical or chemical methods, and (3) imaging. Physical methods are based on the measurement of total body electrical conductivity or bioelectrical impedance, the new technology of which allows a *screening-type* assessment but does not constitute a gold standard as is often claimed. If dietary stability, the level of hydration, and a very careful technique are not taken into account, errors are frequent [64]. Chemical methods are based on the measurement of body water by means of the dilution of deuterium oxide (D2O). Previous physical methods (weight underwater) and of imaging through axial tomography have given way to techniques based on X-ray absorption (DXA) and those obtained by magnetic resonance imaging, which allow precise measurements of body fat (BF) and fat-free mass (FFM). These techniques have provided an answer to the question of whether BMI-based methods can assess body adiposity. The answer is yes, although with certain limitations [65–67]. However, the routine clinical use of such procedures is not justified [68].

Moreover, for more than 20 years, we have known the clinical reality that short- and long-term health risks do not correlate well with either BMI or total fat mass, while they do with the so-called visceral or intra-abdominal fat [69]. The reason may lie in the adipocyte activity itself and in an influence on the metabolic activity of the liver and pancreas through the portal vein, among other actions that will be seen in Chap. 4, Pathogenesis.

It has long been known that the prominence of the abdomen, estimated by waist circumference, was associated with cardiovascular disease, but it is the later studies

of Jansen [70] that consolidate the measurement of waist circumference (WC), and not BMI, as the best predictive value of morbidity in adults while demonstrating its excellent correlation with abdominal fat; and in pediatrics, Moreno [71] showed how the waist is the most appropriate anthropometric measurement for the *screening* of metabolic syndrome in obese children. Maffeis [72] confirmed that larger perimeters are associated with higher basal insulin levels, higher insulin resistance index, and hypertension in obese girls.

Following this line of thought, the study by Lee [73] shows how BMI is associated with total fat ($r = 0.97$) and how waist circumference is associated with subcutaneous fat and fat contained in the abdomen, but by itself WC is also an excellent predictor of visceral fat ($r = 0.88$) in the pediatric population. More recently, in a prospective study of more than 300 children (80% obese) and care design, Palmieri [74] demonstrates the association of waist circumference and especially waist-to-height ratio (WHtR) with truncal obesity estimated by DXA, with dyslipidemia, with insulin resistance, and with high CRP values. Although visceral fat is present in small proportions before adolescence, it already predisposes to insulin resistance and type 2 diabetes, according to studies on insulin sensitivity that will be discussed in the *Pathogenesis* chapter. Until normalized standards for WHtR are routinely available, the easy measurement of waist, which may seem less important, should be included in the auxological routines used in the obesity clinic, since percentile charts are available for our child population [75]. Relative fat mass pediatric (RFMp) values after the aforementioned equations [39] were obtained in a pediatric population of 472 [76]; these values estimated the trunk fat component in boys and girls better than BMI due to the great fat content in girls present in the whole range from underweight to obesity.

Historically, mention should also be made of the brachial perimeter (BP). Since the 1960s, when this simple method was used in the studies of undernutrition by the Jelffe's ratio and in other field studies of the time [77], it has not ceased to be valid although neither has it or had been extensively used. The fact that it is simple to apply and noninvasive means that it is once again being considered but now in the context of overweight. Brachial anthropometry studies the areas of brachial fat and muscle mass using formulas applicable to the cylinder that would be the arm and in which a factor is the tricipital fold that would estimate fat locally. These calculated values do not present additional advantages to the simple measurement of the circumference or arm circumference, obtained at the midpoint between the acromion and the olecranon and which presents a correlation ($r^2 = 0.84$) with local or total fat mass greater than that of the skinfold itself [78] even for a population with a nutritional *stunt* [79].

In summary, it can be said that obesity is an excess of body fat that is harmful and that this is difficult to measure accurately both clinically and epidemiologically. There is clear evidence that the assessment of BMI (kg/m^2 *z-score*) is the best available and most widely used [80] option for assessing adiposity, but it does not predict cardiometabolic risk. Nevertheless, its widespread use has yielded valuable results, such as its application in early childhood or even in preterm infants when expressed in g/cm^2 [81]. But given that BMI changes with age and is different

according to the gender of the patients, it must be interpreted using centile graphs for the description of population data, or preferably by calculating the *z-score*, which would be nothing more than the number of standard deviations (SD) that a given observation deviates from the reference mean of that population [82]. To this assessment must be added that of truncal obesity by means of the simple waist-to-height ratio (WHtR) and, failing that, waist circumference alone due to its prognostic connotations and that of growth rate when the follow-up is prolonged. Finally, and within these quantitative aspects, it is pertinent to point out the growing criticism of the threshold of significance of the value of $p < 0.05$. Lowering it to < 0.005 may make good sense [83].

Milestones in the History of Obesity with Special Reference to Childhood Obesity

To conclude these notions on the concept of obesity, historical reflection can offer us keys that help us to understand the changes that have taken place in different scientific, social, and cultural contexts in the assessment of obesity and its relationship with states of health/disease. It is well-known how, at certain times, this nutritional condition was considered to be protective against possible nutritional deficiencies. A significant example is the representations of female figures (*mulier sapiens*) in the Upper Paleolithic and, among them, the *Venus of Willendorf*, found at the beginning of the twentieth century in the Austrian city from which it took its name and which is found, among other similar statuettes, in the Natural History Museum of Vienna. This statuette shows traits of a significant obesity that we would not hesitate now to qualify as central obesity, with a waist/height ratio of 1.25. This manifest obesity also appears in other prehistoric female statuettes, and they are probably the first documented cases of this condition in the history of mankind. In all these figures, obesity is inevitably linked to fecundity and the ability to raise children. That is to say, to positive values in these cultures. On the other hand, in the representations of men, they are always drawn with stylized lines [84].

Classical Greco-Latin science, the starting point of traditional western scientific medicine, eventually consolidated into a rational body of doctrine, far removed from magical-religious explanations, on the basis of the humoral theory that was valid for more than 20 centuries in Western European medicine. Some of the medical writings of this tradition in which obesity is mentioned are, first of all, texts of the so-called *Corpus Hippocraticum* (fifth to fourth centuries BC), a set of 53 anonymous writings attributed to Hippocrates of Cos, but actually the work of several authors and schools [85]. In the Hippocratic *Aphorisms*, there are direct references to the subject such as:

Those who are excessively fat by nature are more exposed than the thin ones to a sudden death (aphorism 44, section 2^a). And, further on: *Those who do not conceive because they are excessively fat have a fold* (peritoneal fold) *that compresses the mouth of the womb, and they do not become pregnant before they have lost weight* (aphorism 46, Section 5).

With respect to obesity (corpulence in his language), the situation of overweight is described, and therapeutic guidelines are established taking into account what today we call energy balance which factors in the management of what were called the “six unnatural things” or preventive rules that had to be followed to avoid falling into disease, among them, food and physical exercise.

Two other fundamental milestones of classical medicine (the works of Galen and Avicenna) include elements on the subject that concerns us. In the work of Galen of Pergamon (second century), in Roman Hellenism, the author describes two types of obesity (moderate and immoderate) and proposes a lower-calorie diet. For its part, the first book of Avicenna’s *Canon* (tenth century) includes guidelines that, in a way, are linked to what in the contemporary period will be considered the basis of obesity therapy, that is, the dual quantitative and qualitative approach to diet and physical activity. Avicenna related obesity to problems with mobility, breathing, sudden death, infertility, and lack of libido. In order to treat it, he advises reducing food intake and increasing exercise and baths.

The whole traditional Galenic system was based on the first western theory, the humoral theory, as health was considered as the balance between the four humors that constituted the anatomical-physiological basis of the organism (blood, yellow bile, black bile, and phlegm or pituita) which were formed, in turn, by the mixture, in different proportions, of the four basic elements: water, air, earth, and fire. Disease (including obesity) was the result of humoral imbalance (by excess or humoral plethora or by defect). Therefore, the treatment of excess weight would consist in the evacuation of excessive humors, especially the water element and phlegm humor, through purges and bloodletting.

At the beginning of the modern period, in the Renaissance, the general theoretical foundations of Galenism persisted to a large extent, with some novelties such as the new anatomy of Vesalius. In a population which, as evidenced by the data provided by historical demography and epidemiology, presented the characteristics of the at that moment model, with high mortality and morbidity rates and demographic crises caused, in part, by disease and undernutrition and malnutrition. In this situation, obesity was perceived at the popular level as a sign of well-being and prosperity and, therefore, was far from being considered a disease. It is possible that the first observations of adult and pediatric obesity are based on the artist’s eye. Thus, the Renaissance *putti* (Fig. 1.4) are undoubtedly the first vision we have of overweight or *early rebound* of adiposity. The man and woman of Vitruvius in 1490 were the first proportioned models, and although the weight does not appear in the drawings of Da Vinci, they could also be of weight according to his writings in the *Codex Atlanticus* on nutrition and physical activity. However, in the sixteenth century, arteriosclerosis concomitant or not with obesity already existed, as the five mummies of Inuit adolescents or young adults found in Greenland and studied with a special axial tomography technique have clearly shown, and this despite their vigorous lifestyle and their basic diet of fish. The HORUS Study already examined a larger number of mummies with arteriosclerotic lesions that lived 6000 years ago in Egypt.

Fig. 1.4 Titian Vecelli (fifteenth century): “Offering to Venus.” Museo del Prado, Madrid



In the seventeenth century, within the framework of the Scientific Revolution, important changes took place in the approach to scientific problems and, among them, those affecting medicine, with inductive reasoning as a method that moved away from the speculative interpretations of traditional medicine and science. This was based on the collection of observational data obtained from reality and was a very significant change that already pointed to what would become, from the nineteenth century onwards, contemporary medicine. The development of Vesalian anatomy based on the dissection of human cadavers, Harvey’s physiology, or Sydenham’s concept of morbid species or nosological entity, which pushed aside the previous classificatory trees, is other fundamental milestones.

In this context, as well as with these methodological assumptions, two figures represent the arrival of modernity in the field of clinical obesity [86]. On the one hand, the figure of the Italian physician and physiologist who worked in one of the most prestigious institutions in Europe, the University of Padua, Sanctorius Sanctorius, who, in addition to his inventions to measure pulse or temperature, set the standards of what we know today as metabolic balances through a series of experiments on his own body. Together with Sanctorius, the Englishman Tobias Venner [87] is credited with the first use of the term “obesity” in a medical context as opposed to the usual term of “corpulence” which had other and misleading connotations.

However, these advances had little effect on the study and management of obesity as a chronic disease. Bray [88] refers to information contained in a series of doctoral dissertations, all written in Latin, by important authors such as the German Michael Etmüller where obesity (*corpulentia*) was just another section of nutritional or medical deviations, with clinical descriptions and extensive considerations

Fig. 1.5 Rubens
(seventeenth century):
“The Three Graces.”
Museo del Prado, Madrid



of general causal theories. Again, art provides what, at times, are very precise clinical views. *The Three Graces*, by Rubens (Fig. 1.5), shows the arrangement of the subcutaneous and abdominal fat deposit. This feature can be found in the painting of this period in various European countries. In the line of pure pediatric obesity, the character in Juan Carreño's paintings (Fig. 1.6), *The Monster*, either clothed or naked, is clearly suggestive of Prader-Willi syndrome.

From the point of view of the development of the medical sciences, the eighteenth century was a continuation, broadening and deepening of the lines marked out since the beginning of the modern period. The new clinical aspects of obesity in this crucial period were relevant and were supported by the growth and expansion of the basic sciences, the development of clinical and pathological anatomy, and the first attempts to systematize all the innovations that had been taking place since the Renaissance in all areas of medicine. Although the specialty of pediatrics was not institutionalized until the nineteenth century, within the framework of the new Anatomoclinical School of Paris, the appearance of medical monographs specifically aimed at this age group in the eighteenth century is an indicator of the growing interest in and individualization of this area of medicine.

As far as the influence of new approaches in the conceptualization and management of obesity is concerned, there are no major novelties worthy of mention. The sources of data on the subject appear in some cases in university doctoral dissertations, and their language, like that of all science and medicine with few exceptions,



Fig. 1.6 Juan Carreño de Miranda (seventeenth century): “The Naked Monster” and “The Clothed Monster.” Prado Museum, Madrid

is Latin. Two monographs are however significant: those of Thomas Short and the English physiologist Malcolm Flemyng [88]. The etiological approaches are more in line with reality (excess of sweet or fatty foods) but still confusing, since obesity is sometimes considered as one of the ten deadly sins, and this is transferred to its denomination with the terms “gluttony/gulosity” as a sin and therefore involves moral judgments in clinical issues. Also from this period is the work [89] of A. U. Gosky (1658), and after the prevailing thought that obesity was particularly linked to voracious eating, he describes the obese, in Latin, as “slow, lazy and indolent, they tire quickly and develop an irresistible propensity to fall asleep.” This is the description of what we know today as calumnious or stigma, something that will gradually disappear until it is excluded from the medical literature.

The appearance of Giovanni Battista Morgagni’s *De sedibus et causis morborum per anatomen indagata* (1767), rightly considered the starting point of pathological anatomy and modern anatomico-clinical pathology, was a fundamental milestone and included, among the collection of clinical cases and their necropsies, studied with all the rigor possible at that time, information on the subject of obesity. Thus, we find the anatomical dissection of a very obese woman with a virile appearance, describing a prominent abdomen containing a large amount of fat accumulated in the intra-abdominal spaces, with elevation of the diaphragm; this accumulation was also evident in the mediastinum. Together with these necropsy findings, Morgagni

described the association between visceral obesity and hypertension, arteriosclerosis, and sleep apnea [90]. Another of the great figures of eighteenth-century medicine, William Cullen, professor of medicine at the University of Edinburgh, established a classification of diseases (*Synopsis Nosologicae*) and wrote a *Treatise of Materia medica*. In both works the relevant point is that each disease has a constellation of symptoms that configure it [91]. These new visions constituted a reasonable basis for the etiological approach (appetite, sweet, fatty foods, alcohol, etc.) and, consequently, more appropriate therapeutic attitudes. In the eighteenth century, a publication also appears (Fig. 1.7) describing the death of an obese young woman as a consequence of an absolutely arbitrary treatment. It is possibly the first case described and which showed the absence of therapeutic randomization which would take four centuries to be defined and which has not yet been applied to the entire obese population today.

From a pediatric point of view, the interest in nutritional pathology was more focused on undernutrition than on overweight. Thus, the great treatises of the eighteenth century (Nils Rosen von Rosenstein, 1742; M. Underwood, 1795) do not mention the problem of obesity or do so marginally, as in the case of the follower of iatrochemical currents Gustav W. Wedel (1717) in one of his works. The contribution of art through well-known works is more representative of overweight than of obesity itself.

Mademoiselle Lapaneterie l'aînée, fille de condition & riche, jouïssoit d'une parfaite santé, beaucoup d'embonpoint, bon apétit, riche couleur, &c. Cette graisse lui devint suspec-te pour sa taille, d'autant que ses amies lui prédisoient qu'elle seroit à bonne heure comme Madame sa mère, qui étoit une Dame d'une corpulence distinguée; sa couleur même étoit, à son gré, trop animée, elle craignoit qu'on ne l'accusât de boire du vin; la voilà fort intriguée, elle cherche le moyen d'obvier à ces deux malheurs: Que ne fait pas une fille à marier pour conserver sa taille & sa couleur dans leur perfection? Une femme lui conseille de boire tous les jours un petit verre de vinaigre, elle exécute l'avis, son embonpoint diminué, elle vit tomber cette vive couleur: charmée du succès du reme-

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Fig. 1.7 Possible first documented case of death of a young obese woman due to inadequate treatment. In addition to the corpulence of her family, she had an evident abdominal component, was stigmatized by her friends, and died as a consequence of vinegar ingestion which she herself prolonged in view of the good initial results. (Dasault P. Dissertation sur les maladies vénériennes. Avec deux dissertations, une sur la rage, l'autre sur la phtisie. Bordeaux: Pierre Calamy; 1733)

The nineteenth century can be considered as the starting point of contemporary science and medicine, a time in which there was a definitive break with traditional classical medicine and the model of positivist science was institutionalized: Observation and experimentation were the methods that Claude Bernard analyzed in his *Introduction to the Study of Experimental Medicine* (1865), which provided a charter of human physiology based on advances in physics, chemistry, biology, or mathematics applied to medicine. This climate in medicine favored the development of experimental physiology and, in our case, the application of the principles of thermodynamics with Joule, Carnot, Kelvin, Clausius, and Helmholtz, among others, whose cutting-edge work led to the formulation of the first and second laws of thermodynamics, which continue to be the pathophysiological (and therapeutic) basis of obesity, as will be seen in the chapter on *Pathogenesis*. The use of experimental physiology made it possible, still in this field, to discover the relationship between mechanical work and heat production and, later in the century, Max Rubner in Germany developed basic calorimetry for energy balance. The immediate consequence was the appearance of dietary tables and the realization of balances by Max von Pettenkofer, also in Germany. At the same time, pathological chemistry was developed with the identification and measurement of new elements (fatty acids, amino acids, etc.) in plasma and where normality intervals for these elements were already established. The aforementioned French physiologist, Claude Bernard, had demonstrated hepatic glycogenesis and neoglycogenesis, processes of such importance in the genesis of what we know today as obesity comorbidities. On the other hand, the development of histology and cytology was essential for the knowledge of the functional assessment of cells and tissues [92], for example, and in relation to obesity, the first description of the adipocyte by Arthur Hassall in a publication in *The Lancet* in 1849 [93] should be highlighted. Another important description was that of George and Frances Elizabeth Hoggan in 1879 on the “Development and Retrogression of the Fat Cell” by the Hoggans in 1879. Conceptually, the union of medicine and surgery consolidated the curriculum of the present medical schools which already included teaching and research in the areas of morphology, physiology, and pharmacology. In the latter case, the experimental and clinical research criteria achieved the reduction of more than a thousand therapeutic remedies (including those applied to obesity) to a few dozen. Scientific genetics can be said to have begun incipiently at this time, although its development and institutionalization took place in the twentieth century.

The three great mentalities of the nineteenth century—anatomoclinical, pathophysiological, and etiopathological—gave rise, in conjunction, to the direct foundations of the pathology and clinic of the twentieth century. The development of preventive medicine and public health, the advances in surgery and pharmacological therapeutics, and the qualitative change that led to the appearance of the contemporary hospital with its triple curative, training, and research function also have their starting point in the nineteenth century. Scientific-medical journalism, with its roots in the Enlightenment, was another fundamental milestone as an instrument for the dissemination of innovations and contact between professionals. This conjunction of knowledge and actions led to the appearance of medical journals where the

editor/founder was the sole judge. The development of medical libraries that mainly housed books was accompanied by the first catalogues of medical publications. The first edition of the *Index Medicus* dates from 1879, although there is a precedent of cataloguing in 1545 by Konrad Gessner, to whom we will return in the chapter on *Pathogenesis* for his discovery of brown adipose tissue. We have already mentioned above the importance of the ratio devised in 1842 by Lambert Adolphe Quetelet (Fig. 1.8) to classify the weight of people in relation to their height and his application of statistical methods to the social sciences. But in relation to this index, it is fair to mention the prestigious school of the University of Minnesota that was so committed to preventive nutrition and specifically Ancel Keys [94, 95] who in the 1950s renamed it BMI. From there it spread, demonstrating its effectiveness in adults to identify overweight, obesity, and their risks. In pediatrics the first to use it was Cole in 1979 [96].

It is worth noting how in this expansion of the medical literature the share of obesity is very small, although there are nevertheless positive facts, such as that with respect to the previous century, the majority of documents were not doctoral dissertations, with a scope and dissemination more restricted to academic spaces. On the contrary, the number of such printed publications as monographs and other types of books increased. All were descriptive, such as those of Wadd and Chambers [89] which establish the importance of the age of obesity onset in infants or children

Fig. 1.8 Statue of Adolphe Quetelet in the gardens of the Palais des Académies, Brussels



in relation to their future evolution, or aspects of patient management such as the importance of not reproaching non-weight reduction.

Typical of this period is the description of occupational diseases and the appearance of the initially vital statistics (Malthus) that already pointed out the decrease of birth rate in certain populations. It is, however, common diseases that will absorb most of the resources and human potential for both research and medical care. Thus, acute, epidemic, or chronic infections (tuberculosis) were studied and published on the basis of the scientific spirit and the “evidence” of the time. This contrasts with the scarcity of publications on obesity. The *Letters on Corpulence* by William Banting (1863), a non medical person figure [88] (whose ‘Letter on Corpulence Addressed to the Public’ was a particular success because of its reasonable dietary recommendations), or the chapter describing the various types of obesity in the medical book written in German -*Macrobotica or Art of Prolonging Life-* by Wilhem Hufeland (1820), are perhaps the only examples in the vast field of medical publications. It is noteworthy that, despite the numerous and detailed descriptions of diabetes (probably type 1 and 2), this was not related to obesity. This situation of lesser impact of obesity and its basis in the medical knowledge of the time is also reflected in the suggestively titled article *Adipose Tissue a Neglected Subject* [97]. The participation of art in the description of obesity is lesser and perhaps limited to dynamic aspects, as reflected in the picture painted in the nineteenth century by Harold Copping with the title *The fat boy*, described by A. Vogel (1872) in his treatise “Diseases of Childhood”; see Chap. 5 *Clinic* (Fig. 5.3). On the other hand, there is the contribution of art with well-known publications that are representative of overweight rather than obesity itself. Charles Dickens’ magnificent description (*The Pickwick Papers*, 1837) of morbid obesity in adults is undoubtedly notorious.

In the pediatric area, the nutritional problems of concern were more in the field of undernutrition, which was infinitely more frequent, than in that of obesity. The school breakfasts or the Poor Law in some countries (France, England) corroborates this. The names of Escherich, Henoch, Baginsky, Porter (growth), and Jacobi, among many others no less important, give an idea of how pediatrics grew as a specialty. But in the case of pediatric obesity, we can only mention Otto Heubner who, together with the aforementioned Max Rubner, proposed from the caloric point of view only the energy needs of the normal child and those affected by undernutrition, although this step was the starting point for all the development that would take place in the following century.

Current Stage

Historicizing the present in this specific case has two risk factors: the first is the time that needs to elapse to know whether a certain fact should go down in history or not (remember the fleeting success of hospitals by wards versus those housed by a building); the second is the difficulty inherent in the multiplicity of publications or medical actions insufficiently tested, this is well recognized and in this case would

be aggravated by the amateurism of the author. Therefore, only proven facts that occurred mainly in the first half of the last century will be mentioned.

The twentieth century has been interpreted through the prism of the present time as the century of progress in science and, indeed, all the fields mentioned in the nineteenth century developed enormously together with the new ones: genomics, statistics applied to traditional fields (cancer chemotherapy), in the biological field (monoclonal antibodies), and in the field of DNA repair (CRISPR). Mendelian randomization has made it possible to demonstrate the partial role of BMI in relation to socioeconomic status and quality of employment [98], but this is only the beginning. And the same could be said, for example, of the role of tissue-specific transcriptional regulators [99]. In the clinical field, the consolidation of medical specialties is becoming generalized and reaches the level of primary care, with access to laboratory and diagnostic imaging equipment and inter-consultations (electronic medical records). Equally memorable are the advances in surgery, research, functional tests, hormones and peptides, and receptors, not to mention in therapeutics, transplants, cardiovascular medicine, endoscopic procedures, and bariatric Da Vinci surgery. These advances have been accompanied by new techniques for teaching medicine a little more based on bedside learning, and, in addition, research has been revalued as a more appropriate form of updating. In this sense, the classic forum of Europe and North America has been enriched by the extensive research development of certain countries bordering the Pacific. In our case, on a more global level, the emergence of UN-dependent organizations such as FAO (Rome) or WHO (Geneva) have meant great advances in addressing the problems of malnutrition in its double aspect (under and over) and not only in low- or middle-income countries.

In the field of obesity, this important development did not occur at the same level, probably because the number of people affected was not comparable to that of infections, cardiovascular diseases, cancer, or communicable diseases and because the research on “pathological physiology”, and specifically those on the diencephalon, led experts to consider obesity as a disorder of the regulatory mechanism of hunger and, therefore, with a biased and unrealistic therapeutic approach for the moment. Moreover, in the first half of the twentieth century, nutritional concern was much more concerned with deficiency aspects and their relationship with social status (poverty and cultural level). It is worth considering the studies on the evolution of the definitions of excess body weight, from De Giovanni (Padova) to the important bases given by Quetelet [100]¹ who not only fixed the kg/m² ratio but also showed that the normal distribution of Gauss could be applied to these attributes, giving rise to the concept of norm and its possible deviations. The degree of male differentiation of obesities [101], in addition to the detailed pictorial and clinical description stating the comorbidities, has the advantage of laying the foundation for what will later be known as truncal or abdominal obesity. Perhaps the first alarm signal about the risks of obesity did not come from medicine but rather from the American insurance companies which, in the 1930s, identified the association between excess weight and premature death, creating risk tables according to deviations from the ideal body weight. Interestingly, these remained in place until the late

1970s, when they were displaced by the renamed body mass index with its unique overweight and obesity thresholds for men and women [102]. It is surprising that although the laws of thermodynamics have been known since the previous century, the energy balance in relation to obesity was not addressed quantitatively until the middle of the last century. Energy expenditure through physical activity was also addressed at that time and more in relation to the increasing inactivity of the progressively affluent society [103]. During the nineteenth century, the stigma of obesity was merely aesthetic; in the twentieth century, this conception changed due to the association with earlier mortality, through type 2 diabetes, hypertension, cardiovascular disease [104], and the knowledge of insulin resistance and the inflammatory component of adipokines, although obviously the aesthetic connotations persist. This has been especially detected in high-income countries.

From the pediatric point of view and from the beginning of the twentieth century, the logical concern raised by the high infant mortality rate led to a focus (including anthropometry) on the diseases of the infant stage (Finkelstein, Meyer, Nassau, etc.), with special attention to gastrointestinal disorders and often subsequent malnutrition. The childhood obesity described by Arthur Schlossmann in 1934 [105] can be considered a real milestone: description of the skin fold, the concept of *early rebound*, the imbalance between energy intake and expenditure, the family predisposition, the differentiation of endocrine-based obesity, the clinical description, and the diagnosis where the maximum acceptable weight for age is referred to would be valid today. But it is perhaps the therapeutic aspects proposed, through a diet based on caloric needs at rest, the suggestion of progressive physical exercises and the discouragement of opotherapeutic (hormonal) treatment that provide all the conceptual and scientific importance of this contribution, compared to other publications of the time. In the 1950s, the clinical picture was being shaped but with a special focus on syndromic obesity (E. Glanzmann, 1951), probably because the great syndromes (hypothyroidism, Lawrence-Moon-Bieldt, etc.) were diagnosed later with florid clinical descriptions or because obesity due to energy excess intake was not correctly interpreted (adipose-genital syndrome) or simply because it was not so frequent. In Spain and in this context, the *Tratado de Pediatría* by M. Cruz [106] should be cited, because in the chapter on Basic Principles and in its section on Nutrition and Metabolism, obesity is addressed as a non-communicable disease. Although in another field, mention should also be made of the growth charts that were known as Orbegozo's and directed by M. Hernández. The most current and most negative milestone is the expansion of obesity since the 1970s when the obesity epidemic began in the westernized world [107]. Its prevalence has continued to increase until it has become the most common disease in childhood and adolescence.

In the current state of obesity, we must consider a long-standing problem, which is none other than the slowness of its acceptance as a medically chronic disease [86, 104], to such an extent that its well-defined pathological consequences have only become apparent in the last hundred years, both in the adult and pediatric fields. A normal consequence has been the present situation of a "global epidemic," with an upsurge in almost all the countries of the world, including those with fewer

resources. The term epidemic can also be applied without hesitation to the significant expansion of type 2 diabetes that eventually follows obesity. Moreover, all the efforts to improve overall health that have been made in the past two centuries may be slowed down by the overweight epidemic and its already noted reduction or lack of progress in life expectancy. This situation is surprising, since the descriptions of ancient Greece and those occurring from the Modern Age onwards were not inferior to those of other diseases that did put forward effective preventive programs. As a globalized disease, the onset occurred at the end of the Second World War and is closely related to the greater accessibility to food and the reduction in physical activity caused by mechanization [108]. This data should not be ignored because the reduction has only increased over time in blue-collar jobs [109]. In the therapeutic field, two aspects must be considered in this context. The first started in the 1890s with the use of porcine thyroid extracts based on the adiposity of the hypothyroid, evidently untreated and, as with safe medicinal forms (T4), improperly used until recently, well after the isolation of leptin and ghrelin, which confirms the risk of historicizing the present. The second aspect is that of bariatric surgery which began in the early 1950's by means of various digestive bypasses and which has not ceased to evolve as it can be seen at chapter 9 (Treatments). A critical historic review on the discovery of anti-obese drugs summarizes the real pharmacologic milestones [110]. In addition, and typical of the present time, there is the gigantic and incessant proliferation of meaningless literature. But not everything is negative, for instance, from the field of paleontology, we know the real effect on the body size (ichthyosaurs, enormous sea reptile) of large food availability over millions of years [111]. Specifically the good science on obesity has consolidated areas for publication of tested knowledge [87]. The scientific basis of obesity today has brought down the most recent myths and especially inaccuracies such as the statistical phenomenon of regression to the mean or the aforementioned triponderal mass index, the term obesity or the concept [109] of the metabolically healthy obese and the subphenotypes of obesity [110], the concept of the "obesity paradox," or the seven myths questioned in the treatment of obesity [112]. Unfortunately, this situation has spread not only through "fake news" in the social media [113, 114] but also through the bogus science and spin of some systematic reviews that creep into scientific journals [115]. This scientific ambiguity has been encouraged by the tendency of the last century and the present to support nutrient-based guidelines, when support should really be given to food-based guidelines, which are more concise and less speculative but more difficult to organize [116]. A fact of the times, and perhaps negative for the healthcare delivery system, may be provided by a Norwegian report that final-year medical students have inadequate knowledge in the field of obesity [117], leading to under-recognition of obesity at any age and reduced ability to implement weight loss interventions. Similar conclusions are reached in a North American study, which more specifically tests professionals' knowledge of evidence-based guidelines for the nonsurgical treatment of obesity [118] and in a Medscape survey of more than 15,000 physicians in the United States, where 47% want to lose weight. In view of the current state of obesity, above all the reaction of the competent health bodies to the epidemic should be noted, and we might add at all levels. There are

examples of positive changes in some parts of the world, for instance, in the United Kingdom, as in the rise and fall of London's fever hospitals [119], the idea of developing 15 specific treatment centers for childhood obesity [120] should be tested as it was once was with the fever hospitals. This concern at a higher level might be exemplified by the *Commission on Ending Child Obesity*, of the WHO (Geneva), whose *state of the art* is perfectly defined in a recent publication of this organization [121]. It is difficult to avoid the temptation not to mention the striking study in *The Lancet* [122] which analyses the evolution of health progress to the present day and how the projected actions for Sustainable Development Goal (SDG) 2 on malnutrition in its two forms in many countries have a large level of uncertainty with respect to the median of 2017, in other words that the inertia noted in the previous two centuries perhaps is present, albeit to a lesser degree, in parts of the world today. One must allow time, as has been done with the prevention of other diseases, to appreciate the gains that have been made. Due to the peculiarity of the obesity process, and especially in pediatrics, an approach based on training and management must be implemented by health professionals in the face of this important, long, costly, and often unsuccessful process that constitutes the response to childhood and adolescent obesity.

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Chapter 2

Epidemiology in Different Scenarios



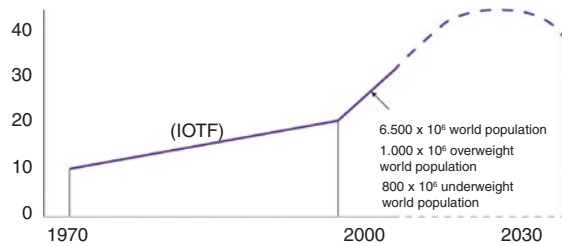
Introduction

It is common nowadays to hear references and concepts, even in the media, about the increase in the frequency of obesity and overweight in the world. Terms such as global epidemic (*globesity*), non-communicable disease pandemic, etc. merely translate a reality and growing awareness. The verification of the higher incidence of overweight versus underweight initially in women from low-income countries was clear evidence of this expansion [1]. In addition to a dynamic concept of nutrition that would condition the epidemiology of overweight and obesity, Popkin [2], in his speech at the Conference of the *International Association of Agricultural Economists* held in Australia in August 2006, concluded that of the 6.5 billion inhabitants of the world at that time, 1 billion were overweight, and only 800 million were underweight, with upward and downward trend lines, respectively. This is the first approximation of the regression of undernutrition against overweight and has also been shown to be rapidly progressive (Fig. 2.1).

After the Second World War and in relation to the change towards overweight, a series of favorable circumstances appear: firstly, food-related, such as higher energy intake due to increased consumption of animal fats, refined sugars, processed and ultra-processed foods, and a decrease in fiber intake; secondly, lower energy expenditure as an increase in jobs with less physical activity, general mechanization, and progressive technification of the home; thirdly, an increase in purchasing power; and, finally, marked urbanization, even in rural areas. All of these factors have an important influence on the development of overweight, obesity, and non-communicable diseases that have had different timelines according to their prevalence at a defined point; see below in the various countries.

The obesogenic milieu is quite generalized: Dr. Lucey's vision [4] led him to discover data indicating that 28–30% of a sample of over 65,000 domestic dogs and cats in the United States were overweight, and he considered this to be nothing more

Fig. 2.1 Weight trends in the global population, according to the estimates of the International Obesity Task Force (IOTF), the WHO, and BM Popkin[2, 3]



than an extension of obesity in humans. He must have been right since in 1996 the FDA, and at the urging of veterinary medicine, approved an antiobesity pill (Sientrol) for nonhuman use. The growing trend of canine obesity has also been demonstrated more recently in 27 countries on 5 continents [5]. Severe obesity in horses [6] confirms the long-term cardiovascular damage.

A good model, which is not only epidemiological, is provided by the well-known NHANES studies (*National Health and Nutrition Examination Survey*), promoted by the CDC, *Center for Disease Control and Prevention* in Atlanta. The four classics are I (1971–1974), II (1976–1980), III (1988–1994), and NHANES 1999–2000. In addition, there are more specific ones that consist of studies of the overall health of a general noninstitutionalized population and are carried out by personnel trained in this field. In their operating system, besides completing questionnaires on demographics, psychosocial status, and health history, they carry out measurements of weight, height, abdominal circumference, blood pressure, and basic biochemistry, in mobile centers.

All this has allowed valuable information to be obtained in diverse fields. One of which has been, from the beginning, pediatric nutrition, because its design can provide subsamples for more in-depth analysis. Its contribution to the knowledge of adult obesity has been extremely important not only for the demonstration of the increase in its prevalence and trajectories but also for aspects with profound clinical repercussions such as the evolution of pediatric abdominal adiposity. This type of programs is now widespread as we will see in the evolutive epidemiology section.

The meritorious work of Osokun [7] made it possible to determine that the average waist of healthy men in 1960 averaged 89 cm against 99 cm in 2000. It should be remembered that abdominal obesity in adults is diagnosed when the perimeter exceeds 102 cm in men and 88 cm in women. A parallel evolution has occurred in the female gender, leading to the increase in cardiovascular diseases and insulin resistance syndrome that has occurred generally in the United States.

The abundant and reliable information provided by the NHANES studies should again be considered when assessing the excess deaths associated with overweight, obesity, and underweight. While overweight (BMI 25–29.9 kg/m²) was initially considered to have a certain protective effect, this is not the case, and once the bias factors have been eliminated, the mortality associated with this cause increases [8]. The decrease in life expectancy in the same population may be related to this factor.

Epidemiological Growth of Obesity in the General Population

The definition of prevalence, which expresses the number of cases at a given time, according to the formula: number of cases/population \times 100, should not be omitted because it is no less well-known; incidence expresses new cases in reference to the total population and is limited to a given time. The World Obesity Atlas [9] constitutes a real breakthrough as regards to the obesity epidemiology. It covers the whole world through the six regions defined by WHO with data from 188 countries. It is important to signal that none of them has reported a decline in obesity prevalence at this time. Global prevalence (estimated just by BMI) is 2020 for overweight 38% and for obesity 14% and all these data will be given at 2025, 2030 and finally the estimation at 2035 will be for overweight of 51% and obesity 24%. This study covers also important aspects such as the existing differences from low-income countries (LIC) up to high-income countries (HIC), from sexes, social levels, etc. even the importance of environmental obesogens or the economic cost from the health care systems to the individual overweight/obese persons.

Despite this global study it is important to consider previous solid studies not only for the given background but for the intermediate data they gave. The OECD [10] which groups 36 high-income countries and is beginning to include those with recent economic development (Fig. 2.2) gives an idea in its 2017 report of the global situation of obesity. It shows an increase in prevalence almost everywhere in the world, but with at a slower rate than in the previous 5-year period studied, it also shows the predominance of obesity in the female population and in general, with a discouraging projection (Fig. 2.3) that mainly agrees with that of the WHO.

This situation is also analyzed in middle- and low-income countries through the exhaustive studies of the *NCD Risk Factor Collaboration (NCD-RisC)*, which is a global network that provides data on risk factors for non-communicable diseases, concerned with strict data processing and periodic publications. With measurements [11] of weight and height of 130 million people, we see that the average BMI increased, between 1980 and 2010, by 3 kg/m² in women and 2 kg/m² in men. We will return to this study later when we discuss the pediatric prevalence of obesity. These increases are repeated when the study reaches 2017 and also denotes an increase. In agreement with Atlas 2023 study, in the urban population from 44% to 55%.

Of interest is the reference to the prevalence of obesity in the United States for the sequenced follow-up and related factors. The CDC [12], taking the national study (NHANES) together with the study at the level of the various states (BRFSS), concludes that in the decade 1995–2005, obesity increased in all states and that it affected 23.9% of all adults. In simple terms, from 1960 to 2002, the average weight of American adults increased by 10.8 kg with a more modest increase in height. From 2011 onwards a number of methodological changes were introduced, and therefore the results obtained up to that time are not comparable with those thereafter. The 2013 edition with self-reported data [13] follows the same approach

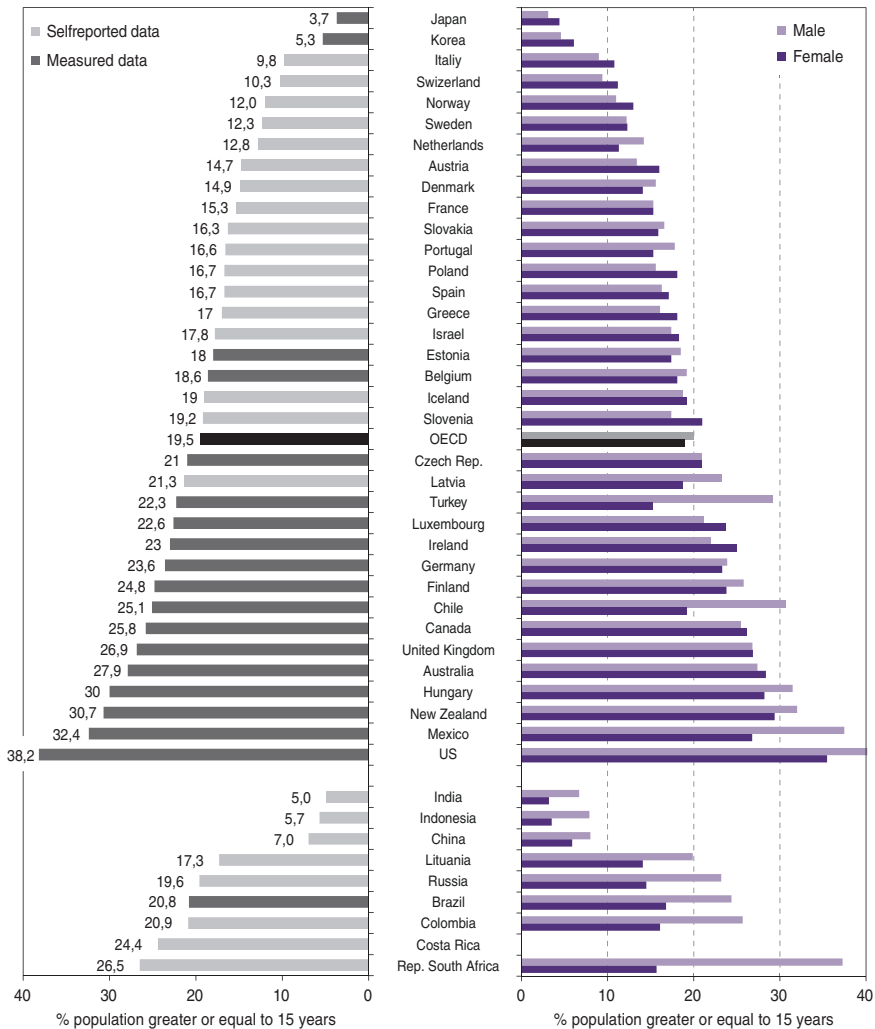
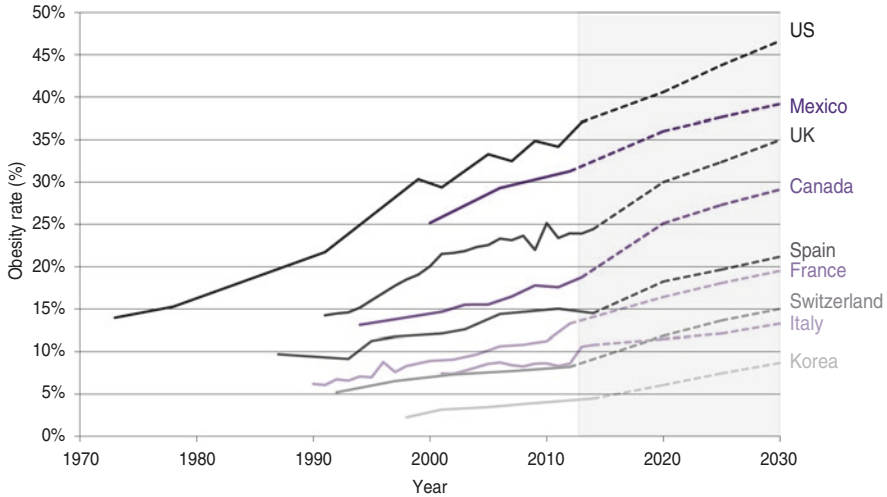


Fig. 2.2 OECD. Obesity in the adult population of member and partner countries. Data are for 2015. The left-hand side of the image shows figures for both sexes, the denser bar indicates measured data. The right-hand side shows prevalence by gender [10]

(prevalence by states and regions according to population groups) and concludes that obesity in no state has a prevalence of less than 20%. The states with the highest proportion of obese citizens are Mississippi and West Virginia, and the ethnic group with the highest proportion is the non-Hispanic black population. In the 2017–2019 [14] edition, the situation remains similar, no state has a prevalence below 20%, and in the regions with the highest prevalence of obesity (midwest 34%, south 33%, northeast 29%, and west 27%), the percentage has increased since 2011. An interesting fact about this unfavorable development is that the prevalence stabilized



Note: Obesity was defined as BMI > 30 kg/m². The Organisation for Economic Co-operation and Development (OECD) forecasts indicate that an increase of BMI will continue as a linear function of time.
 Source: OECD analysis of national health survey data.

Fig. 2.3 Projected obesity rates [10]

between 2005 and 2016, in adolescents and young adults although the causes are not well-known. Studies of prevalence carried out recently in Iran, Indonesia, Republic of Vanuatu, MENA (Middle East and North Africa), South Africa and Bangladesh are worthy because they state together with prevalence the launching of prevention plans. It is also worth to mention that the weight gain of more than 4 million US adults during the first year of COVID-19 pandemic was of 0.1 Kg [15].

It is notable how this trend has been confirmed in some Asian countries. In China, in a study to assess cardiometabolic risk (Zhongua Liu 2018), it has been observed how, since the 1990s, there have been increases in the number of people who are overweight (BMI > 25 kg/m²). Affecting 14% of men and 8% of women, this increase also occurs in the pediatric population. In a more recent study (2004–2018) [16], obesity (BMI >30 kg/m²) has grown by 5.0%. In South Korea [17], and from a study of more than 1.2 million adults, but aimed at determining the relationship between BMI and mortality, this trend is also inferred. In India [18], in a study of more than 77,000 women, this growing trend for both overweight and obesity is unequivocally related to the better socioeconomic position and the modification of lifestyles that it entails. Worthy of note in these countries are the coexistence of the increase in overweight and the decrease in underweight (BMI < 18.5 kg/m²). The Purworejo three paper series [19] provides ample information on this regression also in childhood data.

Other studies carried out in other parts of the world, either because of their size or their design, are only informative from the local point of view [20]. Therefore, the comments [2, 21] related to prevalence and causes of underweight and overweight in women in both urban and rural areas of 36 developing countries are

clearly indicative: percentages of overweight in the cities have doubled, tripled, or more. On the other hand, in rural areas and in traditional poorer countries, the percentages remain steady or undernourishment predominates. This was the case of Niger, Zambia, or Kenya in contrast to the trend in South Africa with the expected double burden of malnutrition.

A study carried out in Europe (1995–2004) [22] recorded the increases in weight averages in various countries, but fundamentally the opinion that Europeans have of themselves with respect to their weight is striking, and the results showed that that 38% think that their weight is too high. The value of these figures is merely indicative because there is a general tendency to optimize weight and height, which means that the data obtained by the simple method of the phone do not correspond to the reality of the measurements. However, this study demonstrates a high degree of awareness of the problems associated with excess weight and the need for effective prevention. Studies in EU countries show that such concern is justified as the prevalence of overweight (~ 40%) and obesity (~30%) in countries with reasonable health status [23] may have stagnated since 2010. But only in a few countries or areas, in the rest of the European Region considered as a whole, has it risen again (~23%), unevenly across countries. The projection for 2025 is 20% [24].

It is now appropriate to consider the so-called double burden, which is nothing more than the coexistence of overweight or obesity with undernutrition in a given country, area, or even within the same family. This situation occurs in countries or economies classified by the World Bank, according to gross national income per capita, as low-income, lower-middle-income, upper-middle-income (countries in economic transition), and high-income countries. Specific aspects of this sometimes called “paradoxical nutrition” will be discussed in the section on Pediatric Prevalence.

In this case the area most resistant to nutritional recovery is Africa since, despite the high prevalence of malnutrition, it is observed how 5% of men and 15% of women suffer from obesity and how T2D and hypertension already present will double by the year 2035 [25]. As we have already stated, these are the ideal areas to establish effective prevention to avoid the serious problems that appear in other parts of the world. With respect to countries or economies in economic transition, this situation is more serious as a comparison of adult obesity prevalence in these areas shows an upward trend in prevalence between 1975 and 2014 [26] with the lowest in Asia (~ 5%), Africa (~ 10%), and Latin America (~ 14%) compared to high-income economies (~ 17%).

The first consequence of this development is that as the economy advances, the prevalence of obesity increases, and in the specific case of transition economies, this increase is mainly in the wealthy classes, in urban areas and especially in the female gender. The emergence of obesity, which is as high as 11% in some low- and lower-middle-income countries, in children with nutritional *stunting*, is a reality [27]. In high-income economies and according to the *NCD Risk Factor Collaboration* of 2016 [28] and in adults (> 20 years), overweight and obesity in these economies have only increased as a result of the growth in urban population, gross national income, and its more direct consequences in this case such as increased

consumption of caloric and ultra-processed foods with reduced micronutrient content and strongly promoted by the transnational industry [28, 29]. And on the other hand, the reduction of physical activity that mechanization entails is a long-term health menace which is not easy to curb: a global study including 1.6 million students [29] showed the majority were insufficiently active (81.0% [UI 95%]). Given the higher number of deaths caused by non-communicable diseases in low- and lower-middle-income countries compared to high-income countries, it is necessary to implement a series of health, social, economic, and environmental measures in these economies to reduce the widespread inequalities that affect global health [30].

Why this comment on the epidemiology of adult obesity? Because this trend towards overweight usually precedes that of children and adolescents (aged 6–18 years), which has been detected in high-income countries such as Australia, the United Kingdom, and the United States, as well as in countries with an intermediate level such as Brazil or Russia and in those with a lower level such as China and Indonesia [31, 32]. If this anticipation holds, the development of overweight and obesity in adults would be indicative of the trend in children and young people. But if it is accepted that overweight is increasing in similar proportions in both children and adults, as is the case in certain countries belonging to the first group, then the outlook is much bleaker, all this in the context of the number of studies that are much more complete when it comes to providing data in adults than those carried out in children and adolescents.

Thus, according to independent and international organizations, the problem is that even in developed countries, the prevalence figures will continue to increase until the 2030s, where one out of every two inhabitants will be overweight (Fig. 2.1). If we also consider that overweight and obesity are unequivocal precursors of type 2 diabetes, their projection from the year 2000 to 2030 is worth considering since the predicted figures would mean a rise from the current 166 million to 366 million worldwide [3]. The considerations raised by this trend since the beginning of the increase in the 1970s and after more recent detailed analyses [33–36] indicate that the excess in energy intake and the decrease in energy expenditure continue to be basic. However, new factors, such as epigenetic factors, have a lesser but undoubted strength of association, the application of mathematical models will be a reasonable strategy for the obesity epidemic. It is worth considering how the life expectancy and mortality can be affected specifically for obesity.

Epidemiological Evolution of Pediatric Obesity

The global epidemic of pediatric obesity began in the westernized world at the end of the 1980s [37], although perhaps a certain increase had already been noted a few years earlier [38, 39]. But it was from that date that its prevalence increased continuously both in the developed world and in the developing world, as we will see with current data from the WHO [37], albeit with some exceptions such as countries in sub-Saharan Africa or Southeast Asia [40]. However, these general figures should

be taken with some caution as the magnitude of the pediatric obesity epidemic is highly dependent on the type of definition used. Thus, applying national or international defining criteria to the same population, the prevalence has already been shown to vary by a multiple ranging from two to seven [41, 42] and with large differences in specificity and especially in sensitivity, which is always higher when national standards are used [43]. Therefore, the overall prevalence is difficult to establish in the case of pediatric age not only because of the different defining criteria—whether they are national, national with wide dissemination such as those of the CDC, international such as those of the WHO, or those of IOTF-Cole as we have just seen—but also because of the nonuniformity of the indispensable variables of weight, height, abdominal circumference (rarely measured at that time) age, and gender, all obtained with the same accuracy, sample sizes, and the best statistical processing of the data. Despite these circumstances, the figures obtained showed a reliable increase in pediatric overweight and obesity and an undoubtedly increasing trend [44]. Prevalence of comorbidities studies are significant not only for the repercussion on the health and psychosocial state of the child but also because of the established fact that both situations persist as the child becomes an adult [45].

The work of Wang and Lobstein [46] on trends in pediatric overweight and obesity in the world today addressed this problem with a broad base and a well-considered methodology and therefore deserves a specific reference as a solid starting point. Firstly, its methodology describes how they incorporated longitudinal and cross-sectional studies collected in PubMed (1980–2005) that were representative of the population of the country or area, for example, rural or urban. This involved analyzing 60 of the 192 countries that are members of the World Health Organization (WHO), spread across the six regions, and representing half of the world's population in the year 2000. However, only 42 countries undertook to analyze trends in preschool obesity. One of the recognized weaknesses of this study is the diversity of definitions used to set the limits of overweight and obesity for each publication, and therefore international references and percentile curves were used with different levels for overweight, percentiles: 80, 85, z -score > 1 , and relative body mass index ($rBMI$) $> 110\%$ and respectively for obesity, 90, 95, z -score > 2 , and $rBMI \geq 120\%$. However, and for the reasons expressed above in relation to sensitivity, it has been possible to obtain trend values in those countries where there were studies separated in time using the formula: prevalence in the second study minus prevalence in the first study, divided by the number of years between the two studies. Returning to the study by Wang and Lobstein, their data together with the previous base of the *International Obesity Task Force* [47] allowed researchers to obtain a projection for 2010 of overweight + obesity in children for the abovementioned WHO regions. America was the most affected region with 46.4%, Europe had an intermediate position with 38.2%, and the Western Pacific region had less negative figures with 27.2%, in accordance with the prediction estimated in Fig. 2.1. The increase in prevalence of obesity with more recent data [10] as mentioned at the beginning (Fig. 2.3) can be seen in practically all countries. After this overview it is necessary to consider more current figures that come from the WHO of 2017 [37] and where in an interactive map one can follow the prevalence (%) of overweight and obesity for children and adolescents from 1975 to 2016 just by *clicking on the*

desired country. In addition, the diagram below shows the increase in both. Access to this page [37], which would allow for the verification with these facilities, is restricted.

A systematic review conducted by *Global Burden Disease* [48] covered data from more than 68 million people in order to assess the overweight and obesity trend between 1980 and 2015. The study estimated the absolute numbers of children and adolescents in 2015 at 107 million obese children worldwide, compared to 603.7 million adults, and concluded that these prefigures although lower than those of adults, nevertheless, show a higher growth rate. There are two more interesting studies on this question; one carried out in New Zealand [49], with self-reported data of almost 80,000 adolescents, showed the obesogenic factor with the greatest impact is that of economic prosperity, while economic inequality is only associated with the female gender. The other [50], in addition to the increase in obesity in the pediatric stage, provides data as worrying as those of deaths and years of life lost when compared to an adult population with normal weight.

Of the plethora of epidemiological studies on the prevalence of pediatric overweight and obesity, it is worthwhile highlighting those that have a proven informative value, and the importance of the NHANES studies is undoubtedly paramount. Comparison of the data from the II (1976–80) and the IV (1999–2000) shows that the percentage of overweight children aged 6–11 years doubled, and for adolescents aged 12–17 years in the same period, it tripled [51]. If we consider now the III (1988–91) as highly representative of the pediatric population of the United States, then the percentage suffering from overweight was 14% [52]. This study also indicates trends clearly influenced by the social situation of the various groups and ethnicities. Thus, in 1998 the incidence of overweight increased by 120% in African-American and Hispanic children, while in the white population, the increase was 50%, which meant actual prevalence of 21.5%, 21.8%, and 12.3%, respectively. Another CDC study [53] demonstrated these increases but with two important nuances, its transfer to children under 5 years of age and its relation to economically disadvantaged classes. More recently the same institution [54] analyzed the evolution of obesity for this age segment (2–4 years) in the period 2000–2014, showing how in the first 10 years the prevalence increased from 2% to 15.9%, while in the period 2010–2016, it decreased by 2.0%. This trend is maintained but with a low profile in the area of the *Special Supplemental Nutrition Program for Women Infants and Children* (WIC) which covers 61% of that country. The higher prevalence among black girls in the United States has been documented previously [55] and is also related to socioeconomic factors. Note how the CDC has gradually replaced the terms NHANES with other more specific terms, although these studies continue to be conducted with the same standards and coverage. With data from the latest study corresponding to the 2013–2016 period [56, 57], the prevalence of obesity between 2 and 19 years was 17.8% (95% CI, 16.1–19.6%), with the associations from the 2011–2014 edition relating to large cities, lower family education level, ethnic groups, and age segment 2–5 years remaining almost unchanged. Because high weight in the first 2 years of life is one of the best predictors of BMI in the obesity range at later ages [58], this age may be a prime situation for obesity prevention. After this deliberate evolutionary sequence, the present situation can be calculated

from WHO data (who.int/news-room/fact-sheet, 9 June 2021) which estimate that in 2019, 38.2 million children under 5 years were affected by overweight or obesity, that this problem had spread to low- or middle-income countries, and that in the population aged 5–19 years, the obesity prevalence of 1% in 1975 had increased to 7% (8% in boys). Another epidemiological update with wide coverage [55] also presents global, regional (WHO), and country figures on prevalence and trends in overweight and obesity in children and adolescents. In the same vein, we should consider the extensive data (~130 million) from NCD-RisC 2017. At this point is perhaps worth to look, now and onwards at the fixed data of World Obesity Atlas 2023 [9] on obesity trends from 2020 to 2035. In it the prevalence of obesity in 2020 is for boys 10% and for girls 8% in the lights of the mentioned epidemiological results just quoted.

This type of circumstances has given rise to what was known as *nutrition paradox* and what, as seen in previous paragraphs, is called the double burden of malnutrition and is common in low-income countries or economies but also in poor urban areas of high- or middle-income countries. This paradox consists of the coexistence in the same family of underweight or even undernourished children with overweight or even obese adults. This new phenomenon is the result not only of the nutritional transition due to changes in diet and food availability but also of the change in lifestyle linked to socioeconomic improvement (Fig. 2.4). This situation and its complexity have given rise to a series of four articles in The Lancet [59] where the

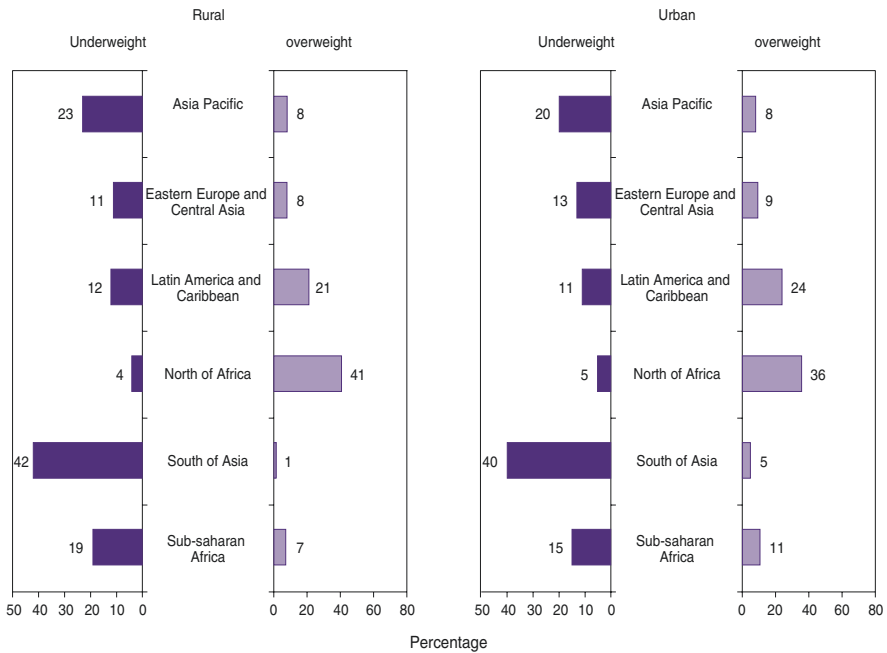


Fig. 2.4 Double burden of malnutrition. Note the percentage of underweight and overweight coexisting in regions affected by malnutrition and according to urban or rural habitat, in this case of 15- to 18-year-old girls assessed according to IOTF standards [59]

dynamics of the double burden and the double actions to be taken, which are not always simple, are analyzed. If the country has a low gross national product, as, for example, Vietnam, poverty itself implies food shortages for all, with the paradoxical nutrition rate being somewhat higher than 2% of families. However, in Kyrgyzstan, with a higher GNP, it affects 12% of families. While the causes of overweight in these countries are clear, it is less clear why underweight persists, implying greater complexity in addressing the problem of good nutrition. In middle-income countries, the recent trend is towards an increase in the prevalence not only of overweight but also of obesity and its usual complications [60]; thus, at very young ages, these increases in the Middle East area represent 7% and in North Africa 8%. The studies carried out in Egypt and Morocco are worth highlighting [40, 61]. In sub-Saharan Africa, there is very little data that can be representative, since the greatest interest so far has been caused by underweight and undernutrition. In Latin America and the Caribbean, it ranges between 4.5 and 7%. Studies carried out in Chile and Brazil, with a time projection of almost 20 years, have been fundamental in estimating this trend. The Asia Pacific region, which includes countries that are different in terms of their socioeconomic development, shows how in Australia and in two periods, one of 10 years and the other of almost 30, figures of 15% for boys and 15.8% for girls have been reached in the prevalence of overweight, with an unequivocally upward trend [62, 63]. In other populations in the area, such as Polynesians, Micronesians, Maori, and others, studies do not allow us to offer representative figures, but an increasing risk of obesity is also detected. In summary, it could be said that in the last 20 years, low- or middle-income countries that have adopted a westernized lifestyle currently have figures ranging between 20 and 30% of children and young people who are overweight. The figures relating to the increase in type 2 diabetes presented in this study are highly important, as will be seen in the Clinic chapter, in the same way that other comorbidities such as hypertension have made their appearance in these double burden areas [64–66].

General extra nutritional factors are increasingly valued. Thus, the study [67] on more than 150,000 individuals from 53 countries with extreme cultural levels shows how, where low cultural levels coincide with low economic income, for example, in Vietnam, the average BMI and its confidence interval was the lowest (20 kg/m²) and where high cultural levels and high income coincide, as they do in, for example, Germany, these values are slightly above 25 kg/m². Countries with low cultural levels but growing economies (Swaziland or South Africa) have the highest averages (~28 kg/m²), albeit with much wider confidence intervals. The study concludes that lower levels of culture imply higher BMIs as long as food is available. An isolated example is the study carried out by a medical school (*Nakuru Medical Training College*) in Kenya on its teaching staff, where 2/3 of the teaching staff were overweight or obese. Although perhaps mitigated, this situation is also found in high-income countries when comparing urban and rural areas. Besides these varied peculiarities of different countries, it should be considered that the ones from single large countries like China [68]. In fact adequate community resources and conditions and particularly adherence to habitual health care policies imply less obesity and greater life expectancy [69].

Developments in the European Region

There are multiple data from almost all countries, even with different series for the same country; however, the lack of uniformity in choosing the defining criteria for overweight and obesity has followed the aforementioned path. The first study with a more general approach is that of Lissau et al. [70], which cross-sectionally collects the prevalence of overweight and obesity in 15-year-old adolescents of both genders in 13 European countries during the 2-year period of 1997–1998. Regarding overweight, the highest figure was for Greece (28.9%), and the lowest was for Lithuania (5.2%) with an average of 13.8% for boys and 13.7% for girls, figures well below those given by the NHANES studies for the United States (28.2% and 31.0%, respectively) and Israel (20.1% and 16.4%). The most representative study with the most data is that of Lobstein, Baur, and Uauy [39] which analyzed data from the *International Obesity Task Force* (IOTF), the *European Childhood Obesity Group* (ECOG), and directly from national publications, which made it possible to assess the evolutionary situation in 18 countries in this region over the following two or three decades. One aspect that stands out is that adolescence does not constitute a peak for the onset of obesity or overweight, and there was even a small reduction in both and in both genders when comparing the figures obtained in the period of adolescence with those of 5–9 years of age. This was subsequently demonstrated in a prospective study [71] in the United Kingdom, involving almost 6000 adolescents of both sexes followed for 5 years. The combined prevalence (overweight + obesity) for the whole sample was 25%, with the highest figures for black girls (29%) and for both sexes when belonging to lower socioeconomic classes. It is worth noting that practically no new cases of obesity appear during this period and, as has been acknowledged, this is probably a demystifying notion about the fatalism of obesity in itself in adolescents [72].

Another aspect to highlight in Lobstein's study is the difference that exists in the prevalence according to the subregions, while in Northern Europe the prevalence of overweight was 10–20%, while in the south and especially in the Mediterranean basin, it was almost double, 20–35%, without there being clear reasons for this. However, it should be taken into account that the figures provided [39] were estimates due to the abovementioned differences in the concepts of overweight and obesity, but also due to the incorporation of unpublished data, self-estimated weight, and countries with more than one study that reflect differences. However, this does not detract from the value of the trend that emerges, as it also includes many informative studies such as those from the United Kingdom [73] or Finland [74]. A meta-analysis including 470,000 children from 28 European countries showed similar results [75]; the same ascending trend also occurred at that time and in more distant places such as Australia [63].

Given the highly individualized situation in the European region of the WHO, the Regional Office developed the WHO COSI (*WHO European Childhood Obesity Surveillance Initiative, COSI*) [76], which consists of a series of studies or waves that collect data in periods of approximately 2 years. The first began in 2007 and the fifth (2018–2020) the results of which were published in 2022 [76] with anthropometric data from more than 411,000 children aged 7 to 9 years of age from 34 countries. This allows trend evaluation based on these cross-sectional

measurements, and because of the rigorous standardization of data, comparisons are possible not only between countries but also over time (Fig. 2.5). The study also includes questionnaires on food and consumption of sugary drinks, physical activities including those carried out at school, sedentary habits, screen time, sleep, and all according to the child’s gender. At present, the progressive comparison of the average prevalence in Europe is not advisable: the data of 2020 (34 countries) cannot be compared with that of 2007 (13 countries) because of the different figures. Overall in the WHO European Region, 29% of children from the participating countries (Fig. 2.5) were overweight according to WHO definition, with a greater prevalence in boys (31%) than in girls (28%). Cyprus, Greece and Spain had the higher prevalence for overweight whereas Tajikistan (Central Asia) Denmark and Israel had the lower. As regards of obesity the overall prevalence was 12%, 14% for boys and 10% for girls, and for countries, Cyprus, Italy and Greece have the higher prevalence and Tajikistan, Denmark and Kazakhstan the lower. These values were prior to COVID-19 pandemic and follow the slow decreasing trend that appeared in the round 4 (2015–2017). In summary and after these five rounds it could be said that children in Northern Europe are taller and thinner in the Mediterranean Basin are the heavier, and in the studied countries of Central Asia the shorter and thinner. The study also includes questionnaires of food and sugary drinks consumption, physical activities and on inactivity. The Finnish study [77] that includes socioeconomic

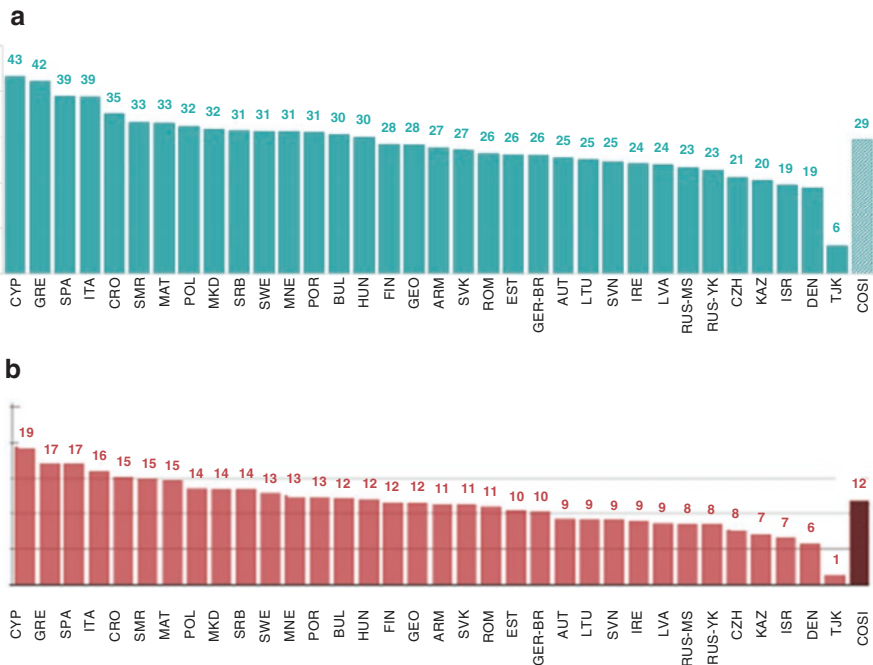


Fig. 2.5 Prevalence of overweight (a) and obesity (b) in children aged 7–9 years (%) COSI round 5 (2018–2020). The figures (numbers?) at the top of each column represent the percentage over a pulation of 441.000 children of these ages from 33 countries [76]

position obtained from administrative registries is undoubtedly an initiative to take into account.

This classification of countries is not absolutely fixed as the data varies according to sex, age, and sociodemographic levels. It should be pointed out that the figures for the prevalence of pediatric obesity in Europe at the end of the last century are merely indicative.

Due to the health problem that obesity causes in Mediterranean countries, the assessment of the prevalence of pediatric obesity in Spain could be illustrative of the difficulties that exist when starting from almost zero, and the framework of the prevalence of overweight and obesity in adults has been fundamental to frame the pediatric situation. The National Health Survey conducted by the Ministry of Health with its successive denominations and administrative divisions together with the National Institute of Statistics collects information on relevant data on the health of the Spanish population, including the population aged 0–14 with a periodicity of approximately 5 years since 1987, all through personal home interviews and a series of specific questionnaires [78]. The study of obesity occupies a justified place in this study, and the self-assessed data allow statistically representative information to be obtained, as will be seen below.

Historically, a number of stages should be considered as an example for the evolution of pediatric obesity assessment. The consensus conference of the Spanish Society for the Study of Obesity (SEEDO) estimated that the prevalence of obesity in the adult population aged 25 to 64 years of age was high and with a clear tendency to increase with age. However, the most important fact was the increased prevalence. In the 1987 National Health Survey (ENS 87), the prevalence of obesity ($> 30 \text{ kg/m}^2$) was 7.8% for adults [79]. In the ENS 03 [80], it was 13.6%, and overweight was 38.5%, but as the values were self-estimated, as detailed in the ENS 87, this probably justifies the differences with direct studies.

In relation to pediatric obesity and its research-based approaches, it is necessary to mention the Paidos study [81], led by M. Bueno, which was carried out in 1984 and which made it possible to establish a starting point for subsequent prevalence assessments. Indeed, subsequent studies covering the 1985–2002 period and with a stratified population aged between 6 and 14 years of age [82, 83] showed an increase (overweight + obesity) in prevalence which in the case of boys rises from 21% to 35% and in the case of girls from 25% to 32%. The Galinud study [84], with a 20-year projection, showed an increase in absolute BMI and waist circumference in Galician children. In Aragón [85] and in a period from 1985 to 1995, with a large base of schoolchildren and using absolute BMI, similar conclusions were reached regarding the increase in obesity and overweight. The Madrid study [86], carried out on some 7000 children and adolescents, is interesting because it applies two different standards to the same population, one national (Orbegozo) and the other international [47], obtaining quite different results both in the prevalence of overweight and obesity in all age strata and in the separation by gender, which is more in line with what is expected nowadays, as they conclude, when the Cole standards were used.

The Cuenca study [87] was smaller in number (1116 children), but, in addition to anthropometric data (using the IOTF standards), it adequately collects blood pressure and a standard lipemic profile. This study is interesting because it compares its data with previous studies carried out in the same areas between 1992 and 2004, and its results are consistent with the enKid study (1998–2009) which will be analyzed below. The study of the Valencian Community [88] covered the entire school population aged 3 to 16 years of age from 1999 to 2005 and used the standards of Orbeago and Ferrández-Longás [89]; again, the differences in prevalence are notorious depending on the standard used. This study, which has a wide coverage, has the weakness of the diversity of the measurement equipment. There is also a set of more local and more general studies [75], some of them of high standards, such as the study of rBMI together with the anthropometry of both parents [90], but their enumeration would be long and would probably contribute little to the real concept of epidemiology in pediatric ages.

For this reason, the enKid study [91] deserves a certain amount of attention. The study was conducted with a scrupulous double cross-sectional design to determine the nutritional status of the Spanish population aged 2–24 years of age and to assess eating habits, which will be analyzed later. It starts from a population of 3534 children and young people, a size that is representative of the population of Spain (not Ceuta or Melilla) for the mentioned age and with a confidence interval of 95%. Six large geographical areas were established: center, northeast, north, south, Levante, and Canary Islands, and from them the population of a total of 85 municipalities was studied, with the classic pediatric age stratifications, being the segment of 18–24 years considered as young adult. The field work was carried out by a team trained for this purpose which carried out the dietary and lifestyle surveys and the anthropometric measurements of weight and height in conditions of the required standardization (underwear, Frankfurt plane, etc.). In terms of results, perhaps the first and most noteworthy is the poor representativeness of absolute BMI for excess weight in growth stages, with the median increasing from 16.4 kg/m² at 4 years of age to 21.4 kg/m² at 24 years of age. This indicates, once again, the inappropriateness of its use as such in pediatrics; this probably led them to choose the Orbeago percentile standards as they were the predominant ones used at the time in this country. In the study we can see how in 2000 the prevalence of overweight and obesity together accounted for 26.3% (percentage of the population above the 85th percentile) in Spain as a whole, with a maximum in the Canary Islands and a minimum in Catalonia, Aragon, and the Balearic Islands. The prevalence of obesity alone turned out to be 13.9% (percentage of the population above the 97th percentile), with a distribution practically superimposable to that of overweight, in which it is evidently included, with a maximum in the Canary Islands and a minimum in the northeastern area.

It is curious how the north-south differences referred to above for Europe would also be present in our country and also the practical absence of waist circumference measures.

An unresolved problem, and probably difficult to solve, is that of the cut-off points: in the enKid study, the Orbeago cut-off points were used, with overweight

being considered as overweight when the 85th percentile is exceeded and obesity as 95th percentile. This diversity of percentile lines and cut-offs and results (we have just seen in the studies cited for Spain how variable they can be) suggests the clinical use of a percentile BMI chart but only for *screening the* general population and, once the group of overweight or obese children has been identified, to apply the rBMI or *z-score* methods that compare them with multiethnic and chronologically consistent standards of coverage. The enKid study, if compared with the previous studies (Paidós), would show for pediatric population an increase in absolute BMI from 18.1 kg/m² to 18.8 kg/m² in 15-year-olds and from 18.4 kg/m² to 21.1 kg/m² in adolescents aged 13. This meant that this prevalence of overweight and obesity led to the first preventive actions that were probably not particularly effective. This tendency panorama of prevalence is a necessary step because of the social and medical awareness it has raised and because it constitutes the recognition of the limited success of the actions carried out and, therefore, of the need for new approaches to this problem.

The most reliable data on the prevalence of pediatric overweight and obesity in Spain are related to the WHO COSI initiative [76]. Spain joined the second wave (2009), and the data in the 2015–2017 report represent the starting point, for further comparisons. Overweight has declined in boys by 4% and by 2.5% in girls and obesity by 2.2% and 0.4%, respectively. COSI should not be interpreted as a mere epidemiological record; its contributions to the importance of the socioeconomic field, or neonatal overfeeding, or the territorial increase of action have been remarkable [92–94]. Spain, through the Spanish Agency of Consumption, Food Safety and Nutrition of the Ministry of Health, and applying the epidemiological standards of the European Region, organized the so-called ALADINO Studies (ALimentación, Actividad física, Desarrollo Infantil y Obesidad) that began in 2011 and expanded successively with the aim of a consistent prevention of childhood obesity and overweight.

The ALADINO 2019 study [95] collects the anthropometric measurements of 16,665 schoolchildren (8513 boys, 8152 girls) aged 6–9 in 280 schools in the 17 autonomous communities and 2 autonomous cities that make up the State, this sample being representative of the Spanish population for that age group. The WHO, IOTF, and Orbegozo-11 growth standards were used, although there was the possibility of using others, as well as uniform data processing. In this wave, the prevalence of overweight (Fig. 2.6) was 23.2% (22.4% in boys and 23.9% in girls) and of obesity 18.1% (20.4% in boys and 15.8% in girls). Given the existence of the 2011 wave, whose overall figures for the same type of population were, respectively, for overweight and obesity 26.2% and 18.3%, it is possible to detect a downward trend in the case of overweight, and in the case of obesity, the decrease is more significant in girls. It is worth mentioning that when using different definitions, a different prevalence appears for the same population: with the WHO standards, the percentages of overweight and obesity are higher in the total sample than when evaluated by the ascending IOTF or Orbegozo-11, and in the case of obesity, the differences are clearly greater (21.5% vs. 6.1% Orbegozo-11). The differences in prevalence between boys and girls are also substantial according to the standards used. Given

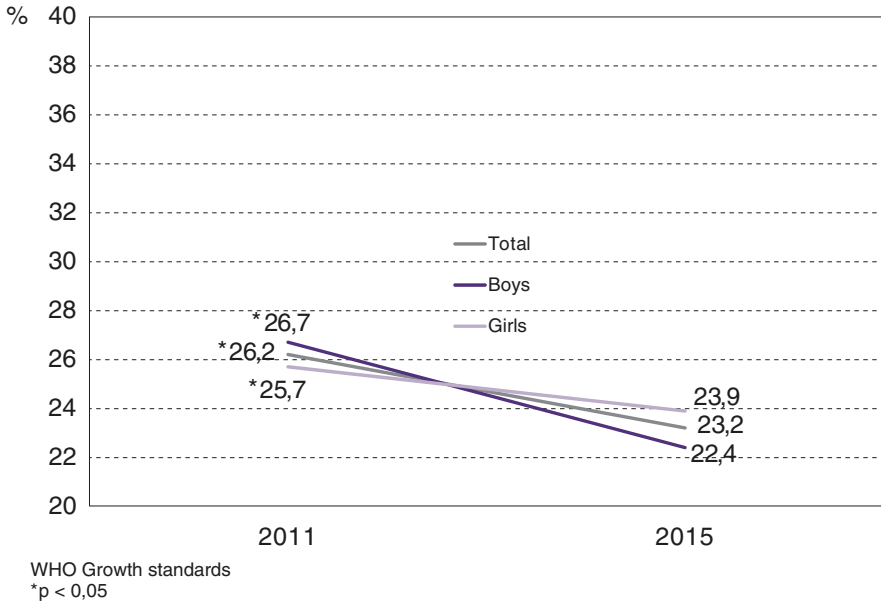


Fig. 2.6 Aladdin Study 2015. In Spain the prevalence of overweight (not including obesity), in the interval 2011–2015 according to WHO growth standards [95]

that the anthropometric values including abdominal circumference and waist/height ratio means and narrow 95% confidence intervals, these differences are more related to the criteria used. The use of the z-score is another positive fact of this study.

Two densely populated countries in Europe (Germany and the United Kingdom) are not part of COSI, and their data are more complex to track and have their own format. In the former, the German Child and Adolescent Health Survey (KiGGS) was designed and implemented under the sponsorship of the Robert Koch Institute. It was nationwide, covered 17,641 children and young people (0–17 years) who were studied between 2003 and 2006 using a precise protocol, and resulted in the present German growth standards whose percentiles and cut-offs for overweight and obesity would be used in successive waves. This first study is considered as the baseline [96], and the following waves were KiGGS Wave 1 (2009–2012) [97] and the latest KiGGS Wave 2 (2014–2017) [98]. This third wave (wave 2) continues to use raw BMI (kg/m^2) and provides prevalence figures for overweight of 14.4% and for obesity of 5.9% with no gender differences. Comparing these figures with those of the baseline (2003–2006), no increase in prevalence is evident in any age group. KiGGS, in addition to the epidemiological trend, supports research on overweight and obesity [99, 100]. In the United Kingdom, the National Health Service has developed the National Child Measurement Programme (NCMP) with online access (NCMP portal) to a wide range of anthropometric, socioeconomic, and physical activity information on the children studied. It covers all nine regions, and the information provided to families and local authorities is particularly important.

Interviews, questionnaires, and measurements are carried out at two different ages: 4–5 years and 10–11 years coinciding with two school phases—the beginning of primary school and the beginning of sixth grade. From the methodological point of view, the researchers used BMI (Kg/m^2) and fundamentally the IOTF and z-score standards. Since 2006 the measurements have been annual. The joint measurements of the 2018–2019 survey in boys show 13.1% overweight and 18.1% obese and in girls 13.8% and 13.2%, respectively. According to the joint data, in the period 2006–2020, and in the 4–5 years age group, the trend of overweight + obesity remains stable at approximately 33%, and obesity is around 10% but with a moderate upward trend in the last 5 years. In the 10–11 years age group, overweight + obesity is at 35%, while in 2006 it was at 32%, and obesity was at 21% compared to 18% in 2006. After this wide range of prevalence and wide range of thresholds used, results are hardly comparable.

This leads us to consider a series of smaller and more personalized projects, such as the one carried out in Scotland [101] which, in the short term and in the area of influence, have managed to reduce not only the absolute BMI but also the prevalence of obesity, although with very little repercussion at a national level [102, 103]. Undoubtedly, efforts at a national level, such as those in Italy [104] or Spain [105], have contributed to this prevalence reduction effect, and within countries, various autonomous communities have undertaken actions to this end.

Epidemiology chapters are often seen as statistical assessments of the present and comparative with the past. Nothing could be further from the truth. Thus, the clinical relevance of the series of adolescents who try to lose weight and relapse is a novel example [106], not to mention the data concerning comorbidities. Consequently, the editorial in Pediatrics [107] entitled “The pediatric obesity epidemic: Still not even at the end of the beginning” summarizes concisely the factors involved in the yet unwinnable battle against obesity and how political will and real collaboration of key social factors would indeed make it possible to reduce this epidemic. But we must not ignore pediatric care in the early years, given the presence of overweight, obesity, and even severe obesity in preschoolers as shown by the Canadian Edmonton study [108]. This is not a theoretical claim; the ultra-processed food consumption percentage among youth in different countries [109, 110] has been growing regularly during the past two decades and no change seems likely. In a different matter such as physical activity, a steady and regular decrease has occurred as can be seen in a large study on more than 1.5 million adolescents [29]. The national or regional BMI disparities [68] are highly resistant to change. Finally unexpected situations such as the recent pandemic [69, 111] are factors that are difficult to manage.

And maybe a good reverse path towards Epidemiology (of pediatric obesity) is the recommendation of the Women and Kids, Health Policy Centre, Adelaide, South Australia [112] asking for tighter regulation of the appropriate use of sugar and fruit puree statements on infant and toddler food packaging.

It is appropriate to end this chapter with the WHO statement [113] which, referring to its target 0–5 years age group and between 1990 and 2016, states that globally pediatric obesity has increased from 32 to 41 million and in the African region

from 4 to 9 million in the same period of time. Moreover, the rate of increase is higher than in high-income countries. They conclude that, if this trend is not reversed, globally there will be 70 million obese children by 2025.

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Chapter 3

Etiologic Factors



Introduction

The causes of obesity have almost always been presented under a complex picture perhaps because they have been intermingled with pathogenic mechanisms to which a causal principle has been attributed when they were probably no more than adaptive responses (remember the interpretations that were given to the plasma variations of leptin). In the current conception of the etiology of obesity, three causal cores must be taken into account. The first is the first law of thermodynamics or principle of conservation of energy according to which in any physical or chemical change, the amount of energy remains constant although it can be transformed. It justifies that through a prolonged positive energy balance, obesity is reached and that through a negative balance, regardless of the etiological circumstances which will be analyzed below, a decrease in the degree of obesity can be obtained.

The second causal nucleus is the genetic one that acts through monogenic alterations which are the cause of a minimal but growing percentage of obesities or through family predisposition (polygenic alterations) and epigenetic alterations in which important clarifying steps have recently been taken for those cases of non-syndromic obesity and perhaps (wrongly) interpreted as due to energy overload.

Finally and classically, the third causal nucleus would be constituted by a set of predisposing or risk factors, enormously varied and with different repercussions in the development of obesity, although due to their fundamentally epidemiological assessment, they have sometimes been overestimated. It should be taken into account that the term association does not imply causality but is worthy of study and assessment. This etiological approach aims to give importance to the chronicity of the positive energy balance, given that even small intakes (100 kcal/day) acting on subjects genetically predisposed or with risk factors will be able to develop and consolidate obesity. However, the positive facet would be in the therapeutic possibilities of negativizing the energy balance which is useful in almost all cases of

obesity with the well-known exception of secondary obesities (e.g., untreated hypothyroidism) or obesities of complex cause such as those of a proportion of preterm infants.

Obesity due to Positive Energy Balance

If in a child there is a chronically positive energy balance, that is to say that he continuously ingests more food than he needs to live, grow, and perform a certain physical activity, then the basic circumstance for the development of obesity is given. Let us analyze the two main components of this imbalance, fundamental overeating and reduced physical activity.

Food Surplus

It has long been considered, and still is, as the main etiological cause, and, in fact, therapeutic efforts have been directed in this direction. Today, in both overeating and non-overeating situations, not only is the copious meal considered, but other aspects such as the energy density, the predominance of various macronutrients, and the pattern of meals have become part of this, as will be seen below.

In a genetically stable population, the increase in the rate of obesity is mostly linked to the overnutrition that has occurred over the last 60 years in most of the world, especially in the westernized world. The joint WHO/FAO report [1] already recognized a link between this and adult obesity. Thus, a well-designed study in adults in the United Kingdom [2] showed that total energy intake and protein and fat intake were significantly higher than those of lean controls in both genders, together with data specific to the age group studied, such as the association of increased abdominal fat with alcohol consumption. It also adds the importance of preconceptional obesity of the future mother, which increases the possibility (OR 3.64) of obesity in the pediatric age of their offspring [2]. Similar conclusions were reached by the Minneapolis school where, in addition to the increase in energy ingested, the decrease in energy expended was considered highly important.

In the pediatric field, excessive energy intake is linked to the earliest stages [3, 4], at least in certain high-income countries and probably in much of the world, a situation not unlike that described prospectively for infants, preschool, and school-age children [5]. It is possible that the trend towards overfeeding begins with the introduction of early and abundant complementary feeding and the widespread idea of offering a bottle or the breast every time an infant cries. In children over 4 years of age, the social or hedonic intake of high-calorie *snacks* along with potato chips and sugary soft drinks and fruit juices and in general the problem of added sugars [6] are not easy to solve.

Against this body of evidence is the fact that while obesity had doubled in American adolescents, energy intake over a similar period of time remained stable or even decreased [7]. Similar facts have been described in other countries such as the United Kingdom and France [8, 9]. It is true that this paradox could be justified by the increasing decline in physical activity, but doubts arise about this because data on energy intake and expenditure are far from accurate. Therefore, some of the older studies are not assessable because of the inconsistency of the methods used to quantify food intake. In addition, other facts must be considered, such as the quantitative variations reported by the patient or his or her family. In our case, it is a reality how foods with a bad reputation are omitted and how the same survey carried out separately to the child and the mother can be different. Also, different energy requirements in relation to gender and growth rates are not always taken into account. All this suggests that the apparent decrease in dietary energy recorded is more apparent than real; in favor of this is the fact of food consumption in Spain [10, 11]. According to the MAPA, the purchase of biscuits and pastries went from 9.8 (1996) to 12.1 (2006) and to 14.1 kg/person/year in 2016 and olive oil from 7.3 to 10.0 and to 12.7 L/person/year. Reinforcing this school of thought is also the fact that the predictive value of future obesity is higher when taking into account the food (and physical activity) preferences of the whole family versus the computation of the data extracted from the surveys. When the surveys were rigorously conducted [12], they yielded means with a large standard deviation (i.e., 1700 kcal \pm 924), and the percentage of macronutrients is also subject to large interpretative variations.

Worthy of note is the work of Ricketts [13] in which he shows how the preferences of obese children for fatty foods lead them to eat them with the consequent body deposit. The inclination for certain tastes and for energy volume can already start in the first year of life if formula feeding is established instead of breastfeeding [14].

With respect to family preferences, it is also worth considering how parental obesity is a reliable predictor of children's preferences, whether or not they are overweight, for fatty foods, which does not occur in the same proportion in children of thin parents. These food (and physical activity) preferences should be taken into account when considering preventive action in the overweight child, as the effects of energy and fat restriction in the pediatric stage do not always produce the expected results. The problem of accurately quantifying food intake is essential in epidemiology and it is practically solved in the case of field studies by means of doubly labeled water or cumulative intake curves, but not in the case of the daily management of the obese child [15].

Energy Density of Food

This concept is defined as the amount of energy expressed in kilocalories (or kilojoules) per gram of food, and its study is relevant for its relationship with obesity, for the greater or lesser overeating, and for the generation of satiety. Initially, energy

density was inversely related to the amount of water and directly to the fat content of the various foods; today it is known that the content of refined carbohydrates is a basic component of the energy load. This led to a situation that is still common today with regard to fat phobia and the misconception that when one eats foods that are poor or lacking in fat, the rest of the food ingested is less important. When the fat content is reduced, the palatability of the food decreases, and this is often recovered, thanks to the addition of refined sugars and the reduction of water (bars, *snacks*) so that the energy density is maintained. However, there are few studies in children on energy density and its impact on total energy intake and its long-term consequences.

In this sense, Beck's study [16] already showed how increased fat intake increases adiposity in obese preadolescents but may have certain protective effects against the severity of obesity. Likewise, McGloin's work [17] similarly does so in both obese and lean children. In those who alternate fast food and conventional food, it is clear that in the first case, the energy density (kcal/g), fat intake, and total kilocalories are higher and vegetable and fruit intake decreases, which, when it becomes a habit, can lead to an increase in adiposity. Added to this is a factor of considerable importance such as economics, as foods are purchased more cheaply and in general those with low-energy density can be more expensive in many parts of the world. Maternal emotional factors are also important in overfeeding [18]. But the situation of food insecurity, which traditionally led people to buy less expensive but high-energy density foods [19], has changed, and today many authors think that this insecurity implies a tendency towards greater weight gain [20]. Energy density has to do with the appearance of the sensation of satiety, and it is an accepted fact that individuals tend to eat a constant volume of solid food per day. Simplistically, a low-density diet would be a good weapon against obesity if it were accepted for prolonged periods of time, which is not usually the case due to the pleasantness of the presence of fat and carbohydrates in food. The increased consumption of fat-rich foods is associated with an excessive intake of food for two reasons, one because of the palatability of the food itself and another because of the postabsorptive slowness of the fat that makes the feeling of satiety come later, which would contribute to a hyperphagia of that food or meal.

In this sense it is worth remembering how carbohydrates have a more intense and more ephemeral effect on satiety and how they generally have a lower-energy density than fat-rich foods. In principle, they would mean a lower-energy intake, although it should not be forgotten that meals which are rich in carbohydrates, especially if they are refined, involve significant energy intake. The combination of both macronutrients, although having different taste attributes, is widely accepted in today's world, making energy-dense foods one of the targets in the prevention of obesity.

Infants and preschoolers are highly sensitive to the sensations of hunger and satiety and thus regulate energy intake by recognizing the energy density of foods [21], which should always be respected, especially satiety. However, from the age of 5–6 years (one of the peaks of obesity onset), factors other than this

hunger-satiety binomial begin to play an important role in food intake and which may justify the increase in overweight even though the energy intake of the general population has not increased over prolonged periods [22].

Current Interest of Macronutrients in Energy Intake

Let us first consider fats, given that there is clear evidence between their consumption and the elevation of total energy intake as an anticipatory situation of obesity. Thus, chronologically, at the University of Alabama [23], it was determined how increases in fat intake and therefore in total energy were associated with increased body fat percentage in preadolescent boys. Subsequently, these increases produced identical consequences and were confirmed by more precise techniques such as bioelectrical resistance [24] or deuterium dilution [17] or even techniques commonly used in the follow-up of obese patients [25]. The preference for fat-rich foods by obese parents may be genetic, and little is known about the specific preferences for edible fats: initially saturated fats were attributed a greater adipogenic component, but once the consumption of oils with higher percentages of unsaturated fatty acids becomes more widespread, this question should be re-evaluated. It should not be forgotten that excess energy intake with a high protein base is associated with obesity during childhood, as demonstrated by the diabetes TEDDY study group of Aurora, CO. More important is the macronutrients imbalance due to low-protein of highly processed foods that will lead to obesity due to higher energy intake driven by a dominant appetite for protein (protein leverage) [26].

The interesting CARE study carried out in Leeds [27] on 1200 mothers with tight dietary control during the first and second trimester of gestation shows the following: for every extra 10 g/day of carbohydrate intake, there is a 4 g increase in birth weight, and this figure doubles if the extra intake is 10 g/day of fat, all with acceptable confidence intervals. During the second trimester, high carbohydrate intake is associated with a greater increase in birthweight. This should imply a stricter regulation of macronutrient intake during gestation. These aspects and the present re-acceptance of saturated fats will be discussed in more detail in the chapter on *Prevention*.

With respect to carbohydrates and as potential obesogens, it would be more appropriate to speak of sugars, since starches are the most effective in reducing caloric intake [28] probably because of their greater volume and higher fiber content and above all because of their less attractive taste. Dietary sucrose was considered at the beginning of the obesity epidemic as an important predisposing factor of obesity, and although today there is the idea of its slight capacity to induce satiety (and satiation), the reality is that it constitutes a significant energy intake through deserts, *snacks*, ice cream, candies, chocolates, soft drinks, and sugary juices. Even despite there is also a hegemonic predominance over the same products made with modern non-sweeteners, aspartame, acesulfame K, sucralose, and cyclamates,

which have no or negligible caloric value. Polyalcohols such as xylitol or lactitol have only 2.4 kcal/g [29].

Special mention should be made of the consumption of non-alcoholic beverages, which include sweetened soft drinks and fruit juices. With regard to soft drinks and since the 1960s, there has been a significant increase in consumption up to the present time. Perhaps it started in the United States and later generalized to almost the entire westernized world [30, 31], affecting both adult and pediatric populations. In the aforementioned British study [8], it was already noted that 17% of the energy ingested in the pediatric age group comes from nondairy sugars and that 75% of the children surveyed regularly drank sugary soft drinks. In Spain and in the MAPA studies [10, 11] covering the aforementioned 20 years, purchases respectively increased from 3.2 to 4.1 and finally up to 11.2 L/person/year. These large quantities of soft drinks contribute to a higher energy intake tipping the thermodynamic balance to the side of obesity [32]. Fruit juices, particularly all-natural fruit juices, have enjoyed a good reputation in pediatric nutrition, and it is worth remembering how Professor Samuel Fomon in the early 1990s gave a serious warning about their energy density and possible adverse reactions [33], yet their use became more widespread particularly among preschoolers because children like the sweet taste, and parents think they offer a healthy, micronutrient-rich drink. It is also worth considering the earlier data on how the consumption of amounts equal to or greater than 350 ml/day in preschoolers in a general population [34] was significantly associated with reduced growth and shorter stature and the development of obesity in 53% of cases.

In contrast to this body of evidence, some subsequent studies have not found such a degree of association [35, 36], but interestingly, others with a more conclusive and analytical design show how reducing the consumption of sugar-sweetened beverages reduced the weight of adolescents [37, 38]. We could conclude this section on soft drinks by saying that there is a positive and certainly direct association between their consumption and energy intake. Also, one strategy to control excessive weight gain in pediatric populations at risk of obesity is precisely to decrease the consumption of these beverages in favor of water.

To sum up these carbohydrate aspects, a few comments on the glycemic index (GI) of foods (increase in the area under the blood glucose curve after consumption of a food and its comparison with that produced by glucose). Knowledge of the GI of various foods [39] is useful for the management of patients, as we will see when it comes to treatment especially in cases where hyperinsulinism is present, but it is also important in this causal context as the feeling of satiety may be higher after ingestion of the same energy load when the carbohydrate has a low glycemic index [28]. Again, the obesogenic environment of the country can be seen in the well-designed MAPA studies over the two decades where in addition to some of the figures given, the increase in prepared food must also be considered. In the last edition, food waste is already considered, but the increase in the acquisition of food in Spanish households together with the extra-domestic consumption of food is not unrelated to the increase in general and pediatric obesity in that period of time.

Eating Patterns

It is in the last five or six decades that the prevalence of obesity has increased and also when the dietary patterns of westernized populations have changed massively. A reasonable question is whether this change has contributed to the development of obesity, i.e., whether the change leads to a higher energy intake. What we might call the classic pattern of three meals for adults and five meals for children, usually prepared at home, has been modified by the increase, firstly, in the number of meals eaten away from home; secondly, in the number of meals; and, thirdly, in the size of the portions. The midday meal at the workplace, at school, or fast-food outlets is a growing reality, in the ages analyzed. The tendencies or food patterns of certain households are also marked by the food insecurity of the adults who live there. A vast study (NHANES) shows how in the last two decades there has been a parallel growth in adiposity which is perhaps reflected in children and young people through the situation of family stress. Household eating patterns have an important impact on children, and if the obesogenic pattern is the usual one, the risk of overweight is a reality [40], and often the eating pattern tends to be of worse quality when it comes to neglected children or when they live in a low-income community or even if there is proximity to fast-food restaurants to which access is a parental decision.

Let us now look at the role of school canteens. With data referring to the Valencian Community (Spain) [41] in 2001, the percentage of users (3–15 years old) was 15.9%, and in 2005 it rose to 27.7% for the same age segment, which meant a total of 120,920 meals per day in the 876 canteens of the centers of the Regional Ministry of Culture, Education and Sport. In a subsequent communication, a partial evaluation is made that affects more than 500 school canteens and in which a favorable evolution is detected, although irregular in terms of the composition of the menus. Despite the existence of rules for the elaboration of menus, the control over their degree of compliance is limited until the present, when a document has been implemented that lists the food offered in the 20 days that the canteen operates per month. The second step, which would be to assess what the child really eats, is difficult to carry out, although there is a general tendency on the part of those responsible for the canteen to ensure that the child eats the total ration served. One fact worth noting after weighing the rations in limited canteens is that they exceed 35% of the energy that the midday meal should provide in relation to the age and gender of the school-children [42]. However, the total number of school canteen meals per year is 170 per pupil, which is small compared to the 1825 meals usually taken over the same period of time, and this number probably has a small impact on the eating patterns of these children. However, the educational potential that can and should be exploited with these school meals is valuable since they are adjustable, especially when they are prepared by *catering companies*.

The increasing tendency in some areas to eat the midday meal away from home at weekends may also contribute to energy overconsumption and should be part of nutrition education.

Fast Food

The first problem that arises in assessing its involvement in the energy surplus is the lack of a precise definition that allows us to identify the foods that really make it up. With data from the food composition tables, in general the comparison of 100 g of hamburger with 100 g of pizza shows a higher energy density (257 vs. 170 kcal), a higher protein content (11.0 vs. 7.3 g), a higher fat content (15.7 vs. 7.2 g), and a higher cholesterol content (47 vs. 0 mg) in favor of the hamburger, yet both are often labeled as fast food, which may limit the value of some studies that are often cross-sectional, and in some cases the assessment of increasing ultra-processed food adds difficulty [43]. Fast-food and ultra-processed foods consumption has increased, according to data reported by St-Onge and her group [44] for New York, and also increased by 300% between 1977 and 1996 when analyzing sales in restaurants and fast-food stands for schoolchildren and adolescents. In another study and over the same period, the consumption of sugary soft drinks increased to 188 kcal/day at the end of the two decades compared to nonconsuming children who only drank water. For the authors, this school meal policy is a contributory factor in the increase in the frequency of obesity [45]. In the aforementioned study in Catalonia [11], it is shown how that population has increased the consumption of fast food and food of lower nutritional value and in that of the Valencian Community [41] of 2018 how the proportion of school canteen users with more adequate diets drops from 35% in the 3–5 age group to 12% in the 12–15 age group. This leads us to believe that the trend previously seen in the United States may already be established in our environment, although longitudinal studies would be necessary to confirm this. The set of lines of work under the heading of the Aladdin National Study, after a longer follow-up, would help to clarify this problem. The challenge in clinical field of fast food [46]; or junk food [47] is that it should alert us to monitor weight after the first birthday and, in cases of family dysfunction, day or night sleep disturbances or its frequency of association with socioeconomic risk factors.

Food frequency. The coexistence of the pattern of three main meals (see “Other Factors”) with *snacking* is a fact as the child gets older, making the (self) control of what is eaten more difficult due to the frequency and irregular intervals. The problem is that this daily increase in the number of meals does not maintain a normocaloric and isocaloric intake as it does not provide a feeling of satiety with respect to subsequent meals, as has been seen in adults and especially in children [48]. Another problem that is seen on a daily basis with regard to snacking is its underestimation in surveys. It is important to remember how in different analyses, including those carried out in low- and middle-income countries [22, 45], the energy and density of foods have not changed substantially in recent years, so that the responsibility of *snacking* becomes more important in overeating. French’s point of view [49] that the frequency of snacking would be more related to previous body mass index is important, although this has not been replicated in other studies [50].

Increased Portion Sizes

This trend began three to four decades ago in the United States and continues to persist there, especially in restaurants and fast-food stands. Despite the fact that since the year 2000 the health authorities in that country have been recommending a reduction in portion size [51] to fast-food chains, the effect has not been significant, as they have continued to increase it. Only one chain reduced it, but the 1988 size is clearly higher than in 1955, all based on servings of hamburgers, fries, and carbonated beverages.

After a series of studies mostly in adults, in some prospective, it could be concluded that larger portions led to higher food and energy intakes regardless of the energy density of the food [48] in adults of both genders regardless of their weight. If we now consider the pediatric population, it is obligatory to refer once again to the works of Rolls in Houston. The first [52] refers to children between 3 and 5 years old, who are offered a larger starter or first course than usual and consume 25% more of the same starter, which implies an increase in the energy provided in that meal of 17%. The second [53] is carried out in children aged 5–6 years, in which the higher energy intake is assessed according to the size of the portion and the energy density. In another study [54], the size of the intake was doubled (250 vs. 500 g), and the density was modified to a lesser degree (1.3 vs. 1.8 kcal/g). All of them showed a significant and summative increase in energy intake after the complete meal which did not vary in its components except for the first course. The effect of overeating was greater in relation to size than density for both genders, ages, and body mass indices.

The consequences of the generalization of these meal patterns could initially be seen in the adult [55] where the larger size and higher energy density [56, 57] imply higher total energy intake and therefore an increased risk of obesity. At this point we should also remember the family's negative attitude of "finishing what's on the plate" during meals. This widespread trait is known to be responsible for higher intakes, comparable to those provided by larger portion sizes [58]. In the pediatric age group, there is a lack of longitudinal studies and studies that include earlier ages, such as preschoolers, and with the "laboratory" design, although there are already some that provide valuable data, such as the study conducted in the United Kingdom [59] which shows that the energy intake can be up to 50% higher in this context of meal size overeating than that provided by the usual diet of the same population. This has been a major wake-up call, especially considering that one or two extra spoonfuls at each meal in a 1-year-old child means an extra 11 kcal/meal that will lead to overweight after 1 year, according to this study, and in addition, the higher frequency of *snacking* does not reduce main meals and is associated with higher BMI and fat mass [60]. Portion size has already been mentioned with the work of Rolls, but perhaps it is worth adding the data from Dr. Picciano's group [61] in which portion size in preschoolers increases energy intake by 16–19% and leads to weight gain.

To conclude this section on the new patterns, it is worth mentioning in particular what we call early etiological factors with longer-term results, the first being chronologically preconceptional obesity followed by gestational obesity (see Risk Factors below) and, once born, nonexclusive breastfeeding up to 6 months of age [62]. As this European study by the WHO in 22 countries shows, unfortunately the results are far from breastfeeding objectives, especially in 6 countries and probably for obesity in the near future. It also refers to another WHO study that demonstrates the high sugar content of certain complementary foods. Similar results are found in the FITS 2016 study carried out in 50 US states.

At older ages it is also necessary to analyze why fast foods have become widespread and, undoubtedly, the fact of being fashionable, the ease of acquisition, the uniformity of its good palatability, and their not excessive cost, aspects that should be taken into account in the general preventive action. Secondly, it is worth remembering how fast food started in the United States but has been spreading all over the world and how children who regularly eat fast food versus those who do not ingest more energy, more fat, more carbohydrates, more added sugars, more sugary drinks, more salt, less fiber, less milk (less than 500 ml/day), less fruit, and fewer vegetables, with an adverse qualitative and quantitative effect, which presumably leads to childhood obesity. Dietary supplements (i.e., n-3 fatty acids) and alternative medicine products are perhaps a minor but growing factor in the development of obesity [63, 64]. Diets observed in principle by large masses of the population are sometimes overestimated. Therefore, and according to the studies from Deakin University (Australia), the once valued contribution of protein intake, if higher rates occur before the second birthday, will be associated with obesity in children and adolescents.

The WHO report [65] comparing the Mediterranean diet with the Nordic diet, despite their differences, concludes that both are beneficial for health and equally preventive of comorbidities; however, another aspect is the degree of adherence and the amount of intake. In addition, overweight adolescents compensate less than their thinner peers for this overeating with a lower-energy intake throughout the day, and it is interesting how restrictive diets, which are sometimes so popular, are even associated with weight gain. There is another component that increases energy intake, and that is the taste for food or sweetness, which relies on a series of receptors regulated by specific genes (pathogenesis). This is linked to the widespread use of ultra-processed foods (UPF) [66] which are often energy-dense and have a high glycemic load. In some high-income countries [67], 65% of the calories ingested by pre-schoolers and children come from ultra-processed foods, and while in low- and middle-income countries the percentage is 13%, the trend is increasing. Ultra-processed foods are made from processed ingredients, lacking fresh ingredients and with industrial additives (flavorings, colorings, etc.) such as biscuits and pastries, packaged *snacks* (bars), sweets, breakfast cereals, sausages, chicken *nuggets*, hamburgers, pizzas, ice creams, drinks other than water, and a long etcetera. They are easy to acquire, are appealing to the palate, and require little cooking. They have a low nutritional profile, and their daily use favors overweight and obesity initially confirmed in adults and also in children [67]. In addition, and in the case of adolescents, the proven association between occasional alcohol intake and the development of subsequent obesity should be investigated at this age.

Physical Activity (PA)

When we express the thermodynamic balance in terms of energy intake and expenditure, the decrease in physical activity as a cause of obesity perhaps unjustly emerges *ex aequo* with overeating. The now classic definition of physical activity by C.I. Caspersen includes any bodily movement caused by the contraction of skeletal muscles that increases energy expenditure above the basal level (resting energy expenditure, thermal effect of food, growth, etc.). Children accumulate PA through play, sport, and movement. The games include running, jumping, throwing, etc., and, as can be seen, they are spontaneous and intermittent both in terms of time and intensity; it is always noticeable that the games decrease as the child gets older and are replaced by more sedentary behaviors. As we will see later on, trying to measure this diverse range of activities is difficult, especially if we try to relate it to a state of health. PA in the school environment is marked by long periods of sitting in class, which limits it to the two recesses, gym classes, and the break after the midday meal. Interestingly, this last period is usually the one in which moderate or vigorous intensity predominates in the group of boys who choose to play. All these periods of recreation should be supervised and never be replaced by complementary sessions that involve physical inactivity (computers, etc.).

Traditional physical education classes do not constitute an important contribution to school PA, firstly because of their duration (generally 2 h a week in many countries) and secondly because the intensity does not usually reach the desirable degrees of moderate-vigorous exercise. The use of accelerometers in these classes will provide more reliable information.

Physical activity outside the school environment is differentiated according to whether it is considered normal days or weekends. In preschoolers and children, physical activity between 5 and 8 p.m. on normal days is still important, but not for adolescents. At weekends, as in other westernized countries, PA often drops drastically, which is closely related to the family lifestyle. The decline in active transportation, i.e., not walking to school, may be a factor that in the last two decades has contributed and will continue to contribute to less physical activity. Safety reasons (traffic, assaults, or even kidnappings), parental work, single-parent families, and longer distances have meant that even in rural areas motorized transport has become more widespread. In order not to overestimate this fact, it should be taken into account that in westernized environments the maximum accepted duration of each trip to school is 20–30 minutes and almost always walking (light intensity). Moreover, there is experience, especially in developing countries, where children who sometimes have to walk long distances to and from school restrict school games.

In summary, physical activity in the pediatric age group is made up of various spontaneous or more regulated games such as sports and activities of daily living that are more for fun than to improve physical fitness. Physical activity is clearly influenced by lifestyle, which we will analyze from a causal point of view and in the chapter on *Prevention*.

Physical exercise is different when it involves a series of structured and repetitive movements that are voluntarily performed with a certain cadence in order to maintain or improve physical fitness. This activity by its very nature is more easily

quantifiable and with greater precision. From the adult perspective, it is important to note that it is easier to increase physical activity than to decrease caloric intake and how inactivity (PA: 0 minutes/week) remains constant in an adult population segment, and presumably this trend also occurs in children and adolescents, whereas moderate PA during 4 years in more than 50,000 nonobese adults was associated with less weight gain [68].

A major problem in relation to PA is the difficulty in measuring it accurately. The method using double-labeled water (deuterium, oxygen 18) allows the total energy expended under normal living conditions to be accurately assessed but is clearly a complex, expensive, and restricted procedure. Other less accurate but reproducible methods include questionnaires, step counters, and accelerometers. Questionnaires reproduce a similar format to food questionnaires, i.e., they try to collect the three parameters (frequency, duration, and intensity) that define the specific physical activities in the last 24 hours, in the last week or in the last month. They suffer from the same defects already known, i.e., the imprecision involved in recall and overestimation (by the child or his family) of the three parameters mentioned when compared with simple observation. In addition to the limiting factor of age—before the age of 10, it is difficult for them to provide reproducible responses—there is also the fact that the PA of children under this age is highly variable. To know with a minimum accuracy, the duration in time or the degree of intensity of a game is almost impossible. In the case of adolescents, questionnaires based on those designed for adults are used. As in many other cases, the encouraging experience with a questionnaire [69] which, unlike others that have a research applicability, has been designed to be carried out during medical consultation is limited, because the time required to answer the 15 questions may be too long, taking into account the other parts of the medical visit.

The most recent proposals of the Movil-Ízate project with a broader vision can be positive. Perhaps, the use of a computer program [70] allows shorter times for obtaining and processing, but in the case of the authors, it can take from 5 to 10 minutes. This difficulty should not be an obstacle for not trying to assess physical activity. In our unit there is a grid that includes four types of activities: physical education, leisure (games), regulated sport, and screen time. All activities are given a rating of “Light, Moderate or Vigorous” (except for the fourth) referring to the last month or 2 months (Fig. 3.1) and according to the type of activity and the fatigue it provokes. Another factor that can undermine physical activity is undoubtedly safety, especially when it is practiced alone and in certain areas [71].

In order to reduce the subjectivity of the questionnaires, researchers introduced the use of step counters, which are small devices that record the number of steps taken by the child for a given unit of time and thus estimate the energy expended. There are data [72] that indicate that normal preadolescents take between 12,000 and 16,000 steps per day. In addition, if the study time is limited to the moments of activity, it can be seen that levels of less than 8000 steps/day [73] could indicate lower than desirable levels. Despite the existing positive correlation, its use has not become widespread, although at the present time the existing applications in mobile phones and watches have allowed its assessment even with recommendations for adults (> 4000 steps/day).

Activity	Weekdays		Weekend days	
	Hours/week	Intensity (L, M, V)	Hours/week	Intensity (L, M, V)
Formal physical education
Games (indicate)				
.....
.....
Sports (indicate)				
.....
.....
.....
TV, Computer, egames	

L: Light; M: Moderate; V: Vigorous

Fig. 3.1 Questionnaire for the assessment of physical activity in children and adolescents in the period indicated

The accelerometer is more accurate, due to its stated advantages (recording of movements on all three planes) and with intervals of inactivity <500 minute counts, light 500–2000, and intense >2001—although these figures vary in the literature [74]. To date, studies on the epidemiology of physical activity are scarce and not easily comparable. The study by Ridloch [75] on more than 5500 preadolescents in the southwest of England, using accelerometers (median 644 counts/minute), for 7 consecutive days concludes that only 5% of boys and 0.4% of girls reached the international recommendations which could be estimated at about 60 minutes/day of moderate-intense PA.

In the United States, a large nationwide study [76] showed that one third of the preadolescent population studied had insufficient physical activity and 11% did practically no activity at all, the easier criteria of light, moderate or intense was used. This study has brought little reversal in obesity trends and is hardly comparable with the data from the United Kingdom cited above. Ten years later and in view of the non-decline in the prevalence of pediatric obesity, [77] several factors were cited, of which the low level of physical activity in children and adolescents was considered particularly important. The “Let’s Move” campaign, promoted by Mrs. Obama, former First Lady of the United States, concludes that much more attention and economic support should be given to populations of color and those affected by poverty, where it has had little impact.

In Spain there is a progressive awareness of the importance of lower PA in the genesis of obesity and how little this has been studied [78]. Some groups (Zaragoza, Alicante) have undertaken epidemiological studies using accelerometers that will certainly provide more reliable data on exercise in our population (Chap. 5, *Clinic*). One fact worth considering that has been obtained from the analysis of the first 120 surveys with the new format on the physical activity of our schoolchildren is that in all of them evaluated physical education classes (generally 2 h/week) as “light.”

In this context, it is worth analyzing what PA tends to be like in obese children. Physical inactivity is something that is usually ascribed to the obese patient but with assessment criteria that are not particularly objective and after cross-sectional studies among obese versus normal-weight children. In the last decade Trost [79] has established a basis for objective measurements of physical activity, especially the duration of such monitoring; in a later work [80], he concludes that the best location for the accelerometer is the hip that the number of days to obtain valid information in children and adolescents is 4 to 9 days (compared to 3–5 in adults) and that the expression in units of counts per minute in the case of children may underestimate the activity. Using these more uniform procedures and with different samples from preschoolers, school-children, and adolescents [81, 82], we see how in preschoolers the variability is so great that with normal age-appropriate activities, it would be difficult to draw any reproducible conclusions. In older children and irrespective of gender, obese children produce a significantly lower number of counts per minute than their nonobese peers over the 12 hours that they tend to wear the accelerometer. Other data of interest show how peaks of activity coincide with periods of physical activity and recess and how obese girls follow the same pattern as lean girls in the sense that they tend to have about 20% less physical activity than boys and how at weekends PA is lower in obese than in lean boys when measured by this procedure (see own data in the chapter on *Prevention*).

Clearly the energy expenditure component is measurable as far as physical activity is concerned, and when this decreases it can be a maintaining mechanism of established obesity and is undoubtedly a predisposing factor. It has a high value in epidemiological studies of overweight and obesity and a low value when applied to individual cases. In the literature, the benefits of physical activity are listed as improved self-esteem, physical fitness, bone mineral content, cardiovascular health, and prevention of overweight. Perhaps a general preventive and socially oriented action should be considered by health authorities in relation to physical activity.

In some countries the concern about less physical activity is evident and demonstrated by the disappointing results of the study of more than 10,000 adolescents and young adults over a period of more than 10 years [83]: 45% of black girls present no physical activity at all, and among the rest of the population who do, on the whole the PA is not satisfactory. If adherence to lower-calorie foods is difficult and short-lived, physical activity follows suit.

The problems of sedentary lifestyles and physical inactivity are dealt with in the chapter on *Prevention*, but we should now mention the GUSTO study [84] in Singapore where the prospective evaluation from birth to 6 years of age showed that at 5.5 years of age, the viewing of 3 hours or more a day of screens, basically TV, was associated with a significant reduction in physical activity compared to those who watched less than 1 hour. At this age a high dose of electronic media is associated with worse psychosocial well-being.

Obesity from Genetic and Medical Causes

At the present time, it should be clear that environmental circumstances and to a lesser extent genes have an important impact on the development of obesity. However, the contribution of genes in a general and familial obesogenic environment remains largely unknown, although, as pointed out in Smith's classic book of the 1970s, there have always been clinical indications. More pediatric in nature, Garn [85] and Poskitt [86] are the ones on both sides of the Atlantic who demonstrated how parental obesity increases the risk of obesity in their offspring. The next important study is that of Stunkard [87] who, taking advantage of the traceability of adoptions in a small country (Denmark), concluded that children have BMIs closer to their biological parents than to their adoptive parents. Studies with monozygotic twins have always been along the same lines, and precisely, once the measurement of energy expenditure at rest or during exercise became more accurate and more applicable, we have seen how the different responses to positive energy balances can be justified by the genetic difference in the case of resting thermogenesis [88].

In the last decade, there have been numerous studies in monozygotic twins in relation to concordance of weight gain, variations in the resistin gene, and even response to treatment including bariatric surgery. However, it is the large-scale genome-wide studies that have brought the field of genetics closer to the field of obesity, although more extensive studies including pediatric ages are required [89]. Farooqi [90] opened a new field when he identified monogenic alterations as a cause of severe obesity and early onset, as we will see when studying the mutations affecting leptin.

Regarding the extent to which the genetic factors explain the variation in body mass index (BMI), the data have been variable. In an initial review of syndromic obesity [91] based on family studies (relatives and parents and children), the conclusion is that the maximum heritability of the obese genotype (BMI) varies, according to the various studies, between 30 and 50% or even 20 and 80%. This is possibly due to changes in energy intake and energy expenditure or use. These wide range values with the new Oaxaca-Blinder [92] techniques would not only have decreased, but the higher BMI values taken in the present study as characteristic of an ethnic group were in fact due to the socioeconomic level of the families.

The most recent *genome-wide association studies* (GWAs) have identified more than 500 *loci* (genes or markers) associated with clinical findings of obesity (mainly BMI and abdominal circumference) and especially in populations of European origin [93]. Obesity-related *loci* generally involve pathways acting in the brain, while those associated with fat distribution are related to the adipocyte. Locating the exact causative gene within each *locus* has not been a simple problem, but association studies (GWAs) are allowing advances not only in pathogenic knowledge but also in therapeutic knowledge.

In this development, the appearance of biobanks has been a milestone because the availability of a substantial amount of data from large cohorts allows the study of complex diseases such as obesity [94]. In all probability, the section of monogenic obesity will be reconsidered on etiological grounds due to the identification of the melanocortin-4 receptor variants with a significant association with common (polygenic) obesity. [95]

Monogenic Obesities

Recent developments in molecular genetics have made it possible to define some cases of obesity due to alterations in a single gene. These are generally rare cases with severe and early-onset obesity that are usually associated with mental deficiencies and other developmental abnormalities, the most important of which are highlighted in their first descriptions. This imply a growing open list with the new severe obese patient with the DNA alteration eg the recent description of heterozygous at the ASIP (agouti signaling protein) gene. These new description entail a better knowledge derived from the treatment of the patient. Some of the representative examples merit these comments now.

Congenital leptin deficiency [95, 96] which in its homozygous form includes hyperphagia, obesity, hypogonadism, and alteration of the immune response mediated by T lymphocytes has an excellent therapeutic response through leptin replacement. This group also includes mutations of the leptin receptor gene (LEPR) which presents with a similar picture to the previous one but with elevated leptin levels (symptomatic in themselves of receptor alteration) and which may represent 3% of early obesity with hyperphagia.

As for obesities related to gene defects in the melanocortin pathway [97], pro-opiomelanocortin (POMC) is a peptide that is expressed in the brain but also in multiple sites, as the precursor of several hormones including ACTH and *melanocyte-stimulating hormone* or MSH. The latter is produced by a fragmentation induced by PC-1, *prohormone convertase*, and there are known cases of early obesity due to a mutation of this gene. In normal conditions when it binds to its receptor MC4R, MSH leads to a decrease in food intake (and reddish hair pigmentation).

Thus, the described gene alterations which affect these protein steps of a more complex system are accompanied by obesity in both mouse and man [98] and other developmental abnormalities. There are 24 known mutations of the MSH receptor, MC4R, and they constitute the best-known forms of monogenic obesity [99]. These initially described in mice result in increased food intake, obesity, and hyperinsulinemia [100]. In humans, obesity is very early (1–5 years of life) and at the expense of an increase in body fat mass but also in lean body mass, and the degree of obesity is higher in homozygotes. Fortunately for these patients, today there is an effective treatment through the use of setmelanotide as a potent agonist of MC4R [101]. A new update led by Dr. Farooqi [102] suggests a greater clinical variability than in previous descriptions.

One of the mutations affecting the *simple-mind homolog 1* (SIM 1) has been investigated in a girl with a balanced translocation who presented with early-onset obesity. SIM 1 is expressed in the paraventricular nucleus and contributes to the regulation of food intake [103]. Another monogenic [104] obesity-causing defect results from decreased expression of *brain-derived neurotrophic factor* (BDNF) and its associated receptor (*tyrosine kinase receptor*, TRKB/NTRK2) that can subsequently affect MC4R function leading to severe obesity in humans [105]. This list has only just begun, and since some alterations occur spontaneously in murine obesity (mice: ob/ob, db/db fat, tubby mice), these mutations have allowed us to find their human counterparts (Lep, Lepr, Pomc, Mc4r) responsible for obesity as we have just seen. In addition, mutations [106] of genes related to the leptin/melanocortin pathway become logical candidates in those clinical cases that coincide with the picture of monogenic obesity (Mendelian inheritance, early onset, significant obesity, etc.), and yet obesity is still not explained. The increased susceptibility to food exposed in stores is related to certain genes (DRD 2/ANKK 1) which are mediators of adaptive behavior.

Mutations of the *peroxisome-proliferator-activated receptor-2* (PPAR-2) require special mention. This receptor and its isoforms are found in the preadipocyte and bind to natural ligands including fatty acids and cross the nuclear membrane, which would establish a link between the composition of ingested food and the formation of mature adipocytes. However, a mutation of the gene encoding this receptor has been described which leads to its overexpression, resulting in rare cases of obesity [107] due to excessive transformation of preadipocytes.

Genetic Variations

Epigenetics is defined as the study of changes in organisms caused mainly by DNA methylation that results in heritable modifications of gene expression (activation/inactivation) without alteration of the coding base sequence as a consequence of environmental changes. Epigenetic studies began almost a century ago, but it has been through the genetic variations recognized more recently after genome studies that their role has been described, as will be seen below when discussing them in the *FTO* gene as a model and their impact on fat deposition, which added some light to this problem. The case of high BMI at early gestation and its impact on offspring is different: association studies and extended epigenome studies (EWAS) have not only shown in which dinucleotide [CpG, cytosine-phosphate-guanine] methylation occurs but also its association with certain clinical features of obesity. However, as mentioned in the *Epidemiology* chapter, the worldwide epidemic growth of obesity in recent years is not due to genetic changes but rather to environmental changes that interact. A recent study has already identified more than 600 CpG (cytosine-phosphate-guanine) methylation sites associated, and 553 confirmed with BMI and poor cardiometabolic health in several cohorts, in another one the DNA methylation of seven clock genes appeared in obese adolescents. In obese pre-pregnant and

pregnant women, placental DNA methylation occurred at 27 CpG sites. Cord blood DNA methylation is associated with rapid growth in infancy which is a risk factor for further obesity. These few examples show that we are before a preventive situation hardly imaginable in the near past.

The concept of genetic variations relies on a change in the order of nucleotide bases, which can occur in coding and especially in noncoding regions of the gene, which are maintained in a population and are progressively described by *genome-wide association studies* (GWAS). They explain why individuals of a species have similar characteristics but are very rarely identical. Single nucleotide polymorphisms (SNPs) are the most common type of genetic variants, as shown by the study of the *FTO* gene and its relationship to adipogenesis. To date and following massive genome-wide studies, more than 700 genetic variants have been identified in cross-sectional studies that are significantly associated with BMI, abdominal circumference, and obesity comorbidities in diverse populations. This is through the neural regulatory mechanisms of feeding, insulin secretion, energy metabolism, adipogenesis, etc., although for many genetic variants the biological mechanism by which they regulate body weight remains unknown. The study of 335,046 participants from the UK Biobank [94] provides two genetic risk scores (GRS) based on 91 and 69 SNPs, respectively, that allow us to see the greater sensitivity of these genetically susceptible individuals to obesogenic environmental factors, for example, the proximity of fast-food facilities. Another recent finding in the field of epigenetics [108] is the transgenerational inheritance of methylations produced at a time of external aggressions, for example, a diet rich in fats.

It is worth noting that in general the contribution of all variants associated with a given trait is not uniform. With respect to weight and abdominal circumference, they contribute approximately 5% of the variation, with those of the *FTO* gene accounting for 0.34%, which is one of the largest effects [109]. It should also be noted that compared to the aforementioned 5%, significant SNPs are responsible for 25% of the variability in height. A list of SNPs significantly associated with human diseases is being developed. The parallel development of mathematical calculations (Mendelian randomization, SMR) involved in GWAS helps these large cross-sectional studies provide an increasingly accurate and growing basis of inheritance. The *next-generation sequencing* (NGS) method, with single-base precision, integrates genomic analysis with biological and medical data by means of statistical analysis, which is an increasingly applied advance in research. Thus, for example, correlating them with more precise abdominal or liver fat distributions by MRI or MRI spectroscopy provides stronger links between these genetic variations and this fat distribution pattern [110].

The study of the *FTO* gene (Fig. 3.2) has been a milestone for the subsequent study of genetic variations, and although its function and pathway of action are still partly unknown, its association with overweight has been identified and is in some way illustrative of the development that this field of obesity has undergone. It was initially cloned [111] after identifying a mutation in mice that was responsible for a fusion of the fingers of the forelimbs (Ft, *fused toes*). This mutation was the consequence of a deletion of 1.6 Mb (Mb or megabase, a unit of length for a DNA fragment) which implies in this case the loss of six genes located in this region of chromosome 8 of mice. The mice heterozygous for the Ft mutation presented partial

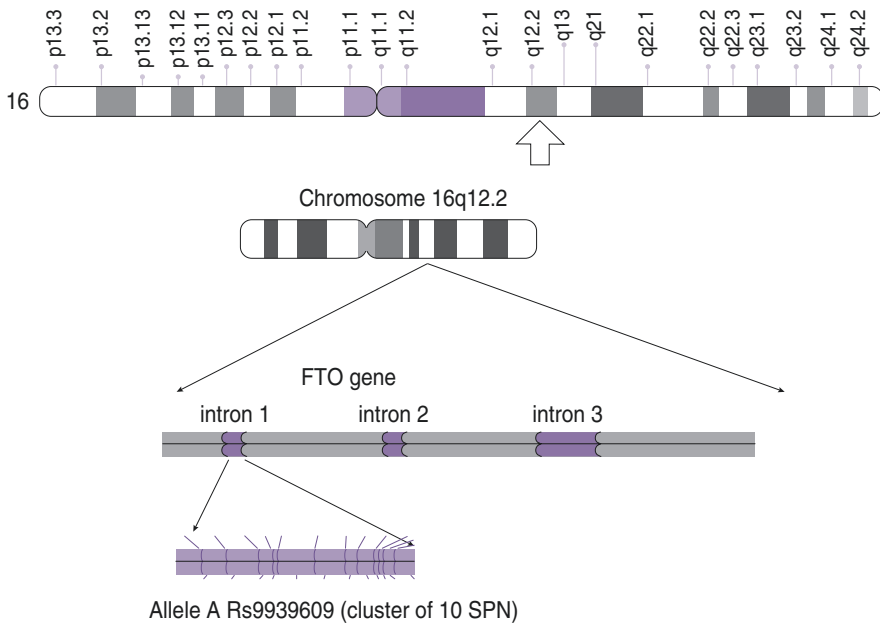


Fig. 3.2 *FTO* gene structure and polymorphisms

syndactyly in the forelimbs and massive hyperplasia of the thymus. The homozygous *Ft/Ft* embryos died in mid-gestation with significant craniofacial malformations and left-right asymmetry. This gene is conserved in mammals and the human homologue has been identified. Heterozygous and surviving mice have never presented overweight or increased adiposity.

The recent important finding came as a result of a cooperative study based at the *Peninsula Medical School* in Exeter, UK [112]. Analyzing a population of type 2 diabetics (T2D) for genes that might be associated with diabetes, they identified a common variation in the *FTO* gene, which clearly predisposed to diabetes but through an effect on body mass index (BMI). Comparing that T2D population with a large control group on the existence of genetic variations also called *single nucleotide polymorphisms* (SNPs), they found that SNPs appearing in the *FTO* gene (Fig. 3.2) located in man on chromosome 16 at *locus* 16q12.2 (long arms, region, band) were strongly associated with diabetes. Especially SNPs rs 9,939,609, which was actually at the time of its description a cluster of ten polymorphisms located in the first intron of the *FTO* gene.

The study was conducted in more than 38,500 participants and found that 16% of adults homozygous for this risk allele were 3 kg heavier (heterozygotes 1.2 kg heavier) and at an elevated risk of obesity when compared to those lacking the allele (control population). In the studies [113] on pediatric subjects (more than 11,500 children of British and Finnish origin) and of which anthropometric measurements are available from birth to puberty, it has been found that birthweight or weight index is not associated with the risk allele rs 9,939,609, but that this does imply that each copy of it means for the child over the age of 7 an increase in BMI of 0.2 kg/m² (≈ 0.12 *z-scores*). The association of increased weight with the cluster of SNPs

located in the intron of the *FTO* gene has been confirmed in an intercontinental study [114]. This is a finding that, unlike the defects responsible for the so-called monogenic obesities that account for 2–7% of all pediatric obesities, can justify the predisposition or tendency to overweight and obesity due to its high presence [89].

After a decade of linking the *FTO* gene to overweight and obesity, it can be said that BMI does indeed have a strong and wider genetic component (40–80% heritability) and that it relies on several genes that are expressed in the hypothalamus with appetite regulatory functions and that genome-wide studies have clarified some points of interaction. The strongest association of obesity is with variants found in introns 1 and 2 of the *FTO* gene [112–114]. In this region, 89 variants are known in a population of European origin, but the fact that there are more than 47,000 nucleotides makes it difficult to identify them precisely because there is no protein alteration. In addition, the identification of the mechanisms through which the association with high BMI is established was not known. However, in the publication of Claussnitzer [115] and after the application of gene editing techniques (CRISPR-Cas9), the point of connection has begun to emerge. More specific studies on pediatric patients [113] have shown the association of a SNP (rs 9,939,609) of the first intron with a higher dietary intake and also in proportion to its dose (homo- or heterozygosis).

On the other hand, the *FTO* allele associated with obesity represses mitochondrial thermogenesis in the preadipocytes of the tissues in an autonomous manner, and therefore there is less heat dissipation by the adipocytes of the beige fatty tissue (which express UCP1 characteristic of brown adipocytes). In addition, there is a second action, which is none other than the increased lipid deposition in the white adipose tissue (see Chap. 4, *Pathogenesis*).

All these studies seek the association of the different SNPs with a certain phenotype, and for this they have used statistical methods, but to date a large proportion of heritability cannot be linked to the *loci* identified. However, new multiple regression biostatistical techniques, such as LAMP [116], allow significant associations of a group of SNPs with certain diseases or clinical traits. This phase has gone beyond the theoretical stage and the *GIANT Consortium* study [117] has identified 716 SNPs associated with BMI in 700,000 individuals, mostly of European descent, and the number associated with height has been much higher. Importantly, this study also shows how more than 50% of the BMI-associated SNPs were located in other previously unknown *loci* and are responsible for 5% of the variation in BMI. The application of Mendelian randomization to extremely large samples of GWAs increases the predictive accuracy of a trait or disease. Equally demonstrative is the study on the genetic architecture of thinness, which shows similar variants to those of overweight and obesity but opposite results [118] and would be worth exploring.

What has (epi)genetics contributed so far? The massive studies of the extended genome have allowed the so-called genetic association studies that are nothing more than examining whether certain genetic variants, in practice SNPs, appear with greater frequency in subjects with some trait or disease. At a given time, more than 10,000 gene variants that comply with this association have been established, but this number will only increase, allowing us to detect weak genetic effects which are therefore different from monogenic disorders. Ninety percent of these variants are

located in noncoding genomic regions and consequently do not directly affect protein synthesis or translation [109]. However, these *loci* containing noncoding variants can alter gene expression by modulating the activity of neighboring cis-regulatory elements which are noncoding DNA sequences within or in close proximity to the gene itself. On this basis it has been possible to see the interaction between the environment and the genome, which is capable of increasing the risk of obesity. This occurs through chemical alterations, such as the aforementioned DNA methylation at the cytosine level, which is the best-known mechanism of activation or inactivation of a gene at the cellular or tissue level. These epigenetic modifications of DNA that occur in response to nutrition and physical exercise can alter gene expression in a stable and heritable way, influencing metabolism, behavior, and state of health [107, 118, 119].

Recent epigenome-wide association studies have shown how physical activity [120] or high-fat diets [121] altered methylation in areas relevant to energy homeostasis where not only the *FTO* gene was expressed but also *GRB14* and *TUB*, which are involved in weight gain or loss and abdominal adipogenesis. Epigenetic mechanisms also affect the response of individuals to gain or lose weight and even the response after bariatric surgery. Epigenetic variants may appear after both maternal and paternal dietary manipulation in addition to those already known from intra-uterine growth restriction or maternal obesity [122]; these aspects will be discussed below in the so-called risk factors.

All these findings indicate that despite the relative infancy of epigenetics applied to clinical practice in general and in particular to the management of obesity and comorbidities, it is already giving results with *odds ratios* (OR) values above 0.837 for type 2 diabetes or hypertension [123]. However, once again the studies are complex and require a very detailed design to be credible. At present, other similar alterations in other genes have also been found to be associated with obesity.

Syndromic Obesity

This heading classically included all those cases that could not be classified as obesity due to positive energy balance, which is what happens in healthy children apart from their obesity and before they develop comorbidities. Syndromic obesity (or secondary to the syndrome) represents a minimal proportion (< 5%) of the total cases of pediatric obesity and is probably decreasing due to biostatistical studies together with those of GWAs. Thus, pleiotropism at a single *locus* has been shown to be associated with a variety of phenotypes and to be distinct from the so-called cross-phenotype associations that may have other than genetic origins [124].

This criterion (primary-secondary) has had great clinical acceptance, and, although today we know that it is excessively simplistic, it is of interest for the clinician to go deeper into the causal study (genetic, endocrine, CNS, and iatrogenic) of the patient. Table 3.1 shows some groups of obesity associated with various syndromes. In these groups, obesity is not the main finding within the more complex clinical picture of the given syndrome. In recent clinical chapters, the most

Table 3.1 Main syndromic obesity groups according to their origin

<i>Endocrine</i>
Hypothyroidism
Cushing disease (spontaneous, iatrogenic)
Hypothalamic lesion (meningitis, craniopharyngioma)
Certain GH deficiencies
Stein-Leventhal syndrome
<i>Chromosomal</i>
Prader-Willi syndrome
Down syndrome
X-fragile
<i>Genetic</i>
Alström syndrome
Bardet-Biedl syndrome
Biedmon syndrome
Carpenter syndrome
Cohen syndrome
Cohen syndrome
Killian/Teschler-Nicola syndrome
<i>Monogenic</i>
(Already seen)
<i>Diverse</i>
Leukemia survival
Psychological factors (dietary patterns, anxiety)

important syndromes of pediatric profile have been described (Prader-Willi, Bardet-Biedl, etc.), but in general we should think of syndromic obesity when it develops or is associated with cephalic, facial, or ocular malformations, with skeletal malformations (polydactyly, syndactyly, kyphosis, with skeletal dysfunctions, etc.), with dysfunctions of the nervous system (deafness, mental retardation, hypotonia), with endocrine dysfunctions (hypogonadism, pubertal disorders), and with renal malformations and all this in the context of an obesity that is very difficult to treat. For syndromic orientation it is useful to consult classic repertoires on human malformations [125] or hereditary diseases [126, 127]. In any case, and in view of the growing information on gene modifications, we must take into account the fact that they can modify the identity of some syndromes that are clinically very close, as is the case of Biemond syndrome II (21035 McKusick Catalog: coloboma, mental retardation, obesity, hypogenitalism, and polydactyly) or Alström syndrome (without mental retardation), which are very similar to Bardet-Biedl syndrome. Something similar occurs between Cohen syndrome and Prader-Willi syndrome. In Carpenter syndrome (acrocephalopolysyndactyly), the onset of obesity is late (Fig. 3.3) and of secondary interest to the large malformations and mental retardation [128]. This former purely clinical description should now be considered monogenic since we know that acrocephalopolysyndactyly type 1 is almost always due to a mutation of the *RAB23* gene located on chromosome 6. Some chromosomopathies, such as



Fig. 3.3 Carpenter syndrome (acrocephalopolysyndactyly)

autosomal trisomies (Down syndrome) or gonosomopathies (XXY, XO), occasionally present with obesity, and therefore karyotyping is often useful in suggestive cases. In general, the concept of syndromic obesity is narrowing as new biochemical and sequencing applications expand.

Risk Factors

In one of the first systematic reviews, [129] seven risk factors were already identified although some of them were included in the genetic and physiological categories. Today the number has increased, and they are better defined through epigenetic studies, especially in those cases related to the theoretical programming during fetal life [130]. From the clinical point of view and as risk factors, we must add birth weight (> 4.0 kg) and rapid growth during the first 6 months of life that is so well

regarded not only by parents but also by certain members of the health-care system, as is the case with the over-average height of the child that is also associated with later obesity [131] even though its association is scarce with the precocity of adipose rebound (BMI) or with pubertal advancement. New risk factors associated with obesity include large-for-gestational-age neonates whenever the mother is overweight, obese or has diabetes mellitus [132] and post-term neonates (> 43 weeks gestation) and large for gestational age [133, 134]. The present interest in such conditions is the possibility of early preventive options, where the social adversity is clearly related [134]. Sleep deprivation (< 10.7 hours/day at 2–6 years of age) is a clear risk factor [135] and renders difficult relationships with peers according to a study of 50,000 schoolchildren aged 6–17 years, which concluded that one third have inadequate sleep [136, 137]. Continuity in adults has also been confirmed especially in LMIC and is also associated with poorer trends in BMI. In the newborn, the establishment and duration of breastfeeding has a protective action, either through the prolonging effect over the introduction of complementary foods (*baby-led weaning*) or acting directly on the infant itself, [138] or through the deliberate longer duration of breastfeeding, even if the protective association with obesity is modified by the socioeconomic conditions of the families [139]. Furthermore, although early introduction of solid foods to infants under 6 months of age does not seem to have a clear effect on pediatric obesity [140], this does not mean that exclusive breastfeeding should not be encouraged during this period. Perhaps socioeconomic factors, rather than the genetic factors more evident when shared by twins, are more important in the well-confirmed development of adult obesity. The importance of socioeconomic status has also been confirmed in the pediatric age group: in a multiple regression study, severe obesity (BMI_r >140%) is strongly and independently associated with educational level (OR: 2.4), with ethnic ancestry and with lower family income [141]. These same trends have been found in Europe [142, 143] and in other high-income parts of the world. In the opposite side eating disorders or famine exposure are also risk factors [144]. Within this social context, two points are worth considering, one being the “contagion” of obesity when the child lives in a community where overweight/obesity predominates, which leads them to normalize excess weight [145]; the other being the support for certain sports and the resulting extra intake of energy and/or sugary drinks [146].

Another less known but possibly important aspect is the speed of meal intake, or the number of meals. The so-called French model of eating (three meals a day, at set times, seated at the table, with other people and considering food as a pleasurable act) has a moderate association with a normal BMI in adults [147]. Along the same lines, in two studies carried out in Japan in adults [148, 149] and with self-rating by the participating subjects as (very) fast, normal, or slow eaters, the slow rhythm of eating is associated (OR: 5.22) with normal weight. A chewing movement counter is currently available and perhaps this small device will allow validation of a possible intervention in this regard [150].

There is a possible association with commonly prescribed medications; in the NHANES study [151] in adults, specific medications (antidiabetic, beta-blockers) have an obesogenic component which must be monitored. In pediatrics, the use of

inhaled corticoid in small children is associated with BMI increase at the age of 6 [152]. Antibiotic exposure during the first 6 months of life has also been described [153]. Subsequently, this association has been seen in the use of antibiotics during gestation and the first 2 years of life. The extensive studies conducted in New Zealand prompted an editorial in JAMA Network [154] which concludes that the association exists and although it is modest requires new observational studies. Similar conclusions are reached by a systematic review [155] which also highlights the weaknesses so frequent in the reviewed studies.

The next group of risk factors is related to preconception and gestational maternal obesity. A study in China [156] of 100,000 mother-infant pairs showed that preconception weight has a strong association (logistic regression methods) with weight gain in the first 6 months of life and the impact of this increased rate of weight gain on future obesity is well-known (see Chap. 7 BMI Trajectories). Less extensive studies show how preconceptional excess weight is associated with lower values in cognitive tests at 7 years of age, especially in males [157], with a greater progression of non-alcoholic fatty liver disease (NAFLD) towards fibrosis in obese children, and is also related to three genes [158]. Obesity during gestation in 2.2 million women [159] is associated with cardiovascular disease occurring between 1 and 25 years of age, and in this cardiovascular area, high preconceptional weight is associated with higher birth weight and with alterations of the retinal microvasculature, as an early sign of elevated blood pressure at 4–5 years of life [160]. These data determine the importance of adequate nutrition in the prenatal period and the “first 1000 days” [161]. Interestingly, current famines suffered by the pregnant woman studied through the China Kadoorie Biobank [162] have shown an association with higher BMIs later in life, especially in women. If we also take into account that the obesity of the father [163], independently of the mother, is associated with higher birth weight and subsequent BMIs and also associated with specific methylations, it is not unreasonable to think that in the short term, these risk factors should not be considered as such but as epigenetic alterations and therefore provide new horizons of knowledge and treatment.

Finally, and with a more nutritional profile, the correct administration of vitamin D during the first 3 years of life is associated with a predominance of later lean mass [164], although winter supplementation of vitamin D has no beneficial cardiometabolic effect in adolescents [165].

The risk factors in pediatric obesity represent an ever more important and better-known chapter. Some are so extensive that they should be confirmed through future study. Such is the case of the influence of xenobiotics, the parents’ smoking habit, the use of artificial sweeteners during gestation, or low spexin levels. Of particular interest is the study of high levels of bisphenol A (and also of the F and S) in the urine of adolescents and their association with obesity [166]. In relation to nutrition, it does not cease to surprise experts how such a widely known problem as the non-maintenance of breastfeeding during the first 6 months persists and even continues to increase in specific areas [167]. Nor can we ignore food insecurity [168, 169] which is also present in vulnerable parts of westernized countries, war zones, and areas facing epidemiological or other types of adversity. On the question of

inadequate sleep, the idea that this was a problem of high-income countries has been undermined by the evidence that it also affects the adult population in medium- and low-income countries [170], while its obesogenic repercussions in pediatrics remain unknown. Similarly, in the same social profile appear children of new families with previous children [171] also known as blended families and almost certainly many more [102]. While in some cases it will be easier to elucidate, in others it will be much more difficult because of the extensiveness of the trend. Within this section, we could also include the prospective, long-term study of preterm infants in connection with the development of obesity and/or cardiometabolic risk [134]. However, the most fertile ground for the study of obesity risk factors is the purely clinical field, with the appearance and application of new medications [151, 152] and clinical research itself especially into comorbidities [20, 46, 47] or monogenic obesity, which is now perhaps not as monogenic as the classic descriptions suggested [172], and the specific application of Mendelian randomization [173].

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Chapter 4

Pathogenesis



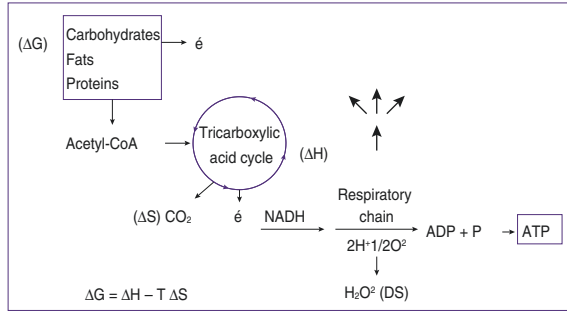
The reserve energy content of the organism and its parallel amount of fat storage has two main regulatory factors. The first is related to the environmental increases in the energy balance that we have just seen in the chapter on *etiology*. The second refers to the endogenous mechanisms of weight control, which are addressed in this chapter.

Bioenergy Balance and Its Measurement

Physiological Basis

The laws of thermodynamics are of adequate application to living beings to the extent that they obtain energy from sunlight (autotrophic organisms) or from organic nutrients (heterotrophic organisms). The complexity of energy management in humans does not detract from the precision of these principles [1]. The first law of conservation of energy states: “Energy can neither be created nor destroyed; energy can only be transferred or changed from one form to another “. The second law states: “The entropy of any isolated system always increases.” This leads us to define entropy as “A thermodynamic quantity representing the unavailability of a system’s thermal energy for conversion into mechanical work, often interpreted as the degree of disorder or randomness in the system.” Thus we can say that the free energy is equal to the energy consumed by the metabolic process, also known as enthalpy, plus the heat dissipated, plus the entropy in this case represented by low energy products (CO₂, NH₂, etc.) and which are barely reusable by humans.

In the cell, obtaining energy from the immediate principles is a complex process that schematically takes place in three phases (Fig. 4.1). In a physiological situation and in the first phase, the energetic nutrients (carbohydrates, fats, proteins) and in the cytoplasm their oxidative catabolic pathways lead to fragments of two carbon



Variations of:
 ΔG : free energy; ΔH : enthalpy; ΔS : entropy; T : absolute temperature

Fig. 4.1 Obtaining energy from nutrients. There are three phases: the first involves the oxidation of glucose, fatty acids, and proteins to acetyl-CoA; the second involves the oxidation of acetyl groups in the Krebs cycle with electron generation; and the third phase involves the mitochondrial transport of these electrons to the respiratory chain and production of ATP. ΔG , free energy; ΔH , enthalpy; ΔS , absolute temperature

atoms, and this acetyl radical binds to coenzyme A giving rise to a common product such as acetyl-coenzyme A (acetyl-CoA). This in the second phase enters the cycle of tricarboxylic acids or Krebs, which is the great transformer of the energy provided by nutrients and where these acetyl groups are enzymatically oxidized to CO_2 ; the energy released is retained in the cofactors nicotinamide dinucleotide phosphate (NADH) and nicotinamide dinucleotide phosphate NADPH₂, both in its reduced form or electron donation. Then, in the third phase, the intervention of the well-preserved respiratory chain or electron transport chain (ETC) and oxidative phosphorylation is required.

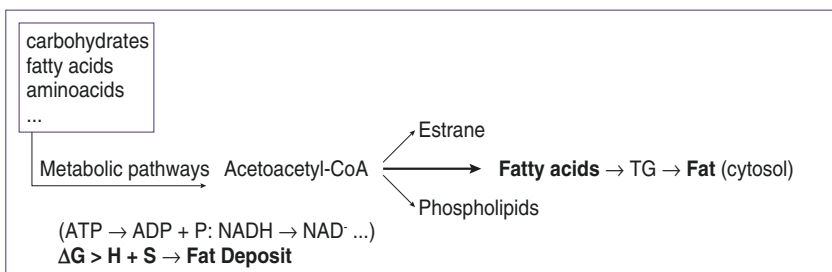
More precisely, this transport chain, which has already started in the Krebs cycle phase, is composed of coenzyme Q, the cytochrome C, and the complexes I to IV also found in the mitochondrion. Both systems, the tricarboxylic acid cycle and the electron transport chain (ETC), generate an electrochemical proton gradient (H^+) which finally allows the cell to produce ATP. We need a more detailed approach to the series of chemical reactions that transfer electrons from a donor (e.g., NADH) to an acceptor (e.g., O_2). In the Krebs cycle in addition to the well-known production of CO_2 , another fundamental process starts in the succinate step: the production of reduced nicotinamide dinucleotide (NADH) from nicotinamide dinucleotide (NAD) and from flavin adenine dinucleotide (FAD) in the case of FADH, which are two of the electron transporters of the Krebs cycle in the so-called respiratory chain which also includes the important nicotinamide dinucleotide phosphate (NADP) and which is present in most cells in both its oxidized and reduced form (NADPH). These are cofactors for the many enzymes that catalyze the oxidation of hundreds of different substances according to the generic reaction of $NAD^+ + 2 e^- + 2H^+ \rightarrow NADH + H^+$; the two electrons and the proton would come from the substrate to be oxidized. The consequence are the well-known biological oxidation reactions: $R-CH_3 \rightarrow R-CH_2-OH \rightarrow R-CHO \rightarrow R-COOH \rightarrow r + CO_2$, which in general are

dehydrogenations in which one or two hydrogen atoms (proton + electron) are transferred from the substrate to an acceptor (O_2) with the production of water.

As indicated, the function of this chain contributes to the formation of adenosine triphosphate (ATP) which is the main source of energy for most of the functions carried out by cells (ATP [gamma, beta, alpha] ADP [beta, alpha] + 7.3 Kcal/mol) and its regeneration through the transport of hydrogen (H^+) to the mitochondria through its membrane according to the well-known reaction $ADP + P_i + H^+ \rightarrow ATP$. This process of energy generation appears in the zoological scale [2] which, for example, allows the *Drosophila* to fly.

These kinds of basic reactions in the whole metabolism play a significant role in the production of energy. If, for example, we consider the oxidation of glucose to CO_2 in its various steps, the energy from the oxidation is conserved in the form of ATP (by passing the electrons to O_2), and the same happens in the metabolic pathway of fatty acid oxidation. This leads to the generation of energy in the form of ATP which will be used after its hydrolysis to ADP for the synthesis of macromolecules, counter-gradient transport, muscle contraction, etc. All this is regulated according to the aforementioned principles of thermodynamics and that, in this case, the entropy component is represented by heat, CO_2 , and water produced in the respiratory chain and perhaps also by NH_2 radicals prior to the entry of amino acids into the Krebs cycle. We will see the management of energy input by brown and beige adipose tissue in the section below.

When there is an imbalance between the free intake (ΔG) provided by nutrients and the energy expended, and given that entropy, which is measurable, accounts for a proportionate but quantitatively less significant share of the ΔG , then this excess energy contained in sugars, fatty acids, and amino acids is transformed by the living being, in this case man through anabolic (and therefore ATP-consuming) sequences giving rise to another common product (Fig. 4.2) such as aceto-acetyl-CoA, which in the case of positive energy balance leads to the formation of fatty acids and the synthesis of triglycerides in the cytosol of the adipocyte. This leads to the substrate of obesity, which is none other than excess fat in the body. Following the equation, the energy ingested allows all known forms of work, external and internal including



ΔG : free energy; H : enthalpy; S : entropy

Fig. 4.2 Imbalance between nutritional energy supplied and energy used. Anabolic reactions lead primarily to cytoplasmic fat synthesis. ΔG , free energy; H , enthalpy; S , entropy

that of tissue synthesis, but the energy not consumed [3] in the adipose tissue (support of the stored energy) will lead to its growth. This concept of oxidation of the immediate principles of C, H, O, and N led at the beginning of the last century to the evaluation of the basal metabolism in strict conditions of rest, the Harris-Benedict equations also dating from that time.

Later, under less strict but more realistic conditions, simpler measurements were taken, such as the so-called resting energy expenditure (REE), which is nothing more than the minimum energy needs to maintain life. Note how the term “basal” has been disappearing because of its elusiveness. Attempts to measure the energy expended by direct calorimetry have failed because of the difficulty of measuring the heat released by the body. Direct calorimetry can be estimated today by using doubly labeled water (preferably with stable isotopes), but because of its complexity, it is relegated to laboratory studies far from clinical practice. It should be noted here how the technique of doubly labeled water ($^2\text{H}_2\text{O}$ ^{18}O) makes it possible to assess the total energy expended (TEE, *total energy expenditure*) in a free environment and over prolonged periods of time and under normal living conditions (schooling, games, etc.).

Calorimetry

Indirect calorimetry is the ideal method for assessing resting energy expenditure and is the method most commonly used in applied research. It is based on the fact that 208.06 ml of oxygen is required to oxidize 1 kilocalorie. Because of this direct relationship between caloric burn and oxygen consumed, the measurement of oxygen consumed (VO_2) is virtually interchangeable with energy expenditure. Recent technological advances make it possible to measure the rate of oxygen consumed and the rate of carbon dioxide production (VCO_2) as well as the respiratory quotient (VCO_2/VO_2) which would indicate whether the source of energy consumed during the test is at the expense of carbohydrate or fat. In addition, samples obtained by chromatography and mass spectrometry allow the measurement of other volatile compounds that are distinct in obese children and adolescents and possibly indicative of liver damage [4]. Oxygen consumption requires very precise measurements of both the volume of exhaled air and the concentration of oxygen in it. This would allow us to know the energy expenditure of the body at rest (basal) which normally accounts for 70%, with a distribution of expenditure of approximately 27% in the liver, 19% in the brain, 18% in the skeletal muscle, 10% in the kidney, 7% in the heart, etc. Another different situation is to measure the energy consumed when physical exercise is performed [4]. Initially it was thought that the resting energy expenditure of obese children was different from that of nonobese children, but when fat-free mass is used as a reference instead of body weight, then the resting energy expenditure in obese and nonobese adults and even in obese people who are no longer obese shows no differences [5]. The same is true when the procedure is applied to pediatric populations of obese or of different races, such as Caucasians

and Pima or Mohawk Indians [6]. But the reality is that there is significant variability in this resting energy expenditure, which at present makes it difficult to predict accurately basal requirements in relation to age and gender.

The availability of individual devices for measuring indirect calorimetry allows measurement of energy expenditure at rest and under normal living conditions [7], i.e., just after exercise, eating, or school work, with an accuracy similar to that obtained with the Douglas bag method, through a disposable mouthpiece and for 1–2 min (6 liters of exhaled air). In addition, it is now known that the elusive basal metabolic rate is not fixed but is modified by daily energy expenditure and thermogenesis capacity and is minimal when environmental conditions are optimal [8]. The increased accuracy gained in the measurement of energy expenditure has clinical implications such as the claimed advantage of intermittent fasting [9]. Therefore, this variability may be linked to the accuracy of the method used or to other genetic factors that may influence it. But it is clear that the equation $\text{total energy expended} = \text{resting energy expenditure} + \text{energy expended in physical activity}$ brings us closer to a clinical quantification of one of the factors of the law of thermodynamics, in this case to the energy consumed during exercise, which is not a primary form of expenditure [10] and perhaps suggests a search more towards increasing heat loss. Progress has been remarkable in the last 30 years, but these measurements have yet to gain in accuracy and simplicity of application. This pathogenetic model for obesity has a reasonable conceptual contribution [11] that we shall see below.

Other Factors Affecting the Energy Balance

Within this section we should introduce thermogenesis induced by food intake, also known as postprandial thermogenesis, which is part of the total energy expended. Since it must be measured under standard conditions, the data available come from studies carried out in adults. From these it can be assumed that this share is small compared to that of resting energy expenditure. Studies by Denis Molnar [12] in 1985 showed that in obese children and adolescents, postprandial thermogenesis is, as expected, a small proportion and with inconsistent differences between obese and nonobese. It is worth remembering how this small and difficult to quantify quota has given spurious bases to diets with a certain degree of popularity, especially in the not so distant past [13, 14].

As a summary of the balance of total energy expended, it should be noted, firstly, that compared to the important basal quota, where postprandial thermogenesis can almost be ignored, the only way to increase this factor of thermodynamic balance has been physical exercise, and although today this is beginning to be valued, to the extent that it remains a valuable method, it turns out to be less than the energy intake factor. Secondly, energy homeostasis also includes the regulation of energy reserves in specific organs (adipose tissue, liver and muscle for glycogen, etc.), and this adds the need to know the neurological regulation based on a series of signals originating

in these deposit organs, both in the intestine after food intake and in the various tissues according to their energy requirements. The ingestion of food and its cessation as well as the neuroendocrine responses are the primary elements in maintaining bioenergetic balance and undoubtedly have a genetic basis depending on the individual.

Appetite Regulation

Physiological Basis

Appetite is defined as the urge to satisfy any physical desire or need once it has become conscious. Hunger is the desire and need to ingest food. The two terms are often used interchangeably, although the former is more general and encompasses the latter. Hunger regulation is very complex and well preserved throughout the zoological scale, as it is an important factor in the neuroendocrine regulation of energy balance, which is necessary for survival and maintenance of health. There are more than 100 different genes involved in the determination of body weight. The products of these genes acting primarily in the hypothalamus and brain stem will consciously or unconsciously affect food intake and energy expenditure. They include genes responsible for the synthesis of brain sensors of the size of body fat stores, caloric flow through the gut, hedonic response to special foods, rates of energy expenditure, and even inclination to physical activity [15]. Large mutations in one of these genes result in rare cases of so-called monogenic obesity (3–5% of all obesities), as discussed in the chapter on *Etiology*. However, genome-wide association studies have demonstrated how single-nucleotide polymorphisms (SNPs) can be associated with certain phenotypes. In this case and as we saw, SNPs or other genetic variants of certain genes determine higher BMIs, although the mechanism through which the higher energy intake is operated is not yet clarified. This has led to the emergence of interesting but not unique theories [16] that emphasize the regulatory aspect of body weight as primary and where hyperphagia would play an important role favored by the elevation of branched-chain amino acids secondary to protein diets.

The neuroendocrine regulation of energy balance in humans rests on a logical functional structure consisting of afferent pathways, a sensor, and efferent pathways. The sensor is none other than the hypothalamus (Fig. 4.3). In its ventromedial area (VMH) is the first station formed by the arcuate (arcuate, bent) and ventromedial nuclei (VMN). The neurons of both have receptors for leptin that convey information from adipose tissue, for insulin (carbohydrate metabolism, adipose tissue), for ghrelin (sensation of hunger), and for peptide YY 3–23 (sensation of satiety) and that constitute the main afferent signals for the receptors of this so-called first station.

The second station is formed by the paraventricular nucleus (PVN) and the lateral area of the hypothalamus (LHA) whose neurons are able to pick up the signals

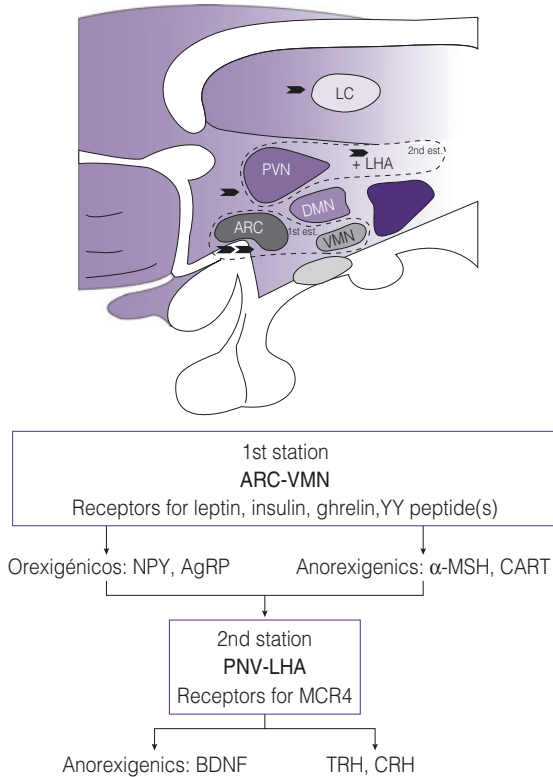


Fig. 4.3 Schematic view and diagram of the hypothalamus in the regulatory aspects of energy homeostasis. The first station of the regulatory circuit lies in the arcuate (ARC) and ventromedial nuclei (VMN) whose neurons have receptors for leptin, insulin, ghrelin, and for the peptide YY3-23 that constitute the main afferent signals of hunger and satiety. A second station is formed by the paraventricular nucleus (PVN) and the lateral area of the hypothalamus (LHA) whose neurons pick up the orexigenic (NPY, AgRP) or anorexigenic (MSH, CART) signals. The third station is represented by the origin of the autonomic nervous system: MSH also binds to the same receptor that is also expressed in the locus ceruleus (LC) activating the sympathetic system with increased energy expenditure. The third station (origins of the autonomic nervous system) is not represented in the figure

coming from the first station [17] and which can be orexigenic as is the case of neuropeptide Y (NPY) or agouti-related peptide (AgRP) or can be anorexigenic as is the case of melanocyte-stimulating hormone (MSH) or cocaine-amphetamine-regulated transcript (CART).

The paraventricular nucleus has a type of neuron that in addition to producing thyrotropin-releasing hormone (TRH) and corticotropin (CRH) produces *brain-derived neurotropic factor* (BDNF). This is clearly anorexigenic as has been demonstrated in *knockout* mice, in the WAGR syndrome consisting of an 11p13 deletion that causes among others Wilms’ tumor-aniridia obesity. Also the presence of variants (SNPs) in this gene will contribute to a predisposition to obesity [18, 19]. The

neuronal production of BDNF is a consequence of the binding of MSH with its receptor MC4R located in the paraventricular nucleus. Neuropeptide Y when it binds to its receptor in the paraventricular nucleus has an inhibitory action on BDNF-producing neurons, resulting in an expected orexigenic action. The gut-to-brain pathway in a basic study (mice) not only is it active but through vagal neurons responds to intestinal delivery fat and if silenced abolish the first station preference for fats [20].

It is in this second station and in the first (ARC-PVN axis) that eating behavior (and other aspects that begin to be relevant, such as blood pressure modification) is really controlled. A series of peripheral stimuli or signals converge in the so-called melanocortin system integrated as follows: POMC neurons in the arcuate nucleus produce (upon the arrival of certain signals) the precursor proopiomelanocortin which will later be fragmented into the various melanocyte-stimulating hormones, the most important of which is α -MSH (*α -melanocyte-stimulating hormone*) which is the one that binds to the melanocortin receptors (MCR4) found in the neurons of the paraventricular nucleus (PVN) and from this binding (upregulated) arise the anorexigenic effectors such as CRH, TRH, and BDNF. In the case of increased adiposity and its consequent production of leptin, it follows this pathway once bound to the specific neurons of the arcuate nucleus and also to the other anorexigenic hormones such as the cocaine-amphetamine-regulated transcript with the added particularity that from this binding the expressed orexigenic hormones are inhibited, AgRP, NPY, and bind with high affinity to the MC4R and the NPY receptor, thus avoiding the efferent orexigenic effect mediated by orexin or *melanin-concentrating hormone* (MCH), which would exemplify in a normal situation the medium-term information of leptin on nutritional adequacy. The alteration of a step in this sequence, for example, the defect of MCR4, leads to morbid obesity and can serve as counter-evidence [21, 22]. Directly or indirectly, the melanocortin system recognizes several signals which are simply peptides whose amino acid sequence and also how it changes in different species are known.

Returning to the hypothalamic circuit and the first station, the following initially known signals must be considered:

Leptin When this hormone became known in the early 1990s, it was ascribed an almost unique role in the pathogenesis of obesity. Today it is known that this hormone product of white adipose tissue is capable of transmitting information on the energy reserve to the hypothalamus and eliciting an anorexigenic response through the RCA-PVN axis. However, given the duration of obesity, its mechanism of action can be considered as another part of the regulatory circuit.

Insulin Insulin receptors are located in the same subpopulation of neurons in the arcuate nucleus that possess receptors for leptin. Insulin reaches the central nervous system via a specific and saturable transporter, binds to its specific receptor (IRS-2-PI3K), and accesses the anorexigenic sequence. Animal experience by means of cerebroventricular infusions, in litters with the insulin receptor functionally non-existent (*knockout*), behaves as expected and in the last case even with clinical pictures (hyperphagia, obesity, infertility) similar to those of leptin-deficient or leptin-resistant

mice [23, 24]. Insulin has a similar action to leptin but as an acute afferent signal. The role that *glucagon-like* peptide-1 (GLP-1) may play as an insulinotropic (and non-insulinotropic) after food intake [25] may be important in this circuit.

The third station would be represented by the origin of the autonomic nervous system which constitutes the beginning of the efferent pathways. In general terms, it can be said that while the sympathetic promotes energy expenditure, the parasympathetic promotes energy storage. We have already seen how the binding of α -MSH with MC4R in the paraventricular nucleus produces satiety, but the α -MSH also binds to the same receptor which is also expressed in the locus ceruleus (LC), and then an activation of the sympathetic nervous system (SNS) and an increase in energy expenditure are produced through an activation of the beta 2 adrenergic receptors of the muscle with oxidation of glucose and fatty acids, of the beta 3 receptors with increased lipolysis in the adipocyte (via the HSL, *hormone sensitive lipase* stimulus), and of the alpha 2 receptors in the pancreatic beta cells reducing insulin release [26]. The vagal stimulus is less well-known in its mechanism but has an opposite sign to that of the SNS.

This would be the most schematic version of the complex regulation of food intake, and that in a perfect world could preserve our ideal weight. It is advisable to review carefully the energy intake especially related to intestinal peptides [27] and new functions. Unfortunately, at present meals are initiated by habits, such as the time of day, social situations, or anxiety, clearly non-homeostatic factors in addition to the pleasurable sensations of palatability and reward or satisfaction experienced after ingestion of food. In the end they turn out to be the most important regulators of energy intake, particularly when there is no need for it, which is what we will discuss below along with the peripheral signals involved [28].

Then, we will discuss a group of peripheral signals that are known as satiety signals [29]. “Satiety” (or being satiated) is nothing more than a feeling of fullness that contributes to the decision to stop eating. Satiety is the duration of the interval until hunger or an urge to eat reappears [30] and was initially related to cholecystokinin levels. Unlike that which does not have or is not known to have a homeostatic system, satiety does and is based on signals initiated in the gastrointestinal tract and to a lesser degree those initiated in adipose tissue. Satiety ultimately controls the amount of food ingested.

Signals from the GI Tract

The enteroendocrine cells are important actors in the regulation of food intake, of the more than ten existing classes that numerically constitute a vast tissue, it is the I cells and L cells that are the most involved in this tilting balance as a consequence of the peptides produced before the daily or specific meal. In the first place, there is the sensation of fullness which contributes to the cessation of eating and, in the second place, satiety with its temporary character and which will only be the interval of time until hunger reappears. At this point it is appropriate to mention the

action of ghrelin given its orexigenic condition increasing the amount of food ingested which has been proven when administered centrally or peripherally. It is normally produced and secreted by specific cells of the stomach (*fundus*) and duodenum during periods of fasting [31] and is linked to the anticipatory aspects of impending food intake. Secretion declines rapidly when fasting ceases. Ghrelin, by binding directly to receptors (GHS-R1a) in the hypothalamus, arouses and stimulates appetite. The vagal afferent pathway may also contribute to the orexigenic effect. Clinically, the hyperphagia of Prader-Willi syndrome is closely related to high ghrelin levels. The interactions with other peptides and physiological functions have been previously described. It is an interesting fact that the hedonic reward provided by some foods, including ultra-processed foods, can create a kind of addiction to certain fats or carbohydrates, contributing to the development of obesity [32].

As an example of the opposite action, we have cholecystokinin (CCK), which was the first compound identified as satiating, as we will see later, which is secreted in response to the lipid and protein content of a meal, activating its receptors in the sensory nerves of the duodenum and reaching the brain through the vagus, contributing to satiety. In addition, the complexity (CH, fats, and proteins) of a consumed meal stimulates a proportional number of satiating peptides that will reach the part of the brain surrounding the fourth ventricle (*hindbrain*) that will activate the sensation of fullness and cessation of eating. First in animal experiments, then in humans, the exogenous administration of satiety factors at the beginning of an individualized meal leads to a reduction in the quantities consumed to below normal levels with a premature cessation of eating, without creating a feeling of discomfort, provided that physiological doses are used [33, 34]. It should be remembered how the intestinal hormones, in addition to the satiety signal, perform other very important actions such as the regulation of GI motility or the secretion of certain enzymes. Cholecystokinin (CCK) was the first to be described [35] as a satiety factor and is secreted by the I cells (endocrine cells of the intestine) when fats or proteins reach the duodenum. It has two types of actions, some gastrointestinal such as increasing intestinal motility, gastric and gallbladder emptying, and pancreatic secretion. The other type of action is to promote satiety, and it does so by binding to the specific receptor (CCK-R) that is expressed in the fibers and terminals of the vagus, and this signal through the same reaches the so-called hindbrain and from there to the hypothalamus where the feeling of satiety is generated. This happens in obese individuals as well as in normo-nourished individuals. Exogenous administration during a given meal makes the meal smaller but does not increase the fasting period, which is related to its short half-life. When the receptor is blocked (CCK-R), then opposite results appear but tend to be compensated by other peptides such as PYY, and in this sense the prolonged administration ceases to have effects precisely because of these opposite effects. The next paragraphs are of special interest because they are the basis for the treatment not only of type 2 diabetes but of obesity itself (see Comorbidities Conditions and Treatment).

In addition to CCK, the main gastrointestinal hormones that promote satiety are:

Proglucagon-Derived Peptides Proglucagon is a protein molecule of 158 amino acids whose synthesis is governed by a single gene and which is expressed in the alpha cells of the pancreatic islets or in the L cells, enteroendocrine cells of the distal ileum

and colon. In the first case, proteolytic fragmentation will give rise to glucagon with its well-known function of regulating glucose metabolism. When such fragmentation takes place in L cells, then a series of peptides appear sequentially: glicentin [amino acids (aa) 1–72]; *glucagon-like peptide-1* (aa 73–111), and *glucagon-like peptide-2* (aa 124–156). Glicentin will in turn fragment, giving rise to oxyntomodulin (aa 34–72).

Glucagon-like peptide-1 (GLP-1) is secreted by L cells in response to the arrival of nutrients and in addition to its action on glucose metabolism (inhibition of glucagon release and stimulation of insulin secretion), it has two satiating actions.

The first lies in the inhibition of motility and GI secretions, but this action is not very efficient given its short half-life (1–2 min) in human plasma. The second action lies in its ability to cross the blood-brain barrier, binding to its GLP-1r receptor, which is expressed in the hypothalamus and thus acts on energy homeostasis circuits and in the amygdala, the binding of which results in a feeling of discomfort, which encourages us to stop eating [36]. More recently and more specifically, it has been possible to see by immunohistochemistry the connections of the *nucleus tractus solitarius* (NTS) which is no more than a series of sensitive nuclei whose efferent tracts go to the paraventricular nucleus (PVN), the LC, the amygdala, and other areas. In addition, the NTS is the major central producer of GLP-1 with easy access to its respective receptor (GLP-1r) which is expressed in the lateral dorsal tegmental nucleus (LDTg); such binding suppresses food intake without nausea or discomfort [37]. Subcutaneous administration of exenatide (a GLP-1 analogue) in healthy, obese, or diabetic subjects demonstrates these actions together with weight loss [38], and GLP-1r agonists act in the same way.

Regarding the different peptides derived from the proteolysis of proglucagon, it must be said that they have a variable effect on satiety. Oxyntomodulin is the most effective and the most studied in humans, probably acting through the same receptor (GLP-1r). GLP-2 has its own receptor, and its most important action is on intestinal mucosal growth. In the same sense, we should consider glucagon itself which is secreted in minimal proportion by the L cells of the distal intestine, and its primary action is still hepatic with increased gluconeogenesis and glycolysis, but it also has a meal size decreasing action caused by its intestinal secretion.

YY Peptides (Peptide Tyrosine-Tyrosine, PYY) It is probably among the most important elements (if not the most important) in the multifactorial process of satiety [39] and is part of the neuropeptide Y (NPY) family that we saw previously when discussing the role of the diencephalon in the regulatory process. PYY is synthesized and excreted by L cells as a proportional response to the amount of food intake and the arrival of nutrients in distal areas of the intestine, especially when they are fats. It is secreted in its 1–36 form, which once it crosses the blood-brain barrier is the one with the highest affinity to the Y2 receptor, which in turn belongs to the family of receptors for neuropeptide Y (NPY) and is expressed in arcuate neurons. The binding of PYY to Y2 produces the reduction of food intake that has been widely demonstrated in animals and humans and has been described as a true “intestinal brake” on food intake. Clinical experience has shown how the amount of appetite correlates with plasma levels of PYY [40]. Exogenous administration of PYY in normo-nourished and obese individuals decreases food intake. However, in obese patients, a lower pre- and postprandial endogenous production after a stan-

dard meal has been demonstrated. In addition, certain PYY polymorphisms are associated with a greater tendency to obesity, while some polymorphisms in the Y2 receptor gene prevent the onset of obesity.

Other Peptides Within this group should be included apolipoprotein i.v., secreted by mucosal cells and arcuate neurons and enterostatin, a pentapeptide derived from pancreatic colipase, both of which decrease the intake of a meal according to its fat content. GRP (*gastrin-releasing peptide*), along with other members of the bombesin family, has the peculiarity of inducing satiety and satiety time if administered between meals. Secretin (water homeostasis) and neurotensin (smooth muscle contraction) although enteroendocrine products seem to have less regulatory importance.

Finally, it should be added that under normal conditions, satiety is achieved not because the capacity of the stomach has been exceeded, as demonstrated by the increased intake of diluted food, but precisely because of this added action of the various peptides against the multiple immediate principles. The fact that some of them are probably synthesized in the brain or that they share sensory stimuli such as hunger and pain requires further research to elucidate this function.

Ongoing research on the neural mechanisms of obesity provides new data of clinical interest. Thus, Rossi's study [41] shows how a group of neurons (glutamatergic) located in the aforementioned second station and specifically in the lateral area of the hypothalamus (LHA) and whose activity is modified by obesity due to overeating are capable of producing changes in transcription that in animal experiments manage to inhibit the sensation of reward provided by the ingestion of food. The field of cellular mechanisms is very broad and with new possibilities, such as the transcription factor Mondo A in relation to the accumulation of lipids in muscle or the elevation of catestatin in obese children, among many other aspects. Precisely because of this hedonic sensation, studies related to the prefrontal cortex have an important role in the genesis of human obesity through factors such as craving or the increase in the sensation of hunger when faced with a plan to reduce energy intake, and taking into account the ease of eating food almost at any time in high-income countries, the approach to the physiological control of energy intake is a field that requires further study. In adolescents, there is some research based on behavioral predisposition to obesity and other more focused on the central self-regulation of energy intake [42], but the molecular and biochemical bases of these complex processes require further study. An example is the *in vivo* endomicroscopy of a cell of the paraventricular nucleus (PVN) of the hypothalamus to determine the activity of a basic regulator of body weight as we have seen in the MC4R [43].

Sweet Taste and Aroma Perception

The newborn infant already has an innate preference for sweetness and the mother's milk with its lactose content (~7 g/dL) will only maintain this preference. This is because the disaccharide provides an intensity of "sweetness" equivalent to that of

a 2% sucrose solution and is further enhanced by components such as maltol. This produces a hedonistic effect that is the first link in the future attraction to sweet foods that increases if during the first 6 months of life, sugary cereals, fruit juices, or sweet fruits are introduced. At later ages, the excessive intake of such fruits or infant juices and sweetened or sweetened desserts [44] will help to establish this preference. It should not be forgotten that this is the time to experiment and incorporate foods with a certain bitter taste (vegetables, etc.). From this age onwards and in high-income countries, the consumption of added sugars continues to rise until it reaches 17% of the daily energy consumed by adolescents. The sensors for the basic tastes (sweet, sour, bitter, and salty) and others for tastes from various compounds are heteromeric proteins and are not only found in the mouth and tongue but also in the intestine and pancreas. They participate significantly in the ingestion of these foods, especially those energetically richer such as fats and sugars. But it can also be the primary cause of food overeating when there are variations in the *TAS 1 R2* gene that encodes the protein sensors of the mouth. In addition to other conditioning factors for the attraction to sweet tastes, the genetic basis demonstrated by genome-wide associative studies must be considered [45, 46]. This tendency to eat more sweet foods should not be confused with *food craving*, where there is a reaction of salivation and anticipation of pleasure at the possibility of eating that food, which carries an obvious risk of obesity [47] or with the additions to food that will be discussed in the *Clinical* chapter.

Signals Initiated in Adipose Tissue

In the early 1980s, it was seen in both primates and humans that insulin, once it reached the central nervous system, completed a negative *feedback* between the magnitude of fat stores and feeding behavior. It was seen as a signal of adiposity, in addition to its usual metabolic actions. In the 1990s, leptin was identified as another signal of adiposity and with regulatory capacity of energy homeostasis [48]. Once these two signals have reached the CNS, and more specifically the hypothalamus, through their own mechanisms and a blood-brain barrier that is not particularly effective in this case, they bind to their specific receptors widely expressed in the neurons of the medial area located in the hypothalamic tuberal region and more probably to those of the arcuate nucleus where they interact with the melanocortin system (Fig. 4.3). Insulin, secreted by pancreatic beta cells and leptin by adipocytes of white adipose tissue (and other tissues) in direct proportion to body fat content influence energy homeostasis. This has been demonstrated by the exogenous addition of insulin or leptin directly into the brain. It has been shown that food intake is reduced, and conversely if the signals of both are reduced in the brain and especially if there is less adipose panniculus, then the individual reacts by eating more food and gaining weight. Unlike the signals of satiety (and satiation) that cause a reduction in the number of kilocalories to be ingested in a given meal, these signals of adiposity are related to the amount and maintenance of the fat deposit. This idea of prolonged action may justify

the scarce therapeutic impact they have had in the treatment of obesity, since insulin due to the hypoglycemia that follows its administration increases food intake, and the administration of leptin in obese patients (and without lipodystrophy) produces weight loss of insignificant magnitude. Perhaps the most significant aspect of this elevation maintained as a consequence of the increase in adipose panniculus is the leptin and insulin resistance that is not only peripheral but also of the CNS (hypothalamus), possibly because the transport to it is diminished, which decreases its possible reducing effect on food intake. Activation of the brain-melanocortin-vagus axis promotes a negative energy balance through lipid mobilization [49] using the vagus nerve as an efferent pathway, independently of energy intake. Extensive experimental research using the CRISPR system that allows genetic ablation of the leptin receptor (LEPR) demonstrates how certain groups of neurons are essential for the regulation of energy balance and glucose homeostasis.

In summary, it can be said that the brain receives mainly two blocks of signals (intestinal and adiposity peptides) to maintain energy homeostasis. Leptin and insulin act continuously on the arcuate nucleus which enhances the brain's sensitivity to satiety signals coming from a specific food, regulating its intake, under conditions of nutritional normality. But this regulation is affected in the case of obesity and by the aforementioned social factors that lead to eating in the absence of hunger, i.e., for hedonism. In the evolution of humanity, the need to eat has been much more significant, and therefore the circuits that govern hunger are both well preserved and multiple to ensure survival. When we reach the present situation where food intake can have more important stimuli than hunger and there is food availability, the possibility of a less developed satiatory pathway becomes real with less self-regulation of energy balance, and that is when there are circumstances that contribute to obesity.

Adipose Tissue

Functional and Cellular Basis

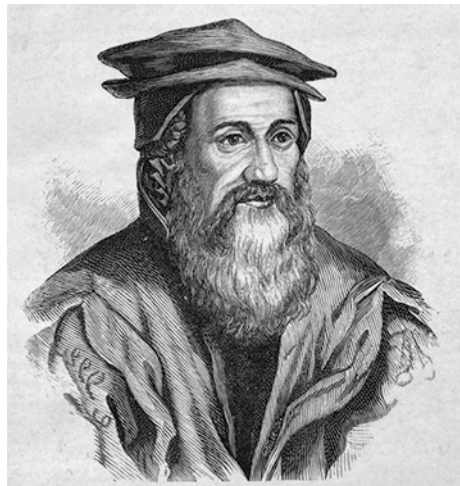
The adipose tissue is far from being homogeneous in its composition, and in the case of obesity, white adipose tissue (WAT) plays a major role but not the only one. This constitutes the most important energy reserve of mammals, and although the energy deposit can have different settlements, three are quantitatively the most significant: the adipose tissue itself, the muscle, and the liver. Each of them can, at any given time, mobilize energy in a regulated manner through the release of fatty acids. In the case of fatty tissue, they pass into the circulation providing energy to other tissues; in the case of muscle, they are a natural substrate to be oxidized; and in the liver they are the building block for reesterification in the endoplasmic reticulum, re-exporting the triglycerides in the form of VLDL, as has been seen in the discussion on insulin resistance on fat accumulation. Brown adipose tissue (BAT), which is quantitatively less than WAT, has physiological interest as it uses glucose and triglycerides to generate heat, which has enabled the survival of living beings in times of great atmospheric cold. Both tissues possess rich interrelations with the

endocrine system. A valuable recent review [47] is dealing with new aspects on structure and distribution, function and communication, and its role in obesity.

Adipose tissue has had a less fortunate scientific past: in 1551 and in Zurich, the naturalist Konrad Gessner (Fig. 4.4) macroscopically described for the first time brown adipose tissue [50] as a tissue that is neither fat nor flesh but something in between, while white adipose tissue, which has always been known, was described by the physician and microscopist Arthur Hassall in the *Lancet* in 1849. Adipose tissue is nothing more than a specialized connective tissue, and in mammals it appears mainly in two forms: white adipose tissue and brown adipose tissue. The presence and distribution of each depends on species, age, and prolonged conditions of low environmental temperatures. Beige AT will be considered below. The BAT owes its color to the rich vascularization and the large number of mitochondria it possesses. The WAT cell has a unilocular fat guttule that fills the cytoplasm, whereas BAT cells have several smaller fat guttules, giving them a multilocular appearance. There is another type of adipocytes which are part of the tissue where they appear (bone marrow, breast tissue) but that at present have little connection to obesity.

White adipose tissue (WAT) has three important functions: firstly, thermal insulation due to its subcutaneous location, since heat conduction through it is one third that of other tissues and is therefore directly related to its thickness; secondly, the function of visceral cushioning in case of mechanical trauma, preventing breakage or tearing; and, thirdly, and most importantly, as an energy reservoir; and closely related to this is its hormone- and adipokine-secreting function. Brown adipose tissue (BAT) is transcendental for the regulation and maintenance of body temperature via thermogenesis without shivering. This is because lipids release heat energy directly through a specific mitochondrial system as discussed below, which does not produce ATP and can counterbalance excess caloric intake. The initial precursor cells (*mesenchymal stem cells*, MSC) of both types are morphologically similar and pluripotent, but they are both different in their immediate origin and destination [51]. The *enhancers* are sections of DNA which increase the level of transcription of a gene and which in this case

Fig. 4.4 Konrad Gessner.
Swiss naturalist

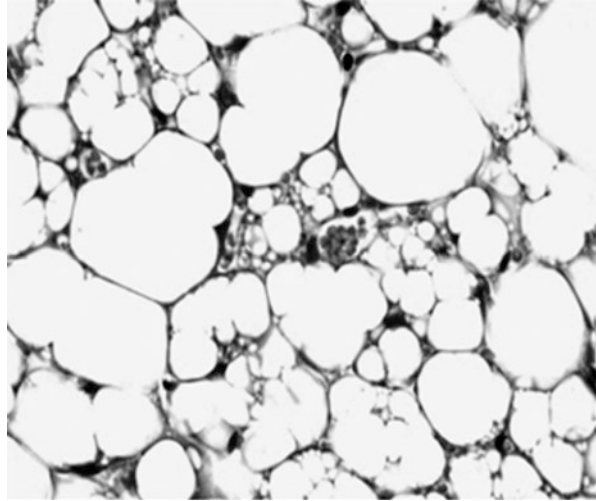


cause the MSCs to differentiate into osteoblasts or adipocytes [52] and in which even a variant (SNP) can favor greater adipogenesis. Although the primitive origin is common, the mesodermal cells and later the fibroblast-like cells, when faced with certain external stimuli, differentiate on the one hand between unilocular cells (WAT) and on the other into multilocular myocytes (BAT), due to the action of certain bone morphogenic proteins. More recently, however, greater importance has been given to the expression of certain gene factors in the various stages of differentiation. In the case of the precursors of BAT cells, there is a decisive moment in which they can differentiate between myocytes or multilocular fat cells depending on external signals, one of which could be myogenin (myocytes) or the transcription factor PRDM16 (BAT cells) and which in the latter case conserve enzymatic endowments characteristic of muscle cells, as will be seen in the description of BAT. This separation is not as clear as it may seem, and in obese subjects the WAT expands, becomes dysfunctional, and develops a low potency inflammatory state. At the same time, the activity and content of the BAT decline in the obese mainly as a consequence of the conversion of brown adipocytes into apparently (unilocular) white adipocytes [53]. Other adipocyte transformations in the mammary gland into milk-producing epithelial cells have also been described during pregnancy and lactation. Recently it has been described genes associated with waist circumference, and derived indexes, as well as allelesensitive enhancers underlying not only the female adipose distribution in women, but also the metabolic dysfunction [54].

White Adipose Tissue (WAT)

In mammals the largest proportion of adipose tissue is precisely the white one and is composed of lipid-filled cells called adipocytes held together by a framework of collagen fibers. In addition to the adipocytes, there are vascular stromal structures since each adipocyte is in contact with at least one capillary endothelial cell through which its metabolism affects and is affected by changes in the body in relation to body weight and postprandial and fasting periods and amounts thereof. It also contains the preadipocytes whose cytoplasm is not yet filled with fat. The mature adipocyte has a single (unilocular) guttule that pushes the nucleus and mitochondria against the plasma membrane giving it a ring-like appearance of about 100 μm in diameter (Fig. 4.5). Contrary to initial ideas, hyperplastic growth also occurs in the adult when the increase in volume (hypertrophy) has reached a limit. With weight loss only the size of adipocytes decreases and the amount of apoptosis that could affect preadipocytes is unknown. From a quantitative point of view, it is worth remembering that fatty tissue is the only tissue that can double its mass (10–20 kg in a normal adult) and later reduce it with barely any consequences. Finally, it should be added that the lipid content of the adipocyte consists of 90% triacylglycerols and the remaining 10% is free fatty acids, diacylglycerols, phospholipids and cholesterol esters; the predominant fatty acids of the triacylglycerols are usually myristic 14:0, palmitic 16:0, palmitoleic 16:1 n-7, stearic 18:0, oleic 18:1 n-9, and linoleic 18:2 n-6 but may vary according to diet.

Fig. 4.5 In the center of the image, there is a beige adipocytic accumulation in the breast of the TAB contrasting with the unilocular guttule morphology of the white adipocyte



Metabolism in Lipid Tissue

Lipogenesis

The energy ingested and not consumed will be stored in adipose tissue, fats will do it more directly, and carbohydrates will be initially stored in the liver and muscle as glycogen. However, if the higher intake follows the carbohydrates, expressing it schematically, it will be converted in the liver after an elaborate process into fatty acids to then be esterified as triglycerides and transferred to the WAT for storage. The amino acids of the ingested proteins are initially used for the synthesis of new proteins, but when there is an overload, they can be transformed into carbohydrates and fats and therefore stored. This process is carried out in the following way: in a first phase, the triglycerides contained in the chylomicrons coming from the complex intestinal absorption of fats or those contained in the VLDL, and also lipoproteins coming from the hepatic synthesis reach the capillary of the adipose tissue. Products from the two origins they possess the c11 apoprotein, which is capable of activating an enzyme, lipoprotein lipase (LPL), that is synthesized by the adipocyte and secreted to the adjacent endothelial cell and which splits the triglyceride into fatty acids and glycerol. The former, due to a transmembrane transport protein, reach the so-called adipocyte free fatty acid *pool*. The glycerol is mostly returned to the circulation. In a second phase, lipogenesis involves a combination of the fatty acid with coenzyme A to synthesize the thioester and stepwise resynthesize the triglyceride (MG-P DG-P TG). The glycerol comes mainly from the glucose supplied by the capillary which is transformed in the narrow cytoplasm into glycerol phosphate. In this way the adipocyte's fat deposit grows. Insulin, however, which is secreted also in the pancreatic cells in accordance with the adipose depot, plays an important role here through lipogenesis, since it stimulates the LPL function and thus promotes the entry of fatty acids into the adipocyte and also of glucose, which ultimately promotes the formation of triglycerides in the adipocyte.

Lipolysis

It is produced in situations where the energy required is higher than the energy ingested. It is carried out by an enzyme complex called *hormone sensitive lipase* (HSL); this lipase also acts in steps on the known sequence $TG \rightarrow DG \rightarrow MG$ giving rise to free fatty acids and glycerol. The first step is carried out by HSL which acts on the hydrolysis of triglycerides, and this is basic in the regulation of lipolysis, since its lipase activity is low. Once triglycerides are hydrolyzed to fatty acids and glycerol, the former enters the cellular *pool* of free fatty acids where they can be beta-oxidized or released into the circulation as energy substrates for muscle, cardiac muscle, and the liver where they enter by passive diffusion, but their rate of incorporation is proportional to the extra intracellular concentration difference. Once inside this cell and if they are to be beta-oxidized in order to obtain ATP, their activation is required through classical coenzyme A binding and thioester formation. Insulin is also involved in the regulation of lipolysis as it slows it down and consequently decreases the arrival of fatty acids in the peripheral tissues and the liver. Physical exercise in the context of the approach to obesity favors lipolysis and therefore the reduction of the adipose panniculus and consequently hyperinsulinism.

WAT Locations

Visceral fat or perivisceral fat [47] is located in the abdominal cavity, between the internal organs and torso and also includes the mesentery, perirenal fat, and epididymal fat. Intramuscular fat is located between the skeletal muscle fibers. Subcutaneous fat is found under the skin but not uniformly, fat stored in the hips, buttocks, and thighs is of the subcutaneous type, and this possibly justifies its better prognosis compared to upper body obesity which is of the visceral type fat. In addition, we must consider what is known as ectopic fat, which is nothing more than the deposit of triacylglycerols inside cells of non-adipose tissues that normally contain small amounts of lipids. Initially it was considered in the liver and muscle, but the use of magnetic resonance spectroscopy has allowed us not only to quantify the deposit but also to extend it to the myocardium and pancreas. This muscular and hepatic ectopic localization is of great significance in the development of insulin resistance and therefore of comorbid conditions [55]. By following the energy overload, the adipocytes and especially the hepatocytes in this case they hypertrophy but up to a limit after which dysfunction appears and through adipokines they exert a patent inflammatory action as it happens in the advanced stages of TD2. The location of adipocytes in the bone marrow [56], which account for 10% of the total fat mass, is of twofold interest at the moment: their interaction with the survival of hematopoietic cells and their possible lipolytic activity and their relationship with cholesterol metabolism. These different locations have an important clinical repercussion; data from longitudinal studies of more than 15,000 adults [57] show that over a period of 6 years, the possibility estimated by the *hazard ratio* (HR) for DT2 was 2.30 (95% CI 0.87-6.05), being considerably higher in the case of ectopic locations, especially for the female gender.

Adipokines and WAT-Derived Hormones

Once the preadipocyte has become a mature adipocyte, in addition to its capacity to store triacylglycerols and their subsequent release as free fatty acids, it is capable of synthesizing more than a hundred different proteins known as adipocytokines or adipokines, which are released as enzymes, cytokines, growth factors, and hormones, almost all of which are primarily involved in energy homeostasis. These adipose-derived molecules act via endocrine, paracrine, autocrine, and juxtacrine pathways and regulate or intervene in metabolic processes as well as in modulating the size of fat deposits and their distribution. But they also act as proinflammatory mediators, such as C-reactive protein (CRP), which was initially thought to be synthesized exclusively in the liver as an acute reactant and which is now known to have an important fraction of adipose origin, being more reactive than proinflammatory if compared with the high levels of IL-6 that are directly involved in the processes of atherogenesis [58].

It is difficult to classify the plethora of proteins and other products synthesized by the adipocyte. Certain adipokines involved in obesity and its long-term complications (atherosclerosis) are listed in Table 4.1, some of them, e.g., IL-6, are listed under two headings for their various actions, and some hormones such as leptin are listed for their paracrine effects.

Some specific actions on these adipocyte products will be mentioned, especially those related to obesity: first of all, the capacity to modulate estrogen synthesis due to the transformation of testosterone into estradiol by means of the aromatase present in the WAT. The presence of dehydroepiandrosterone and androstenedione in the

Table 4.1 Selected adipokines associated with obesity and late complications of obesity

Influence adipogenesis
– Lipoprotein Lipase (LPL)
– <i>Cholesterol ester transfer protein</i>
– Angiotensinogen
– Adipsin
– Adiponectin (or C1q)
– <i>Acylation stimulating protein</i> (or Arg C3)
– Interleukin-6 (IL-6)
– Prostaglandins
– <i>Tumor necrosis factor</i> (TNF-)
– <i>Adipocyte differentiation factor</i>
Proinflammatory adipokines
– TNF
– IL-6
– Leptin
– <i>Plasminogen activator inhibitor-1</i> (PAI-1)
– Angiotensinogen
– Resistin
– PCR
Anti-inflammatory and anti-IR substances
– NO
– Adiponectin

case of obese girls, although due to aromatase [59], will be precursors of estradiol but maintain their virilizing action in girls, while the increase in estradiol contributes to gynecomastia in boys and increased skeletal maturation in both genders and cancers in the reproductive tract in adults.

Beforehand, it is worth considering, among the adipogenic factors produced by the adipocyte, those that are more related to insulin resistance, which is nothing more than a reduced action of insulin on its target tissues: muscle, liver, adipose tissue, and vascular endothelium. Insulin resistance is preceded by a state of adaptive hyperinsulinemia capable of controlling blood glucose levels and which is a precursor to the development of type 2 diabetes. Insulin resistance may correlate with the degree of abdominal obesity, but other factors cannot be excluded [60].

Leptin An adipocyte hormone that functions as a molecular signal when it reaches the diencephalon and completes a negative *feedback* in the process of weight control. It is now known that plasma levels are proportional to body fat content and that they decrease much more noticeably during fasting or with a hypocaloric diet. On the contrary, in cases of continued energy overeating, subsequent obesity, and elevated plasma levels, leptin resistance is produced in which there is no decrease in the sensation of hunger, perhaps due to alteration of the diencephalic Mmp-2 (matrix metalloproteinase-2) receptor. This situation is possibly concomitant and concordant with that of insulin resistance. Recently it has been seen that pancreatic alpha cells present receptors for leptin and that they reduce glucagon secretion; this fact demonstrates the existence of a communication pathway between the WAT and the endocrine pancreas [61]. In addition, its proinflammatory capacity is clear, manifested through an increased synthesis of a potent endogenous vasoconstrictor, ET1, which would also explain its hypertensive action [62].

Resistin A white adipose tissue hormone that directly induces insulin resistance in muscle and the liver in rodents. It was therefore thought to be related to T2D, since neutralization of resistin with specific antibodies resulted in lower blood glucose levels and increased insulin sensitivity [63]. However, studies in humans have not demonstrated this relationship since no differences appeared in obese, healthy lean, or diabetic individuals [64, 65]; therefore the role of resistin on human physiology remains to be clarified, and perhaps the lack of homology between its encoding gene in mice and humans may explain this difference; something similar also occurs with the conservation of its proinflammatory action, when expressed in macrophages or monocytes. Elevation of plasma resistin is associated, in a recent study, with the degree of hepatic steatosis in obese pediatric patients [66]. Resistin plays an important role in the subclinical process of inflammation that occurs in obesity and is manifested by cardiovascular disease, while visfatin would be more related to the development of T2D [67].

Visfatin Nicotinamide phosphoribosyl transferase (Nanpt) is initially an enzyme related to nicotinamide dehydrogenase, NAD, and has two forms, one is intracellular and catalyzes the synthesis of NAD from nicotinamide [68]. The extracellular

form of this protein acts as a cytokine produced in the visceral WAT called PBEF or visfatin [68]. This protein has a proinflammatory and hormonal effect. Due to the latter, it lowers blood glucose levels due to its ability to bind to insulin receptors, but without competing with it, so it can contribute to improving insulin resistance by circulating at lower levels than insulin, and it does so after sustained elevations in blood glucose levels. Further studies in humans are probably needed on its role in blood glucose homeostasis. New adipokines have been described, some with adjuvant properties (omentin, proinflammatory) or, for example, the effective anti-*Staphylococcus aureus* factor described in the mouse, or regulatory (asprosin), the latter not only for its insulin resistance but also for its “browning” action on white adipose tissue as we will see below.

Adiponectin A factor of the complement (C1q) amply expressed in adipocytes due to the action of nitric oxide synthase (eNOS, *endothelial NO synthase*) in the mitochondria [69] and with beneficial actions generally different from those shown by the adipokines just mentioned. Their high circulating concentrations suggest an important physiological role that can be circumscribed to three poles: regulation of glucose metabolism, blood pressure, and inflammation, all of them initially described in adults, but already confirmed also in obese children and adolescents [70]. In this sense, adiponectin levels are decreased in obesity and correlate negatively with insulin resistance or CRP levels, and when there is weight loss after therapeutic intervention, the levels usually go up again. Finally, adiponectin, unlike the aforementioned adipokines, also exerts an antiatherogenic action by suppressing the endothelial inflammatory response by inhibiting the proliferation of smooth muscle fibers mainly through the decrease of the vascular adhesion molecule (VCAM-1). It is interesting to understand how protective adiponectin levels in a recent study [71] are associated with cancer in individuals with T2D.

In summary, it could be said that adipokines, whose normal plasma levels [72] for adults are shown in Table 4.2, are polypeptides secreted by the WAT in a regulated manner. Some of these molecules are expressed only by adipocytes, while macrophages and components of the vascular stroma of the tissue can also express them, as a consequence favoring a tissue inflammatory reaction in accordance with the aforementioned adipokines. Moreover, the vascularization of the visceral adipose tissue drains directly into the portal vein; consequently the best known (leptin, resistin, adiponectin) and the most recently studied (TNF-, IL-6) have a direct effect on the liver, ranging from fatty infiltration to differentially modulated steatosis, inflammation, and fibrosis [73]. T2D starts long before it is diagnosed, and its complications are not only due to hyperglycemia, but adipokines play an important role and with plausibly earlier elevation which will allow an earlier diagnosis through leptin and adiponectin variations [74]. It should not be forgotten that these two important cytokines that regulate appetite decrease their levels with exercise at high ambient temperatures [75]. Orexins [11] provide a new approach to this vast group of peptides because of their implication in physical activity, especially during normal lives. Therefore, obesity through these mechanisms causes late comorbidities

Table 4.2 Plasma levels of the main adipokines in healthy adults

Leptin	5–6 ng/mL
Resistin	7–7.5 ng/mL
Adiponectin	11,000–12,000 ng/mL
IL-6	1–1.5 pg/mL
TNF-	8.5–9 pg/mL

including metabolic syndrome/insulin resistance, as we will see in the next chapter, and more specifically by increasing proinflammatory cytokines and decreasing anti-inflammatory and insulin-sensitizing cytokines (adiponectin). However, their gene regulation, the internal molecular mechanism through which they act or the efficacy of their action, remains unknown. We do know that leptin and FABO4 (fatty acid-binding protein 4) levels coexist with elevated adipose tissue deposits, while other adipokines mentioned play a considerably lesser role [76]. The real role of the so-called inflammatory diets [77] should be confirmed by concomitant determination of adipokine levels and the most frequent SNPs in obesity.

Brown Adipose Tissue (BAT)

Origin

During the gastrulation phase, the mesoderm fills the gap between the outer layer (ectoderm) and the inner layer (endoderm). Two cell lines of a diverse future originate from the lateral mesoderm: on the one hand myocytes, brown adipocytes (BAT), and to a lesser extent chondrocytes and, on the other, pericyte-like cells associated with arterioles and capillaries and white adipocytes (WAT). This is the origin of the two known types of adipocytes, the one that stores energy in the white adipose tissue and the one that dissipates energy, or brown adipose tissue through mitochondrial uncoupling due to the mitochondrial *uncoupling protein 1* (UCP1) and that produces heat without tremor. What is essential and characteristic of each of the two types of adipocytes? Until now there have been several theories about their origin, but recently and following the proposal of Tang [78] which gives a double origin for both lines, the expression of myogenic factors such as Myf 5 only in myocytes and in brown fat cells corroborates this relationship between the two. This conclusion was reinforced by the expression of the transcription factor PRDM 16 in myoblast cultures which then became brown adipocytes, with an obvious counter-evidence, i.e., when *knockdown* for PRDM 16 is established in brown adipocytes, then myogenesis is induced [79].

Beige adipose tissue (BEAT). Perhaps more appropriately, the beige cell sub-population is found in humans in cellular accumulations within the WAT of supra-clavicular subcutaneous location, and perhaps also for the spinal cord, they also have a greater number of mitochondria and iron which gives them their intermediate

coloration (Fig. 4.5). They present some cell markers and transcription factors that in theory should guide about their embryonic origin, but it is known that in the WAT there are cell precursors that already express UCP1 and other characteristics of beige or brown adipocytes when they are appropriately stimulated (PPAR-gamma, or low environmental temperatures) and then the large and unilocular white adipocytes are transformed into beige adipocytes [80]. This process is called *browning* because it contributes to increased heat production and expenditure of energy that would not be stored [81, 82] and has also opened a possible therapeutic avenue [83]. Precisely the gene expression of the brown adipocyte marker UCP1 when studying the subcutaneous WAT shows correlation with the BMI of obese adults. Given the regulatory action of melatonin in the beige adipocyte [84], its therapeutic use could be reasonable in the future, and perhaps later on, it will be the growth differentiation factor 5 (GDF 5) capable of promoting thermogenesis in white adipose tissue. All these circumstances about the origin of brown adipocytes are of interest for a possible therapeutic action that increases their energy expenditure action, as will be seen below after analyzing their activity through positron emission tomography/axial tomography (PET/CT).

Location

In newborns and infants, the BAT is located in the interscapular space, and, as the patient progresses towards adulthood, it was thought to disappear. However, in adult patients with catecholamine-secreting tumors (pheochromocytomas and paragangliomas) and when applying the combined technique of PET and axial tomography for the identification of metastases, a significant development of BAT in the supraclavicular areas could be observed, which evidently did not correspond to any extension of the tumor [85]. After a considerable study of almost 2000 patients [86], the most specific location of BAT in adults is in the cervical-supraclavicular area which constitutes the main deposit. But the distribution in adults and presumably in children is as shown in the sequence in Fig. 4.6, where in addition to the clavicular hollow, it can also be seen in different fascial planes of the neck, in the sternocleidomastoid, between the subscapularis and pectoralis muscles, in the posterior part of the brachial plexus, and in smaller amounts in the descending paraspinal or perirenal areas. The activity of the BAT is modified in an important way by the ambient temperature in the sense that it increases with cold and, to a lesser degree by gender, in females it increases more easily. Under normal conditions, i.e., no cold environment, the amount of BAT is estimated at about 10 g as a total amount in the areas described.

Function

Before going into the functional aspects better known today, the biological aspects of the brown adipocyte must be addressed. The abundance in mitochondria has been noted above. The mitochondrion in any cell has a primary mission which is the production of energy from the metabolic products of glucose, fatty acids, and, to a

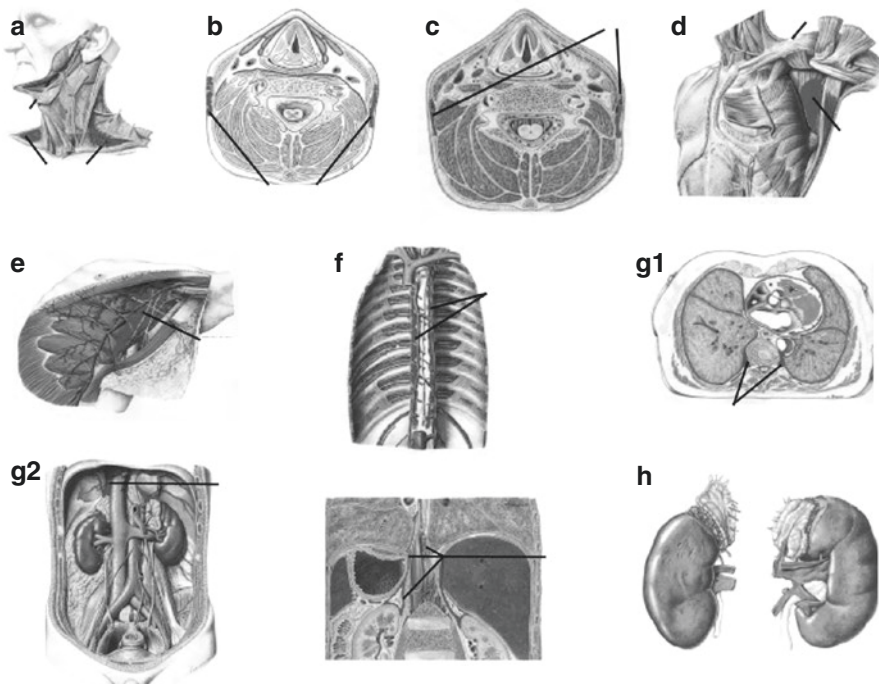


Fig. 4.6 Distribution of brown fat in the adult. **(a)** Supraclavicular deposit. **(b, c)** Ventral neck in different planes. **(d)** Lateral and superficial part of the sternocleidomastoid. **(e)** Deposition between the subscapularis and pectoralis muscles; **(f)** Posterior part of the brachial plexus. **(g¹)** Paraspinal thoracic and **(g²)** abdominal deposits. **(h)** Peripheral deposits. Note that the end of the straight line indicates the location of the deposit

lesser extent, amino acids. Due to their own enzymatic systems and that in general converge in pyruvate and acetyl-coenzyme A entering the Krebs cycle and after the process known as oxidative phosphorylation (transfer of electrons to oxygen and phosphorylation of ADP, see above), ATP is generated, which is the form of energy that cells use to live and perform their functions. BAT cells, however, do not exactly follow this universal pattern in regard to energy production. While, in the rest of the cells, the electron transport chain can generate a proton quota (H^+) able to return to the mitochondrial matrix, and then ATP can be synthesized after F_1F_0 -ATPase. In brown (and beige) adipocytes, these protons will not contribute to ATP synthesis. This different process is known as “mitochondrial uncoupling,” and after stimulation by β -adrenergic signals, the electrochemical gradient energy of these protons will allow the release of energy in the form of heat. This is possible due to the presence of a proton channel known as uncoupling protein or UCP1, which is a 33 kDa protein specific to the brown adipocyte and which prevents this electrochemical energy from being coupled to oxidative phosphorylation [46]. UCP1 is first regulated by triiodothyronine produced in the brown adipocyte itself by type 2 deiodinase (DID2) and leads to a deiodination at position 5 of thyroxine, creating a local and specific hyperthyroid state, independent of circulating levels of T3 and T4.

These triiodothyronine levels may in turn be regulated by food intake [87] and more importantly by the well-known activation of 3-adrenergic receptors after binding to epi- and norepinephrine as dopamine end products [88]. In patients with pheochromocytoma, this excess of catecholamines is able to increase BAT [89], and as counter-evidence one can point to the weight gain in hypertensive adults when receiving beta-blockers. Other regulatory factors of BAT and UCP1 lies in the presence of PGC1 (*peroxisome-proliferator-activated receptor coactivator 1*), and that would be responsible for the activation of the same and therefore of BAT when the subject is exposed to cold, or to high fructose intake in pregnant rats [47], and the same can be said about the role of AMPK (*AMPK-activated protein kinase*) that in both BAT and beige increases thermogenesis without shivering [90] or even liraglutide. In addition to UCP1 that can be histologically demonstrated in biopsied tissue, the role of mTOR (mechanistic target of rapamycin) should be considered for its role in addition to its functions as a protein kinase, in the thermogenesis without shivering precisely in beige adipocytes and its possible browning [85]. BAT cells can release bioactive lipids capable of inducing glucose and fatty acid incorporation thereby increasing its thermogenic capacity. Furthermore, among other mentioned effects which require further research, the activation of BAT produces beneficial changes in the homeostasis of cholesterol.

Assessment of the BAT's Activity

As we have just pointed out, the generalization of positron emission tomography (PET) techniques complemented with axial tomography made it possible to discover that radioactively labeled glucose (18 F-fluorodeoxyglucose, ¹⁸FDG) was incorporated by metabolically active tissues, mainly neoplastic. It was then seen how in the cervical region there was an important uptake, which could conceal the extension of the tumor and which in reality is nothing more than brown adipose tissue, making it possible to evaluate how the use of beta blockers reduces the activity of BAT, thus reducing the number of false positives in the practice of diagnostic scans and how its activity detected through the uptake [91] of 18FDG by BAT is associated with less central obesity and less hepatic fat deposition [92]. The tracer 18 F-fluorodeoxyglucose (¹⁸F-FDG) is used since this glucose analogue is avidly taken up by BAT [85]. The presence of fat in the area under study is confirmed by axial tomography (or by magnetic resonance), and together with the PET, they show through their own individual or combined images their symmetrical incorporation in the neck and upper part of the thorax in concordance with those obtained by means of the CAT scan, which with its gradation of colors indicates the amount of incorporation of the tracer and therefore of the activity of the brown adipocyte. Both series of images can be integrated and reconstructed in transaxial, coronal, and sagittal images and all this with a minimum radiation of 2.8 mSv. The new multimodal technique [93] that uses PET, MRI, and associated infrared thermography and activation of the BAT by ingestion of capsinoid or exposure to cold allows a more accurate assessment than PET/CT, but is not yet widespread. In summary, with the results provided by PET/CT, it can be said that after a high number of determinations, the BAT is present in a high percentage of

people studied, unlike what was previously thought (disappearance in adults) and how there is an inverse correlation between its activity and body mass index (kg/m²) and fasting blood glucose levels [86]. It has been clearly demonstrated that BAT activity increases when the body is subjected to an ambient temperature of 17–19 °C for 2 hours [85]. The use of this technique and cold-induced stimulation in a group of healthy individuals has demonstrated the aforementioned inverse correlation between BAT activity and BMI, with the percentage of body fat, estimated by DXA, and with lower core and skin temperatures. However, it has a positive correlation with the resting metabolic rate being especially significant when the sample is subjected to moderate cold. This study carried out on 25 adult volunteers adds data to the metabolic action of BAT. On a practical basis, it could be concluded that brown adipose tissue is present and active in human adults, and therefore it is logical that it behaves as such during childhood and adolescence. Cold-induced *browning* is via central sympathetic pathways and through catecholamines produced by local macrophages. Continued exposure to cold normally offsets this energy expenditure with increased food intake and probably better food absorption [94]. The inverse correlation of its activity with certain parameters ascribed to metabolic syndrome in pediatrics and in adults makes BAT one of the next targets for research in the growth stage, where it regresses [95, 96]. In the same way, it is useful to analyze its behavior in thin children and especially in obese children with their fatty layer of white subcutaneous adipose tissue which decreases thermal dispersion and makes the obese exposed to cold temperatures maintain their core temperature better. We have seen how in normal conditions an adult has an average of 10 g of BAT and with the various stimuli it can reach up to 50 g, and this, after classic calorimetric studies [97], would represent around 20% of the energy consumed in the resting state. This important quota, which is basic for maintaining temperature in the newborn and also at other ages, can be a form of control of energy balance [98]. Asprosin is an adipokine secreted by the white adipose tissue, and in addition to the regulation of hepatic glucose metabolism, on account of the central orexigenic activity, its overexpression in the WAT [99] inhibits the browning process reducing body thermogenesis and increasing lipid deposition in the adipocyte. The ability of BAT to lose calories by releasing heat has been an acceptable therapeutic target. In fact new clinical trials implementing energy expenditure are being carried out through anthraquinone derivatives [100] or sildenafil among others, more frequent in human cell cultures or in the ideal model such as the mouse [101].

Other Pathogenetic Aspects of Interest

Epigenetic Modifications

The Dutch famine that began in 1944 and affected mothers (and newborns) peri- and postconceptionally is perhaps one of the first clear examples of the negative nongenetic consequences that these descendants subsequently suffered and in this case linked to the methylation of noncoding DNA (mDNA) but close to the *IGF2*

gene [102]. In a later study on the same population [103] and with a double control, conventional of the same number (~400) of siblings, and genomic (~20,000), the association of mDNA with higher BMI and higher plasma levels of triglycerides in those who suffered the famine of the winter of 1944–1945 is evidenced 60 years later.

Unlike the stability of coding sequences (exonic), epigenetic modifications are dynamic and even reversible, being highly influenced by external factors such as nutrition. Thus, the intracellular methyl donor par excellence (5-adenosylmethionine) is affected by the unbalanced supply of micronutrients. DNA methylation at the cytosine level is the best studied epigenetic modification. It is known how it gives rise to different phenotypes that were initially studied in animal models (*viable yellow agouti*) where the diet rich in phytoestrogens (soy) was able to change the color of the hair coat of the mouse. To date, this evidence of how epigenetic mechanisms regulate the expression of certain genes related to obesity has been studied with respect to physical exercise, certain drugs, and even birth weight [104] or socioeconomic status. These studies are perhaps the best known, but the breakthrough in this important chapter comes from Mendelian randomization that adds precision [105].

Body Weight Regulation Independent of Conventional Homeostasis

It is that which acts outside the hypothalamic neuronal circuits and which, to date, has little significance in the regulatory role of the hypothalamus, as shown by the noteworthy publication in *Nature* [106] on transcription factors in the double population of neurons of the arcuate nucleus (control of energy intake and expenditure). Recently [107], areas of the brain outside the hypothalamus have been identified in mice that regulate appetite under conditions of metabolic stress through specific receptors for factors (GDE 15) that modify food intake. The same could be said of the set of enzymes regulating the intracellular fate of triacylglycerols, in particular of the FITM 1/2 [108] or the function of the lipin family of proteins so important in energy balance according to fat intake [109] or the regulatory importance of lean body mass [110]. In the intracellular field, mitochondria play perhaps a less well-known regulatory role. It is known that underweight in humans is associated with a higher activity of the mitochondrial matrix [111] when evaluated against normal-weight individuals by the higher number of mitochondria, higher respiratory capacity, browning rate, and adipocyte size. These mitochondrial functions are altered in the WAT of the obese individual [112]. The reasons are relatively unknown, and this field might include the vagal sensory endings both mechanical and for nutrients [113].

In the pathogenetic process of obesity, the interaction with clinical situations cannot be ignored. Insulin resistance will be discussed in detail in the chapter on *comorbid conditions*, but it is worth mentioning now how this resistance, after a Mendelian randomization analysis [114], is more closely linked to energy and carbohydrate intake than to genetic variants; this has opened up new avenues of research such as

the inhibitors of the glucose transporter families (GLUT 1-4), especially licogliflozin as a dual inhibitor of SGLT 1/2 (*sodium glucose co-transporter 1/2*) which, by also acting on the intestine, improves weight loss in obese adults. There are still many aspects that require more detailed studies, such as the case of oxidative stress or the personal response to the development of fibrosis [115] which, although general, in this case would affect the evolution of non-alcoholic fatty liver disease or the blockade of receptor II for activin with monoclonal antibodies and would benefit sarcopenia in TD2 [116], or the accumulation of chemical substances or heavy metals [117]. The positive aspect of physical activity and its relation to irisin levels [118] of adipocytic and/or muscular origin is a pathogenetic factor worthy of research.

If we go back to the beginning of this chapter where the importance of bioenergetic balance (first law of thermodynamics) is highlighted, it would seem that if we were able with our clinical means to balance energy intake with energy expenditure, the problem of overweight and obesity would be solved and also in a homogeneous way. We must however take into account some of the singular facts exposed, such as the measurement of balance [119] which is not applicable in clinical care, the variability that exists in the complex regulation of appetite [120], the neuroendocrine regulation with a multitude of actors and receptors [121] whose activity occupies a spectrum that varies between 0 and 100%, the fact that there are more than 2500 genetic tests available [122], the diverse functions and proportions of the adipose tissues [123, 124], or the importance of belonging to one gender or another. After extended studies in the line of GWAs, it has been possible to establish patterns called methylomes and transcriptomes [125], which can be highly useful since they show differences in methylation according to the location of the fat tissue, whether visceral or subcutaneous, and given the prognostic implication of the visceral fat tissue, all this allows a new approach to epigenetics. Only then do we become aware of the obvious clinical differences in apparently equal situations thus necessitating the need to consider accurate medicine for the problem of obesity. For example, if someone has more BAT or higher UCP1 activity, which would imply that a greater proportion of the energy ingested would be lost as heat and therefore would alter the outcome of that energy balance with lesser fat storage than someone in similar external conditions; or how the sustained elevation of a certain peptide may, in itself, imply significant pathologies, as will be seen in the next chapter when discussing the metabolic syndrome [126, 127]. From a pathogenic angle, even if a negative energy balance is the most effective weapon against this growing obesity, it is conceptually insufficient and not only because of what appears above. For this reason, new models are gaining relevance [11, 128], not only due to individual differences in the hypothalamic regulatory mechanisms, absorbed energy utilization mechanisms, or the final use of this energy, but all these lines of present studies [129] that are clarifying the functioning and activity of the affected tissues are absolutely necessary because more effective therapeutic actions will follow. Again, an ongoing Norwegian study [130] analyzes how among the more than 100,000 subjects genetically predisposed or not to obesity and after almost 40 years of follow-up the former have a higher BMI than the latter, but the latter not predisposed to obesity has also significantly increased their BMI, so the obesogenic environment has probably been the major contributor.

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Chapter 5

Clinical Features



Introduction

The clinical approach to the affected pediatric patient must be careful since, before establishing the diagnosis of overweight or obesity due to positive energy balance, endocrine disorders or syndromes that could be responsible must be excluded and the possibility of comorbidities examined. This desirable diagnostic accuracy is not a clinical nicety but a current requirement based on BMI z-score and waist circumference z-score without underestimating the stigma suffered by obese children, or the diagnostic delay of comorbid states, or the new aspects related to food intake, to mention only the most relevant questions. Undoubtedly, this will help in the better care and outcome of this, in general, long process.

The diagnosis of obesity does not pose major difficulties, since it is even made by schoolmates themselves but always requires delicacy. The stage of overweight that is often interpreted as a robust or corpulent child is different. Hence, at the slightest suspicion, the appropriate waist circumference (WC) and pediatric BMI should be calculated, which could perhaps be extended to a whole pediatric population or group in order to gain precision. Excess adiposity, ideally measured by MRI or DXA techniques, is quite acceptably estimated in clinical practice by BMI z-score (see Chap. 1), or the relative body mass index which is so precise and easy to use, also seen in Chap. 1. Indispensable WC or derived indexes such as waist-to-height-ratio (WHtR) [1, 2] are also informative in the 2–5 years age group, as was seen when this is applied to a large number of children [3] and also because of its better correlations with abdominal/truncal fat content [4]; in practice, in children aged 0–2 years, they have also been used acceptably. Unfortunately, the absolute index (kg/m^2) is not applicable in the growth stage because it varies over time, as discussed in the *Introduction and Concept* chapter. Figure 5.1 [5] shows how the cut-off points that by definition indicate overweight ($25 \text{ kg}/\text{m}^2$) and obesity ($30 \text{ kg}/\text{m}^2$) in adults have a decreasing value, which in the case of overweight would go from $25 \text{ kg}/\text{m}^2$ at 18 years of age to $17 \text{ kg}/\text{m}^2$ at 5 years of age. These curves, with a multiethnic basis

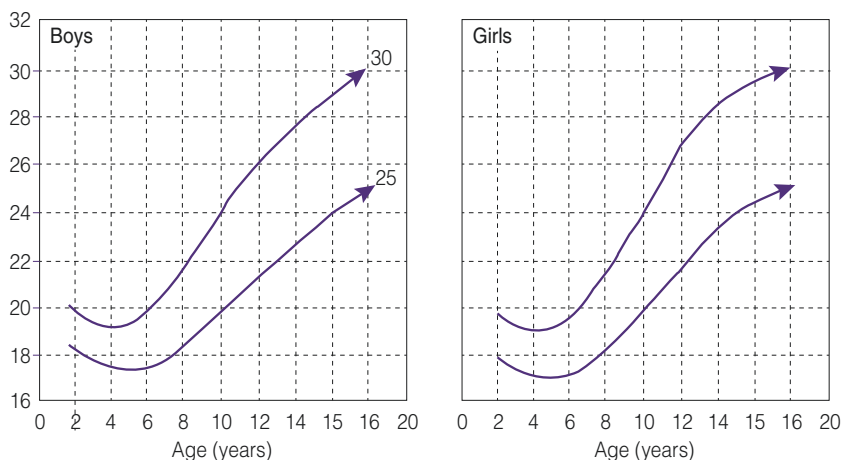


Fig. 5.1 BMI (kg/m^2) in boys and girls aged 2–18 years (Cole TJ, et al) [5]

and therefore with international applicability, could be used as *screening curves* to identify pediatric overweight and obesity. In the first 2 years of life, WHO *weight-for-length* charts have been used but have been less accurate in assessing obesity than the aforementioned BMI *z-score* in that time period [6]. That term should not be confused with the *waist-to-height ratio* [7], which would identify very simply excessive central adiposity when the ratio is ≥ 0.5 in the adult, but in the normal child, this ratio varies from 0.69 in the newborn to 0.41 in the adolescent, which would lead to the application of the *z-score* method to this ratio as it is a simple *screening* not only for obesity but also for risk factors for obesity, as will be seen later. The analysis of these curves allows us to assess the so-called adipose rebound, which is the period in childhood when the BMI begins to increase with respect to its lowest level. If this rebound is early, between 3 and 5 years of age, adiposity at 15 years of age is greater and correlates with its earliness more than when it is late (>5 years) [8]. This study also confirms how the precocity of adiposity should be taken into account, unlike the classic assumption that the onset of obesity begins at 5–6 years of age. In addition, early adipose rebound is associated with an increased risk of obesity persistence. The interest in obtaining a history of body weight or BMI is beyond doubt [9] and likewise the consideration of sex not only because of the SNPs (single-nucleotide polymorphisms) that according to sex are associated with obesity but also because of the greater fat deposit, now measurable or estimated, in girls. Within anthropometry there are clinical measurements, such as skinfolds or waist-hip ratio, which due to their lower reproducibility have fallen into disuse [10], although this is not the case of abdominal circumference. The classic WHO definition of 1995 is still valid: horizontal circumference measured at the midpoint of the distance between the lower edge of the last rib and the iliac crest loosely and at the end of a normal expiration (see full detail in Specific Anthropometry section in this chapter). When it exceeds 2 standard deviations (SD), it has very important prognostic implications, as will be seen in the discussion of metabolic syndrome, and its measurement and assessment should be mandatory. Once the overweight or obese state has been identified by *screening* with percentiles, the next step is to label it

correctly by calculating the *z-score* for BMI and abdominal circumference. This point is basic to assess accurately the preventive and therapeutic response.

The first visit should be framed in the maximum delicacy and understanding of the problem, and it should be pointed out that obesity is a chronic condition that will require a shared effort. The terms “obese,” “severely obese,” and of course “fat,” “chubby,” “pot-bellied,” “dumpy,” etc. should never be used and should be replaced by overweight or high BMI, as we will see later in the section on stigmatization. The anamnesis should include the degree of obesity of the parents and if possible, measure, weigh, and take the abdominal circumference of the accompanying parent. Specifically, it should be noted whether the following four circumstances are present: maternal obesity, maternal diabetes, if the birth weight was greater than 4.0 k, and if the duration of exclusive breastfeeding was <6 months due to their condition as risk factors for obesity from an early age [11]. The age and adipose rebound should be evaluated through BMI *z-score*, particularly where it is higher than the previous one. All this is completed with a semiquantitative survey [12] or a more elementary one on eating habits: the memory of the previous 24 h gives a good idea of food consumption but not the usual or episodic consumption, such as eating in the absence of hunger or snacking between meals or portion size [13]; never forget that, both to gain or lose weight, the energy intake is much more important than the composition of the diet. It is also necessary to note physical activity and screen time both on weekdays and, at the weekend, the child’s school performance and the family structure and lifestyle. Moreover, it is important to ask about the perception that both the parents and the child have of their own obesity and the desire to change, since this conditions future treatment [14], especially as 10–40% perceived themselves as normal [15, 16].

Finally, and within this family scenario, it is important to know the weight status of siblings, including children under 2 years of age who are not traditionally considered obese. There are two circumstances that possibly justify this: one is the increasing frequency of overweight at this early age, and the other is the greater respiratory morbidity and hospital admissions. It is beyond the scope of this chapter to discuss the accuracy of the methods for assessing calorie intake and those related to the hedonic reward of the perception and act of ingesting food already present in the child [17], but a tried and tested way in the adult can be found on the web (*Evaluating Calorie Intake*. <https://datasciencecampus.ons.gov.uk/2018/02/15/eclipse>) or the Yale food addition scale for children [18] and for the assessment of intake of sugar-sweetened or artificially sweetened beverages. For a complete history taking it should be considered the panel of six elements: General history, Growth history, Complication history, Famili history, Social history and Behavioral risk factors [19].

Clinical Findings

Within the general appearance of the obese child (Fig. 5.2), it is worth noting how in the face there is less facial fat deposition even in the seriously obese and hardly any double chin which is so typical of the adult. Deposits are more striking in the mammary area and in the pelvic area, which give rise to a buried penis (false hypogenitalism), which are worrying in the case of boys, leading them to abandon sports



Fig. 5.2 Obesity general appearance. Note the relatively minor fat deposition in the face and neck, gynecomastia vera, abdominal obesity, and genu valgum

that use common locker rooms and opens the way to isolation. The abdominal fat deposit should always be assessed, not only by abdominal circumference but also by more specific methods, as will be seen in the section on complementary examinations. The skin examination should be careful and complete. Acanthosis nigricans (blackish color of the back of the neck and armpits) could indicate a type B resistance (anti-receptor antibodies) to insulin. Red stretch marks appear on the abdomen, inner thighs, and breasts in the case of preadolescent and adolescent girls and are a cause for concern (it should be explained that while they are red, if you lose weight, they will disappear). Intertriginous dermatitis, especially in the groin areas, is frequent due to excessive friction and maceration. But there are no other longer associations [20]. There is a certain tendency for psoriasis to appear in obese adolescents, especially if it coincides with changes in the lipid profile. The conventional cardiocirculatory examination is usually negative but not the specific one or the blood pressure measurement tests, which often exceed the 90th percentile for gender and height, or the incipient increase in ventricular mass, as we will see below. Early fatigue is almost always observed in relation to excess weight and axial deviations (genu valgum). Something similar could be said with regard to the respiratory

system, but mention should now be made of sleep apnea, which sometimes leads to drowsiness (see below), although this is distinct from adult Pickwick's syndrome.

Some clinical aspects will be dealt with now, while comorbidities due to their own personality, especially cardiovascular disorders, type 2 diabetes, and fatty liver, as well as metabolic syndrome will be dealt with in the chapter *Comorbid conditions*.

Puberty and Associated Disorders

The obese patient has a greater height and growth rate than his or her age-mates. This is misleading because the maturational advance is related to the transformation of dehydroepiandrosterone (DHEA) into testosterone that takes place in adipose tissue (see Chap. 4, *Pathogenesis*). This results, among other things, in earlier closure of the fertile metaphyses and cessation of growth, with a lower final height. A large study [21] of nearly three million adolescents strongly contradicts this "dogma," concluding that elevated BMI is not a limiting factor for final height. Hypertrichosis, which is so often present in obese girls, may be part of this mechanism. The reality is that obese adolescents have an advanced puberty, with an advanced menarche, although in the male gender, this advance is not so constant. Polycystic ovary syndrome usually begins at puberty and is much more common in obese adolescents, and, although related to hyperinsulinism, it does pose specific problems in girls, such as hirsutism or menstrual irregularities. Recent data from the Danish studies [22] of preadolescent and adolescent girls show that overweight also leads to pubertal advancement compared to the comparative group of 3.1 months in boys and 5.5 months in girls, with very narrow 95% CI.

Gynecomastia

Obese boys very frequently present with gynecomastia, usually due to an imbalance between free estrogens and free androgens. During normal puberty and in its intermediate stages, the testis and other tissues may produce more estrogens before testosterone secretion reaches adult levels, resulting in the transient gynecomastia of that period [23] which usually lasts about 6 months. In addition, testosterone and low potency androgens such as DHEA can be converted into estradiol in peripheral tissues (fat) through the action of aromatase [22], as has long been known in cases of thyrotoxicosis or Klinefelter's syndrome but also because aromatase activity increases with age and especially with the increase in body fat which also includes subareolar fat [24]. Finally, and within this important hormonal basis, it should be added that estrone and especially estradiol bind less avidly to their normal transporter (*sex hormone binding globulin*, SHBG) than testosterone, thus increasing the bioavailable fraction of estrone and estradiol [25]. Free estradiol and also estradiol bound to albumin bind to their receptors in target tissues and initiate gene and transcription activation. In the genesis of gynecomastia, a series of factors must be taken

into account, such as the ingestion of certain herbal products (phytoestrogens), anti-androgens, phenytoin, metoclopramine and certain chemotherapy drugs. From the diagnostic point of view and in obese adolescents, the first step is to find out whether they have a true gynecomastia, bilateral in 50% of cases, or a pseudogynecomastia due to an exclusive increase in subareolar fat and therefore without glandular tissue. To do this, with the patient in the supine position and with the hands behind the head, placing the first and second fingers on the breast, we will try to bring them closer together. In the case of gynecomastia vera, a rubbery or firm, but not hard, mass is detected, which is concentric with the nipple-areola set, while in patients with pseudogynecomastia, this is not detected. It should be explained that during the early months, gynecomastia produces a feeling of discomfort in boys. The analytical determinations that should be performed are chorionic gonadotropic hormone (hCG), LH, testosterone, and estradiol, preferably in the morning due to the maximum peak of the circadian rhythm of LH and free testosterone. Usually, these determinations tend to be normal, thus ruling out the underlying pathology that most often causes gynecomastia. Of particular interest would be the finding of low free testosterone levels coincident with elevated LH, indicative of primary testicular failure, while low free testosterone levels with normal or low LH would be suggestive of secondary hypogonadism [26]. Gynecomastia should always be addressed therapeutically in the obese child or adolescent because of its negative repercussions. If the gynecomastia lasts more than a year, it is very difficult for it to return due to fibrosis, in such cases subcutaneous mastectomy plus liposuction is probably the treatment of choice. In the proliferative development phase, the use of estrogen receptor moderators (tamoxifen) has been useful in adult gynecomastia, but there is very little experience in the pediatric field, and it is limited to raloxifene. Neither have aromatase inhibitors (anastrozole) been widely used in the initial management of this condition. In general, these types of drugs should not be used here.

Sleep Disorders

They can be subdivided into two groups: first, those related to breathing and, second, those in which the shorter duration of sleep is conducive to the development or maintenance of obesity [27].

Obstructive Sleep Apnea (OSA)

The first group of sleep disorders includes *sleep-disordered breathing*, the best-known clinical exponent of which is obstructive sleep apnea or repetitive pauses in breathing despite respiratory efforts. This situation was well-known in adult men and postmenopausal women, but from the 1970s onwards, the most serious cases began to be described in pediatric patients, [28] and since then the correct

identification of the condition has only increased. In the now classic survey carried out in the United States by the *National Sleep Foundation*, the frequency was 1–3% in children under 10 years of age. These data were later confirmed (3.7%) after the analysis of the prevalence of *sleep disorders* in a population of more than 15,000 children aged 0–18 years [29], figures that increase considerably when they are referred to children with obesity [30]. The causes are mainly two: one, the increase of soft tissues around the airway, such as larger tonsils and adenoids and/or adipose tissue in the case of obese children, and, two, the decrease in muscle tone that occurs during sleep, especially in the throat and neck, which contributes to the collapse to varying degrees of the airway with non-hard tissue walls. The increase of adiposity, also affects the tongue, nowadays quantifiable by magnetic resonance imaging and its fat reduction improves apneas [31]. In addition to these two circumstances responsible for the chronic picture, there may be structural changes in the nose, mouth, or jaw, as is the case of Treacher Collins syndrome, Pierre-Robin syndrome, or Down syndrome in which macroglossia joins hypotonia. The family histories that are often collected suggest a genetic predisposition different from the syndromes mentioned above. Transient episodes of OSA are more typical in adults and perhaps adolescents (ingestion of alcohol or inhalation of irritants) but can also occur in children with acute upper respiratory tract infections. These apneas almost always occur during the REM (*rapid eye movement*) sleep phase, which accounts for 25% of all sleep time, in which dreams can be remembered, GH is released, and a restorative effect is produced, facilitated by the aforementioned hypotonia. Because of the alternation with the four stages (dozing, light sleep, transitional sleep, and deep sleep) of non-REM sleep, it is not always easy to locate it. Apart from apnea, it is perhaps worth remembering that stage 3 (or 4, according to the various designations) is where parasomnias occur (behavioral disturbances and short episodes of partial awakening) and when enuresis takes place. Apnea and decreased airway caliber [32] lead to blood gas disturbance, and when this becomes chronic, then the neuronal function of the hippocampus and right frontal cortex may be altered, which may account for the neurocognitive deficits that have sometimes been attributed to this disorder. From the clinical point of view, it should be considered that between the ages of 2 and 5 years and in nonobese children, a picture of OSA may appear in which the difficulty in breathing and sleeping at the same time is caused by muscular hypotonia and hypertrophy of the adenoid tissue. In the case of obesity, adipose tissue increases hypoventilation proportionally. The earliest and best recognized symptom is snoring, which is nothing more than the vibration of soft tissues, but it is the presence of documented apneas (>10 sec) that configures the clinical picture. In addition, oral breathing and restless sleep, in atypical positions and with micro-awakenings of which there is no subsequent awareness, are also recorded. For all these reasons, it is important to collect these data from the parents since, if the child is asked, he/she usually answers that he/she has slept well. The relationship between OSA and enuresis has been well established so that if a child is obese and also has altered breathing, then OSA should be suspected [33]. In severe cases there may be growth retardation, partly due to respiratory effort, as well as daytime sleepiness (Fig. 5.3) and a feeling of tiredness, but always less than

in adults. More questionable may be the neurocognitive deficit that has sometimes been described but which more recent studies do not corroborate. From the evolutionary point of view, this situation could lead to systemic and pulmonary hypertension, which can even be life-threatening.

The most appropriate complementary determinations are serial blood gas measurements (home pulse oximetry) and perhaps the finding of high levels of leptin or norepinephrine and epinephrine [34], which may justify new therapeutic actions. Special mention should be made of the polysomnographic study. In short, it is a multiparametric study (EEG, REM, EMG, ECG, SatO₂, airflow apneas, etc.) that records the physiological changes that occur during sleep through strategically placed electrodes that record REM or non-REM sleep and its phases (electrooculogram), muscle tension or excessive physical movement during sleep, basic cardiac function (two electrodes), and nasal and oral airflow through the pressure transducer. The indications for polysomnography are varied, from narcolepsy to restless legs syndrome, but in the case of obese pediatric patients, it is the suspicion of OSA or when fatigue or sleepiness appears during the day. As a result of this technique, *apneas* are identified as a complete or almost complete cessation of breathing lasting more than 10 seconds and followed by a micro-awakening which is nothing more than an interruption of sleep (EEG with alpha waves) lasting about 3 seconds and/or a desaturation greater than 3%–5%. The micro-awakening allows the recovery of the respiratory rhythm. *Hypopnea* consists of a 50% reduction in airflow for more than 10 seconds followed by micro-awakening and desaturation between 3%

Fig. 5.3 The fat boy. (This historic picture has the caption inside)



The Fat Boy, *The Pickwick Papers*, by Charles Dickens.

"And on the box sat a fat and red-faced boy, in a state of somnolency, whom no speculative observer could have regarded for an instant without setting down as the official dispenser of the contents of the before-mentioned hamper, when the proper time for their consumption should arrive. . . . 'Pray, come up,' said the stout gentleman. 'Joel—damn that boy, he's gone to sleep again.'"

and 5% [35]. In this situation it is necessary to assess serum bicarbonate levels. It should be made clear that polysomnography is not a routine indication in pediatric obesity and would only be indicated in cases of significant obesity and with obstructive symptoms. From the therapeutic point of view, tonsillectomy and adenoidectomy may be the preferred option in pediatric age groups. This operation is not trivial, and, in addition to the unresolved questions such as the natural evolution of OSA or the most appropriate age, any cause of muscular hypotonia or the existence of craniofacial anomalies must be ruled out previously, and, of course, the existence of this hypertrophy must be verified, for which magnetic resonance imaging is of greater precision. If this is the case, the results are usually positive as long as the degree of obesity decreases, the OSA disappears, and even the cardiocirculatory complications improve and the growth rate recovers in those cases where it had been reduced [36]. In Prader-Willi syndrome, upper airway obstruction leads to longer periods of hypoventilation than in children with apnea-hypopnea syndrome of similar BMI [37]. The treatment of adult OSA has brought new opportunities in the pediatric age. These include the application of continuous positive airway pressure (CPAP) or the use of oral applications for tongue positioning or mandibular advancement *splinting* [38].

Sleep Duration and Obesity

We have discussed in several chapters how, despite traditional preventive measures, the frequency of pediatric obesity is increasing, which has led to a search for factors that may contribute to this trend. A systematic review [39] of 31 cross-sectional and 5 prospective studies has already shown the independent association of sleep restriction and weight gain especially in younger children. Two proven facts in adults deserve to be taken into account: the first is that in the last 30 years, the percentage of people sleeping less than 6 h has increased significantly, [40] and the second is that when sleep duration is measured objectively by accelerometers, [41] the association is proven not only with higher BMI but also with T2D and hypertension. The reduction of daily sleep in normal children has also a negative effect on the mental health and cognition [42] therefore this effect is an added risk factor for the obese. This situation, more habitual and typical of adults, is already present in the pediatric age group, as shown by the FLAME study, [43] in which sleep duration was estimated by both a questionnaire and accelerometry. This study concludes that each additional hour of sleep between the ages of 3 and 5 years (the average was 11.3 h/day) reduces BMI by 0.48 SD at the age of 7 years and that this reduction is at the expense of fat tissue assessed by impedance and from the age of 5 years onwards by DXA. The study also points out how an excessive increase in sleep hours is associated with an increase in BMI. Therefore, the duration of nocturnal sleep should be considered normal when its duration at 2–3 years is 11–12 h, at 6–9 years 10 h, and in adolescence 9 h (www.nhs.uk/live-well/sleep-and-tiredness/). Given the large number of confounding variables (reported sleep duration, parental obesity, physical activity, etc.), more studies of this type are needed but with an adequate design.

The valuable Canadian study of more than 1100 children with assessment of the hours of sleep reported by parents showed how at 6 years of age a duration of less than 10 h a day from the age of 2.5 years was associated with excess weight. The same occurs when dealing with a preadolescent population where an hour less sleep at 10 years is associated with overweight (OR 1.55, CI 1.28–1.76) or obesity (OR 2.07, CI 1.55–2.84) at 13 years [44]. The same group later found [45] an association between less than 10 h of nightly sleep and poorer vocabulary (receptive) at 10 years of age (OR 2.67, CI 1.24–5.74). This is significant, not only because the debut of overweight at 6 years of age is a determinant of later obesity but also because it occurs in an important school period. Precisely the New Zealand study [46], carried out on more than 1000 children with information on the hours of sleep at ages 5, 7, 9 and 11 years and evaluated at 32 years, linear regression, adjusted for confounding effects, shows how sleep deprivation in childhood is significantly associated with higher BMI values in adulthood. Confirmation of the association between shorter sleep duration and the development of obesity in preschoolers, children, and adolescents has been provided by a systematic review and meta-analysis [47] that prospectively included more than 75,000 participants. Analytical data on sleep duration such as its association with telomeric length or the reduction of micro-RNAs (miR-26b-3p and miR-485-5p) in blood is coincident with fewer hours of sleep [48] may open new diagnostic and perhaps causal fields.

Psychosocial Problems: Stigma

In Anglo-Saxon literature, the term *weight-based stigma* has emerged with increasing force. It is the equivalent of the psychosocial problems of the obese child and which include less integration of the child in his or her network of friends or social network, low self-esteem, and depression, with the negative consequences that these three situations bring. The stigma of weight is experienced by both the child and adolescent and their family. The most important, most common, and least valued aspect of stigma is poor integration in the network of friends in their social environment [49], which initially leads to passive marginalization because of the well-documented group reaction to the overweight child's or adolescent's diminished attractiveness as a friend. This marginalization is sometimes augmented by a dislike response of the obese child to the group. It is noteworthy that this aversion to fatness has already been detected in normal preschools [50]. In a memorable reflection [51] on the stigma of weight, the following points were made:

The presence of stigma is a significant but largely ignored factor in the management of these children, despite its documented negative effect on treatment.

The components of stigma have a long-term effect, given their continuity in the obese adult, but another immediate effect by affecting the psychosocial well-being of the child or adolescent.

The fact of blaming the child and especially the parents only contributes to their inhibition, with the consequent therapeutic harm.

The neglect towards these patients also sometimes occurs in the medical establishment, as has been seen in adolescents undergoing bariatric surgery. It is striking that in the decade from 2007 to 2017, there has been an improvement with respect to social tolerance for other stigmatizing situations (disabilities, skin color, etc.) but not for excess weight [52]. Without going to such extremes, health professionals can favor the development of stigma not only through the terminology or language used with the child and the family but also by not placing themselves in the role of the patient [53]. With regard to the terms used, especially when the course of the disease is not satisfactory, the use of positive language is crucial, and the first step is to put the person first and the disease second: *a child with high or unhealthy weight rather than an obese person*. This should also be a factor when writing clinical histories and reports. Harsh (morbid obesity) or embarrassing terms are never motivators for weight loss. Sometimes, and to complicate this problem of stigmatization further, there are cases in which neither the child nor the family perceive the reality of the BMI, as they have an acceptable body image of themselves. And, on the other hand, there is also sometimes an excessive and not well-documented magnification of the psychological consequences of stigma. The application of simplified psychometric studies [54] to adult obese populations has been shown to be useful in detecting the internalization of stigma, and it may be worthwhile to encourage a pediatric adaptation of these studies. The psychosocial problems of the obese child or adolescent have generally been considered secondary to obesity and blamed on comfort eating or lack of satisfying interpersonal relationships, although this contributes to its continuance. However, the well-designed study [55] on 869 twins aged 7–13 years shows how worse executive functions of cognitive processing and selectively regulating attention are inversely associated with higher BMI values and with a primary character. The origin of this is in the discrimination and prejudices of the lean population, more evident in adulthood but already present in the child, who in the past could already be totally or partially considered as “lazy, dirty, stupid, ugly, cheater and liar.” [56] Once again, and adopting the message of the New Zealand multi-center study of Aotearoa, the most appropriate term to refer to obese children is high body mass index. With this prelude to passive marginalization, the next problem is that of *bullying* or victimization, which is followed by reduced self-esteem and, more rarely and in severe and prolonged cases, a depressive state.

Bullying

Bullying occurs when a boy or girl is exposed to repeated negative actions by one or more peers through physical contact, speech, or in other behavior, with the intent to harm or annoy and where there is an imbalance of power in favor of the *bullies* over the victims. The frequency of bullying appears to be increasing in places where no preventive measures are in place. In the European Union, there is a large study (16,000 children and adolescents aged 8–18 years) where the average number of bullied children was 20.6% of the whole sample [57], while in Switzerland and because of anti-bullying measures, the percentage is lower [58]; moreover, the fact

of suffering from a chronic pathology increases the risk (OR 1.53). In the specific case of obesity [59], its association with bullying has been demonstrated (OR 1.63). From a clinical point of view, it should be remembered that in 90% of the cases, the bullies are the victim's own classmates, including obese schoolchildren due to their greater corpulence. Adults (gym teachers, parents, and teachers themselves) can also victimize, and in this case the child tends to hide it more [60]. In 25% of the cases, the first to recognize the existence of the abuse is the child herself/himself, in 34% it is the teacher, and in 45% the mother [58]. Predisposing factors are an unfavorable school environment, a poor relationship with parents, and the fact of having suffered some other form of violence. Aggression can be direct, such as hitting or beating, stealing, threatening even with objects, or verbal aggression with name-calling or humiliation. Indirect aggression is produced by exclusion from the group or by slanderous rumors, and here cyber aggression plays a significant role (mobiles, *chats*, etc.). The response to bullying is very varied but always has a depressive base, with school failure, behavioral problems, isolation, or psychotic symptoms that can sometimes even end in suicide. These aspects should be taken into account if they appear in an obese child, since life at school and the school environment should be investigated. The chronicity of this situation is a fact and leads obese adults to develop comorbidities and to maintain or increase their degree of obesity.

Low Self-Esteem

Self-esteem consists of an emotional self-evaluation of one's own worth that involves thoughts such as "am I competent or incompetent, attractive or repulsive" and emotions such as success or failure, pride, or shame. In psychological terms, self-esteem contributes to the acquisition of a certain state of happiness or unhappiness. Low self-esteem, in general and in adults, is manifested by a series of reactions such as high self-criticism and dissatisfaction, hypersensitivity to criticism and resentment, chronic indecision and fear of error, hostility and irrational irritability, pessimism, and a general negative perception, among many others. In obesity, and especially in pediatric obesity, fortunately not all of these reactions are present, and low self-esteem is generally more limited. It is generally measured through the well-known *Self-Perception Profile for Children* [61] test, which is nothing more than an assessment of the perception of their body shape or appearance. In the important Australian study [62] which included more than 2800 11-year-old boys, other tests were used in addition to the aforementioned test to evaluate the physical aptitude and capacity, as well as the body dissatisfaction perceived by these boys. Using these parameters, the frequency of low self-esteem was found to be one in three boys and two in three girls. In another large study, [63] it was observed that at a 4-year follow-up and not initially, preadolescent or adolescent obese girls had a significantly lower self-esteem level than their normal weight peers. From the clinical point of view, a notion to consider is that not all obese people have low

self-esteem and even a small proportion of boys have high self-esteem. In the cases in which low levels appear, they usually manifest in the form of school absenteeism, school failure, perception of incompetence in sports, poor physical appearance, and poor relationship with their peers, and this leads to the appearance of sadness, isolation and nervousness, and, more rarely, eating disorders, being the greatest predisposition for this flowery picture the fact of belonging to the female gender, being preadolescent, and a high BMI and overweight parents. School absenteeism could be one of the initial and subtle signs of low self-esteem [64].

Up to this point, we have seen the reactions of obese children to the society around them, but society also plays an active part in their marginalization [65]: overweight adolescents are socially isolated and are much less accepted in social networks than those of normal weight, despite the fact that their list of friends is similar. Furthermore, they receive fewer friendship nominations from these circles (OR 1.71). This isolation aggravates the social and emotional consequences of overweight in this age group, creating an evident tendency to consume alcohol or tobacco or adopt risky behaviors.

The study of quality of life in relation to health [66] is a method that globally assesses psychosocial functioning, in this case in obesity, and its alteration indicates the imminence of depressive symptoms in adults with greater reliability than BMI, although in pediatric ages it is not clearly standardized.

Historically, the NHANES III study (1988–94) already showed the association of obesity with adult depression.

Depressive disorder [67] in obese children and adolescents may present in its three variants (*Diagnostic and Statistical Manual of Mental Disorders, DSM-IV-TR*):

- Major depression, which is a severe condition with recent onset (2 weeks), which manifests through sadness and loss of interest or sense of pleasure in any activity and in which what predominates sometimes is irritability.
- Bipolar disorder, in which episodes of mania appear, i.e., unexpectedly happy or enthusiastic, unreal high esteem, and also irritability.
- Dysthymic disorder, which is the most frequently found in obese boys, is of long duration (1 year) and where half of the days the boy appears depressed or irritable.

In subsyndromal depression, depressive symptoms are present but are not sufficient to confirm any of the aforementioned disorders. Therefore, if there is suspicion of depressive symptoms or a somatic symptom disorder (SSD), especially in morbidly obese adolescents, psychiatric support should be sought. However, it should not be forgotten that if the BMI decreases, competence and physical appearance improve, which should also be taken advantage of after bariatric surgery [68], and at that time it is important to adjust the aspirations of the child under treatment.

Musculoskeletal Disorders

The origin of these changes lies in the fact that neither the bone, nor the cartilage, nor the still open metaphyses are prepared to support this excess body weight. These changes in the musculoskeletal system are evident in the hip due to the increased load on it, which leads to a concentric contraction of the hip flexors [69], while at the same time, there is a greater load transfer to the more distal joints such as the knee and ankle and through plantar flexion. All of this causes a change in the gait of the obese child (with greater step width and longer stance phase), which is more evident when flat feet appear [70]. This leads to different pictures of the pathology of the obese adult (degenerative osteoarthritis) and will be discussed below. As for their prevalence, in a cohort study, obese adolescents showed a significant association (OR 1.33) with any type of musculoskeletal pain [71], the most frequent being knee pain. Although other locations vary with the various studies, the ankle and foot are frequent sites, and back pain is rarer and clearly related to higher BMI values [72, 73]. The frequency of fractures is significantly higher in obese boys when compared to a control group. Because of the excessive load on the hip, slippage of the femoral head is rarer in the acute form, but in the progressive form, the altered femoral head-neck *ratio* is a premonitory sign to look for in case of pain. A significant fact is the difficulty in mobility, due to the greater mass and axial deviations of the lower limbs of obese children compared to nonobese children, which increases the greater risk of falling and fractures (forearm fractures). If the bone mineral density estimated by DXA is related to BMI (BMD/BMI), the prediction of the risk of fractures increases considerably in the obese adult and, probably, also in the case of the adolescent. Prolonged excess adiposity in children and adolescents affects bone development and leads to greater bone fragility (reduced mobility, 25-hydroxycholecalciferol lower levels) which must always be taken into account [74]. Sarcopenia is a pathology specific to adults, but if a dual absorptiometry (DXA) scan also detects a lower muscle mass, a functional muscle scan would be indicated.

In the clinical examination it is common to find the presence of *genu valgum* with intermalleolar separation and flat feet proportional to excess weight and more rarely *genu recurvatum* due to hyperextension of the knee or Blount's disease (*genu varus*). All of them will last if the overweight is not reversed. This forced sedentary lifestyle due to motor difficulties, together with the possible chronic pain and inferior cardiorespiratory fitness, leads to lower quality of life indices than those of the nonobese [75]. Finally, and within this section, overweight children should perform certain physical activities, such as cycling or swimming, which relieve the load on the joints of the lower limbs and, therefore, the discomfort of other exercises.

Vitamin D

In relation to musculoskeletal alterations, it is pertinent to remember that adequate levels of vitamin D are necessary for adequate bone mineralization and for adequate muscle tone, among other actions in relation to the presence of receptors (VDR) in

various tissues and organs [76] and whose description goes beyond the present limits. However, it is appropriate to cite data from the NHANES 2003–2006 study [77] in which 25-hydroxycholecalciferol (25 D) values below 20 ng/ml are taken as deficiency levels. Thus, 29% of the population of overweight children present deficiency, 34% of obese children, and 49% of morbidly obese children, compared to 21% of normal-weight children. The proportion of deficiency increases according to the dark color of the skin. These data make it necessary to check 25 D levels in the obese population, especially in periods with less ultraviolet irradiation [78]. The causality that has been claimed for vitamin D repletion and the appearance of obesity and comorbid conditions has not been demonstrated, for the moment.

Additional Determinations

These are the ones that arise in a clinical case in order to establish the causality of overweight or obesity and if there are already comorbidities in the child and adolescent. This last circumstance will be discussed in more detail in the sections on metabolic syndrome and abdominal adiposity. It is essential to clarify what these basic determinations, which are normally limited to an evaluation of the blood count and basic biochemistry, should be. Basic determinations should not be confused with those that are the object of clinical research in childhood obesity and that sometimes appear to be necessary or even important. Typical examples may be the determination of microalbumin in urine or hemostatic alterations, all of them related to hypertension, cardiovascular disease or atheromatosis, or biomarkers in the deterioration of cognitive function, although if a hearing defect is suspected in association with obesity, an audiometry should be considered. A complete blood count is informative in a quick and easy way, and the assessment of iron status is possibly justified by the higher prevalence of iron deficiency detected in the NHANES III study and the more recent anemia of inflammation [79]. With respect to basic biochemistry, they are particularly informative, but they also show how ambiguous the border between basic determinations and those of research is; see the valuable cooperative study [80] where certain genetic variants are associated with the distribution of body fat and the elevation of plasma triglycerides among other aspects of the homeostasis of the obese and which imply diagnostic precocity. Serum levels of glucose, total cholesterol, HDL cholesterol, triglycerides, alanine aminotransferase (ALT), and uric acid must be assessed. With respect to uric acid, its elevation is an indication of larval hypertension, diabetic nephropathy, or CVD, as has been seen in adults when it is higher than 6 mg/dl. The daily urinary sodium and potassium excretion is an indicator for cardiovascular risk in children and adolescents particularly if higher of 2730 mg/day for boys and 2336 mg/d for girls [81]. In adolescents, the resistin/uric acid index would be prognostic for the evolution of BMI. The determination of basal insulinemia, if it is routinely available, is useful when considering the situation of insulin resistance. Also, if available fasting ghrelin elevation would indicate the insulin sensitivity recovery in favorable evolution [82]. For the moment, the study extended to certain amino acids, phospholipids, or acylcarnitines would not

be justified. The basic hormonal determinations (TSH, free T4, LH, FSH, estradiol, testosterone, 17-OH progesterone, DHEAS, etc.) should be performed when there is clinical suspicion that justifies it, such as the determination of cortisol in the hair as a symptom of stress. C-reactive protein should be mandatory in obese children and adolescents because by applying the fractional polynomial approach, the prognostic reliability of BMI can be increased, as has been seen in one of the collateral studies of NHANES 2001–2010 and also in west Mediterranean countries has demonstrated the usefulness of quantifying the levels of interleukins and other inflammatory markers already present in pediatric obesity.

Genetic Studies

There are several genes that affect energy pathways that predispose (or protect against) obesity. The question, at this point, is how many variants exist and whether they are common. Genome-wide association studies (GWAs) and exome-wide association studies are becoming increasingly available. The advantages of whole-genome (*next-generation*) sequencing are currently superior in scientific performance to whole-exome sequencing due to its resolution down to a single base [83]. These studies detect and reproduce associations between single-nucleotide polymorphisms or copy number variations and common diseases; see the chapters on *Etiological Factors* and *Comorbid Conditions*, where the relationship between gene variations and obesity is discussed. However, this type of study is not designed to link rare gene alterations to somatic alterations in a given individual. The increasingly better-known epigenetic reprogramming of maternal origin or as a consequence of environmental exposure is not addressed by GWAs, but the determination in saliva of epigenetic markers with DNA methylations characteristic of obesity could predict the future occurrence of overweight/obesity in a child with a still normal BMI [84]. Genetic obesity, specifically monogenic obesity as already seen, is rare and should be suspected in cases of severe obesity with onset in the first months of life, in cases of highly abnormal dietary patterns, in cases of associated endocrine or pigmentary disorders, and especially if there is consanguinity between the parents. Perhaps the MC4R gene mutations are the most frequent causes of monogenic obesities. It may be especially helpful to detect mutations of the complex locus GNAS [2] capable of producing varied transcripts responsible for diverse illnesses (McCune_Albright, pancreatic tumors, etc.) but also obesity alone, which, in that case, could be interpreted as caused by a positive energy balance.

Blood Pressure and Cardiovascular Assessment

Before entering into the necessary methodological aspects, it should be taken into account that, unlike in adults where the consequences of hypertension are widely known, in childhood and adolescence, such cohort studies hardly exist. However, it

is known that high blood pressure in children/adolescents is associated with silent intermediate cardiovascular states that are the origin of more serious situations in adults, among them, blood systolic and diastolic pressures, left ventricular hypertrophy or increased interventricular septum [85], increased carotid intima-media thickness, and VO_2 peak oxygen uptake if available, without forgetting routine markers [86] such as liver enzymes, plasma lipids, inflammatory markers, and uric acid, all in the context of the persistence of hypertension from childhood to adulthood [87], as already described in the Bogalusa study in 1995.

The description of this important chapter and the use of the available equipment will be dealt with in the section on comorbid conditions.

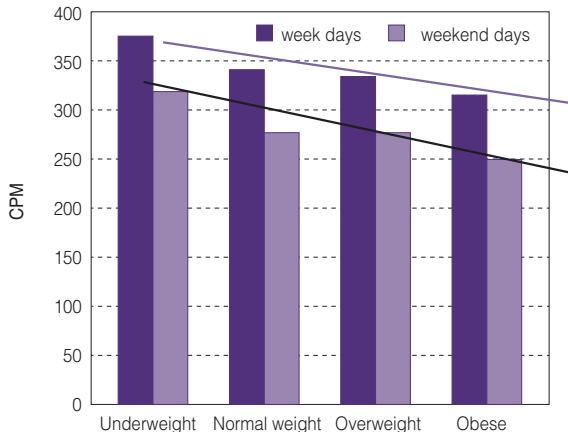
Assessment of Physical Activity

Physical activity (PA) is a basic component of energy expenditure that should always be attempted to be quantified with the same precision that is normally applied to energy intake but which is more complicated and probably less accurate despite the progressive use of accelerometers. These measurements are necessary given the trend towards sedentary lifestyles. According to a study of almost 52,000 participants, [88] the time spent by adolescents sitting (generally in front of screens) has increased from 7.0 h/day in 2007 to 8.2 h/d in 2016. This negative data should be known and contrasted with how greater physical activity, as shown by the Framingham Heart Study [89] conducted in adults with precise control of physical activity, is associated with a greater total brain volume estimated by magnetic resonance imaging. This implies a reduction in brain aging, which has long been suspected. The step counter, due to its simplicity and new personal availability, continues to be useful, as shown by the association of lower mortality from any cause with a higher number of steps (4000 vs. 12000 steps/day) [90].

When dealing with older children or adolescents, the use of the International Physical Activity Questionnaire [91] can give acceptable results, always bearing in mind the subjectivity that exists in the seven questions that refer to the last 7 days. As the child is younger, the difficulty increases, but the type of activity should always be recorded (the duration of the activity and whether it makes the child tired or not) and the time spent in front of screens (minutes/day), and this should be repeated for weekend days.

In the pediatric age, this more objective measurement was attempted through the use of step counters, although due to the type of movements, they have gradually been replaced by the use of accelerometers. These are based on the displacement of a mass contained in the sensor that is fixed to the body and that takes place with the movements that the subject makes. These displacements are stored in the sensor itself until they are downloaded to the specific computer program. The type of accelerometers has been changing up to the recent models that measure acceleration in three orthogonal planes (vertical, anteroposterior, and mediolateral), providing a vector with the activity counts of the three axes. The accelerometer used by us (Actigraph GT3X) measures $3.8 \times 3.7 \times 1.8$ cm and weighs 27 g. This allows it to

Fig. 5.4 Trend lines of physical activity expressed in counts per minute (CPM) in the underweight (UW), normal weight (N), overweight (OW), and obese (OB) groups on 2 weekdays (first column) and 2 weekend days (second column). (Note. Y axis represents CPM (counts per minute) going from 0 to 400. X axis represents nutritional groups from the original UW, N, OW, OB)



be attached by means of a light elastic belt on the nondominant hip at the level of the anterior axillary line. It measures accelerations between 0.05 and 2.5 Gs and with a frequency of up to 30 Hz covering the usual human movements. One problem, which in our experience is not completely solved, is the determination of the periods of activity and inactivity, and therefore in this prospective study, whose summary appears in Fig. 5.4, these sensors were worn for 4 consecutive days (Friday, Saturday, Sunday, and Monday) from 8:00 to 22:00 h, with the exception of the time that could be dedicated to aquatic activities. The results correspond to 207 schoolchildren between 6 and 10 years of age who attended 3 public schools. It is observed how PA decreases during weekends and how it also decreases according to the degree of overweight. The conclusion at the time of this study, in line with others of similar design [92], is that physical activity is not particularly intense, that it is lower as body mass index increases, and that, for the total population, it decreases significantly during weekends, possibly in favor of leisure time in front of screens. Recent evidence of excellent agreement between the values obtained with this technique and those obtained using double-labeled water techniques supports the use of accelerometry at the present time [93]. These circumstances of inactivity constitute a risk and contribute to the continuance of childhood obesity, especially when a certain lack of family response to the knowledge of these objective data is added.

Specific Anthropometry: Abdominal Fat Assessment

Anthropometric measures should always be taken with maximum rigor (stadiometer, electronic scales, inextensible tapes, dinamap blood pressure devices (oscillometry), specific waist circumference methods, WC): child in a standing position and the tape horizontally placed at the midpoint between the lower costal and upper anterior iliac apophysis. The tape should not be too tight or too loose and reading should be to the nearest 0.1 cm at the end of exhalation. Before recording the result,

changes in the centimeter readings are assessed (left to right) with respiratory movements. For height and WC readings preferably in centimeters, centiles, and z-scores should be obtained through any anthropometric program based on IOTF standards. Also is important the target height (Molineri) and midparental height ± 6.5 cm for boys and girls.

To frame the clinical importance of abdominal fat and its association with comorbid conditions, it is convenient to take into account the data offered by the CDC [94] which, in relation to diabetes, can be summarized as follows: 80 million Americans suffer from prediabetes mellitus, 95% of whom are prediabetic type 2 (DT2) and 27% of those who are already diabetic are unaware of it. In young people from 10 to 19 years of age, the proportion of type 2 diabetes is 0.46/1000 (these values include American Indians). In the general European population, the incidence is 5–10% of diabetes mellitus (95% DT2) and corresponds to that mentioned for the United States. The importance of abdominal fat is supported by the careful systematic review published in BMJ [95] and where higher values of anthropometric indices and methods that assess it are significantly associated with a higher risk of all-cause mortality and the important issue is how this fact is in general ignored.

In adults, the comorbid conditions with the greatest clinical impact are cardiovascular disease (CVD), T2D, and sometimes nonalcoholic fatty liver disease (NAFLD), all of which were almost always preceded by metabolic syndrome. The MS comprises obesity, impaired glucose metabolism, hypertension, and dyslipidemia, according to the widely accepted definition of the *International Diabetes Federation* (see Chap. 6). Insulin resistance, which is closely linked to central obesity, is now considered, together with certain adipokines, to be the most important mechanism in the development of these conditions. In addition, comorbid conditions are already present in pediatric obesity, including reduced bone mass in the case of insulin resistance, and this is steadily increasing worldwide, as shown by several prospective studies [96].

This lesson from adult medicine [97] soon permeated the field of pediatric obesity. Truncal obesity in the child is a key factor for the development of this situation of insulin resistance [98], and its persistence (and estimations) from childhood to adulthood is a basis for the genesis of the aforementioned comorbid conditions. Due to their continuity into adulthood, where all comorbid conditions represent a health problem, their prevention is currently gaining interest among pediatricians.

Evaluation of the Central Fat Content

In Chaps. 4 and 6, visceral or abdominal adiposity is described in the light of quantitation, namely, through new imaging with precision obtaining information on the risks of this fat location. Therefore, more pragmatic methods are of interest and have been assessed on their higher sensitivity for detection of fat in this area. Margaret Ashwell [2] accepting a boundary value for the waist-to-height ratio of 0.5, i.e., waist circumference, should measure exactly half a person's height.

Woolcott [99] developed two equations for two age segments:

The labels are relative fat mass peditrics (RFMp), and results are estimated as a percentage (%) of total body fat.

$$\text{RFMp}(\text{for 8 to 14 years}) = 74 - (22 \times \text{height} / \text{waist}) + 5 \text{sex}$$

$$\text{RFMp}(\text{for 15 to 19 yeas}) = 64 - (20 \times \text{height} / \text{waist}) + 12 \times \text{sex}$$

Note that for both equations, male = 0 and female = 1, and results are given as percentages.

The abdominal perimeters, WHtR (waist-to-height ratio) and RFMp (relative fat mass peditric), are simple anthropometric estimators that assess the risks of truncal fat [100] and are considered a reliable method but probably subjected to the same controversy as the cut-off points for the definition of waist circumference obesity, overweight or underweight, etc. Furthermore, it is not easy to obtain a unified standard either for adults [101] or for children or adolescents [102–104]. The use of computer programs (Seinaptracker) allows the calculation according to age and gender of the value, not only of the percentile but also of its *z-scores* [105]. This distance to the mean value of a reference population allows a precise comparison of a person or a group of people in relation to that reference line. In our case, it is considered to be overweight when the *z-score* is between 1.0 and 2.0 SD and obese when it is greater than or equal to 2.1 SD. At present, this use facilitated by the *z-score* simplifies *screening*, follow-up, and better comparability between different populations. The reality is that this simple parameter is not as widely used as it should be, given its ability to estimate abdominal adiposity as demonstrated in a study of more than 70,000 Chinese children and adolescents [106]. There is a biochemical marker, erythritol, which is synthesized from glucose, but its clinical use requires longer studies.

Evaluation of Body Composition

Visceral fat is located (Table 5.1) in the abdominal cavity between the stomach, liver, gallbladder, spleen, pancreas, small intestine, and mesentery and large intestine, all of which are intraperitoneal. Perirenal and epididymal fat is considered visceral even if it is extraperitoneal. Fat stored in the hips, buttocks, and thighs is considered as subcutaneous, with much less relevance in the genesis of comorbidities. How the various locations are evaluated is another problem that has given rise to much speculation regarding the techniques used. In a general way, it can be said that current ultrasonography is not recommended for a total assessment, but it is recommended for quantifying the fat content of the liver or pancreas [107], as will be seen in the next chapter.

Certain terms are used synonymously but should be used more appropriately. Thus, for example, *visceral fat* and *total abdominal fat* are appropriate for fat

Table 5.1 Harmful effect or no effect of fat according to its location

Visceral fat is found in the abdominal cavity between:

- Stomach
 - Liver
 - Biliary gallbladder
 - Spleen
 - Pancreas
 - Small intestine
 - and mesentery
 - Large intestine
 - Perinephric fat and epididymal fat
-

Subcutaneous fat comprises:

- Trunk
 - Hips
 - Buttocks
 - Thighs
-

measured by MRI, which is the gold standard for these measurements, whereas *truncal fat* and *total body fat* should be used for DXA measurements. The correlation between the two measurement systems is excellent, as is, to a lesser degree, abdominal circumference [108] (or waist-to-height ratio) as the primary indicator of *abdominal obesity*. The truncal fat values are those obtained with the dual energy X-ray attenuation technique, and the name responds to the assessment of fat in the trunk area that normally ends in a line that is located on the highest part of the iliac bones, and the top line can have different heights depending on the technique used; this is an advantage over the determinations by means of axial tomography that measures a series of slices of about 10 mm thick. The regions studied by DXA can be the trunk, the abdominal cavity, the limbs, or the whole body. This is achieved with reasonable precision, with little radiation for the patient (0.2 uGy), and with no discomfort [109, 110]. This technique does not allow the separation of subcutaneous fat from visceral fat, but its precision has been increasing even with simple procedures such as patient positioning [111]. Currently it is possible to measure and differentiate the superficial subcutaneous, deep subcutaneous, and visceral fat by means of volumetric magnetic resonance imaging. Elevated interscapular fat mass evaluated by MRI is associated to insulin resistance [110].

To see the usefulness of this technique, it is appropriate to comment on the results of a previous prospective study [112] that allowed us to evaluate the possible action of conjugated linoleic acid (CLA), particularly the 18:2 c10- t12 isomer due to its moderate anti-adipogenic effect shown in obese adults [113] and in children and adolescents [114]. Two groups were formed (CLA and control) with the same therapeutic regimen (diet, physical activity program, and lifestyle change). Only the CLA group ($n = 26$) received CLA, at a rate of 40 mg/kg/day (milk), compared to the control group ($n = 27$) which received semi-skimmed milk in a similar volume. Every 2 months and until completing the year, the patients were evaluated in the nutrition clinic, where height, weight, arm, abdominal, and hip perimeters were measured, as well as the degree of adherence to the therapeutic program. A

biochemical determination and a DXA scan were performed at the time of incorporation and approximately 1 year later. The most relevant results are shown in Table 5.2. From these data it can be seen that in both groups (control and CLA), there is a significant decrease in rBMI and BMI *z-score*. In the case of the former, as the results are given as a percentage, it is better understood by the parents and by the children themselves, and the BMI *z-score* allows for a more appropriate study. The same significant reduction occurs in the *z-score* of the abdominal circumference. Another data that deserves a comment is that of the growth rate: there was no reduction in it, which may be related to a better adjustment of the energy intake that did not reduce growth. The biochemical parameters that define MS in our unit (fasting insulin, glucose, cholesterol, HDL cholesterol, and triglycerides) showed no changes after the study period when considered as a whole, but they did improve in cases in which there was initial MS, and blood pressure was reduced in all cases. When assessing the evolution of the percentage of fat, a significant reduction was also observed both in the whole body and in the trunk, especially when considering the trunk as a region, that is, when assessing fat tissue, lean tissue and bone tissue together. The total body fat content decreased significantly in both groups, control and CLA, and the trunk fat content behaved in the same way. The differences in the *z-score* of the percentage of trunk fat when subtracting those obtained after 1 year of evolution from the initial ones did not show any significance between the control and CLA groups, although in the latter the differences were even smaller. This was not in agreement with the anti-adipogenic effect of CLA that was described in adults and which led to its abandonment. At the present time, there are more than 200 children assessed by DXA, and when the percentage of truncal fat is higher than 40%, this is when we can speak of visceral adiposity as a criterion of metabolic syndrome. After the study of correlations between the different variables, the strongest association was obtained between the percentage of fat in the truncal region and abdominal circumference ($r = 0.67$; $p < 0.0001$).

Table 5.2 Main anthropometric differences after 1 year of intervention [112]

	Initial	Final	P
CLA group	<i>n</i> = 26	<i>n</i> = 26	
IMCr	154,8 (14,5)	140,6 (13,8)	0,028
IMC-ZS	4,2 (1,6)	3,01 (1,1)	0,001
PA-ZS	3,1 (0,8)	2,3 (0,8)	0,002
% Total fat	45,4 (4,7)	42,4 (6,3)	0,002
% backbone fat	47,5 (4,8)	45,1 (6,5)	0,002
ZS-zero speed of growth	0,29 (2,2)	0,69 (2,7)	0,1
Control group	<i>n</i> = 27	<i>n</i> = 27	
IMCr	147,8 (20,1)	141,4 (23,1)	0,002
IMC-ZS	3,5 (1,5)	3,0 (1,6)	0,005
PA-ZS	2,4 (1,7)	2,1 (1,5)	0,003
% total fat	42,2 (6,5)	39,7 (7,1)	0,02
% backbone fat	44,3 (6,0)	41,7 (6,4)	0,2
Growth rate-ZS	0,21 (2,5)	0,62 (2,2)	0,1

CLA conjugated linoleic acid; mean (SD); BMI, body mass index, relative; z-score; BP, abdominal circumference

It is evident that the abdominal girth or its derivative estimators can be a simple method to approach the fat content of the abdomen, but it is not free of sampling errors. Moreover, it is probably not ideal considering that in children and adolescents, the secretion of insulin and leptin, respectively, by the beta cells and by the adipocyte of the white adipose tissue is only proportional to the fat content of this area. Therefore, the greater the precision in the assessment of this fat location, the better the diagnostic and intervention possibilities will be.

One of the drivers for the assessment of truncal fat, in addition to the aforementioned insulin resistance, is leptin resistance [115]. The increased production due to the increase in adipocytes during the prolonged period of obesity leads to resistance in the arcuate-paraventricular axis, with a consequent decrease in satiety [116], which contributes to the continuance of obesity. The finding of a relationship between visceral adiposity and cognitive function in the child [117] has led to functional magnetic resonance imaging and diffusion tensor imaging of the brain (DTI) studies of food supplies that will have therapeutic implications [118]. This leads us again to assess the existing correlation between abdominal circumference or waist-to-height ratio (>0.5) or RFMp ($>30\%$) and central fat, especially in overweight children [119, 120], which is where prevention should be targeted. The truncal fat estimated by DXA [121] showed the existing correlation with insulin resistance, and with this same technique, it has been possible to see the association of fat content with inflammatory markers and with hypertension [122]. In addition, it allows a more precise assessment of the anti-adipose effect of certain products, as we have seen above. But perhaps the most important consequence that can be drawn from measurements of truncal fat is that it is itself a predictor of the duration of obesity [123]. There are also important consequences associated with truncal obesity, such as accelerated growth [124], increased ventricular mass and interventricular septum [125, 126], impaired endothelial function, [85, 127] or non-alcoholic fatty liver disease [128, 129], all of which are of profound clinical significance but whose risk can be reduced by an early therapeutic approach to pediatric (truncal) obesity. This should be initially assessed through the established *screening method* (abdominal perimeter *z-score* and especially according to the waist-to-height ratio). However, when it comes to cases of severe obesity or with the occurrence of one of the aforementioned comorbid conditions or a clinical trial, then a more precise assessment of central fat is probably more appropriate. New technologies based on a 3D photonic laser /3 dimensional optical images (3DO) are highly sensitive in detecting body shape changes on fat mass when compared with DXA, providing more accurate measurements and maintains good correlations with common variables at lower cost and no radiation [130].

To conclude this chapter on clinical aspects, it is necessary to point out an unresolved problem, which is that of the pharmacodynamic alterations that obese children present [131] and that sometimes involve administering inadequate doses that are often toxic (aminophylline) or insufficient (antibiotics) when using total weight as the only criteria [132].

A similar type of reflection could come in response to the emergence of certain (neuro)peptides as responsible in open or hidden models [133], or new gene mutations [134] that probably have a future in clinical obesity, but we should avoid over-enthusiasm, as this requires more time.

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Chapter 6

Comorbid Conditions of Pediatric Obesity



*To make the perishable last well, to delay the scheduled time.
Marguerite Yourcenar, Opus Nigrum 1968*

Concept

In the 1970s the term comorbidity or comorbidities was coined by Alvar R. Fenstein in the USA for the presence of a different disease or conditions with the primary disease or disorder, usually adding complexity to the patient of any age as in the case of obesity. In reality, it is a generic term that encompasses the complications that accompany obesity. The borderline between what is purely clinical obesity, for example, sleep apnea or *genu valgum*, and the appearance of a comorbidity (hypertension, hyperuricemia, etc.) is not always well defined. The list of comorbid conditions can vary depending on the approach, as may be the case of health insurance, but usually includes those that have their own pathogenic substrate, their own therapeutic context, and are usually severe. Hence, the term cardiometabolic risk (CMR) is increasingly used for its designation. The pediatric field usually includes associated conditions appearing in adult ages, among others, hypertension/cardiovascular disease (CVD), type 2 diabetes (T2D), and non-alcoholic fatty liver disease (NAFLD), while dyslipidemia, respiratory, hemostatic, osteoarthritic, soft tissue infectious, cerebrovascular, obesity-related gastrointestinal disorders and depressive or chronic fatigue disorders are commoner in adults. The next three conditions T2D, hypertension, and non-alcoholic fatty liver disease are considered the most significant in children obesity, because of their frequency and because they can result in premature death. The presence of pediatric psoriasis should be assessed due to the predisposition for suffering comorbidities. Although these three appear in pediatric obesity, they are often not adequately evaluated due to their clinical

subtlety and the general idea of the absence of these problems in children's health; that probably mean that an early preventive opportunity is lost, and also in the subsequent years as young adults this specific comorbid status will have a high economic cost that has already been quantified in some countries. Within the concept of comorbid conditions, it should be mentioned that their basic causality lies in adipocyte hypertrophy and expansion of adipose tissue, and, therefore, the simplest, most widely accepted screening method with the best correlation with cardiometabolic risk (CMR) is the body mass index (BMI) (z-s or centiles), in addition to the assessment of abdominal circumference. Although a series of pathogenetic factors intervene to a greater or lesser extent in its genesis, the procedure within our reach and the least harmful for its prevention and treatment lies in a negative energy balance.

Prevalence

For the analysis of the prevalence of comorbidities and their pathophysiological bases, a literature search was carried out using *PubMed*, *Cochrane Database of Systematic Reviews*, *Medscape* (for treatment), and *Scopus*. After the search the number of references obtained was *Scopus* 286, *PubMed* 142, *Medscape* 78, and *Cochrane Database* 17. In the first two searches, the time limit was 10 years and restricted to humans. Only the *PubMed* database allowed a controlled search, and the ad hoc descriptors used were *Fatty liver*, *Metabolic syndrome X*, *Comorbidity*, *Obesity*, and *Abdominal Obesity*, after the primary selection, the results obtained from the *PubMed* database were chosen due to the fact that they united the free and combined search, the summary of which is given below.

It is logical to think that as the prevalence of obesity increases, so will the prevalence of comorbidities, but while this is clearly the case in adult obesity [1], it is not so evident in the pediatric age group due to the lack of longitudinal multicenter studies. Nevertheless, it is important to know the trends of overweight and obesity because these will mark those of the various comorbidities (see Chap. 7). It is therefore necessary to assess the incidence and present trends in obesity. The data on prevalence of overweight provided by the *Global Burden of Disease Study 2013* [2] are clearly informative due to an impeccable methodology that has collected the evolution over the last 33 years of data from 188 countries (developed and developing) of the 6 health regions of the world and referring to population groups defined by gender and age. A summary of this serious and global increase is shown in Table 6.1. In adults, overweight is defined as when the body mass index (BMI or Quetelet's index, weight in kg/height in meter squared) is over 25 kg/m², and obesity is defined as when it is over 30 kg/m² and, as an indicative reference, when the abdominal circumference is over 100 cm (or the waist-to-height ratio > 0.5). In addition, the respective definitions in children are when the relative BMI (actual BMI/50th percentile BMI × 100) is over 110% or a *z-score* > 1 SD, in the case of overweight, or a relative BMI (rBMI) of 120% or a *z-score* > 2 SD, in the case of obesity. The abdominal circumference can also be assessed by means of the *z-score*.

Table 6.1 Estimated global prevalence of overweight and obesity by age and gender, 1980–2013 [2]

Population	1980 (%)	2013 (%)
Men > 20 years old	28.8	36.9
Women > 20 years old	29.8	38.0
Boys < 20 years old	17.1	23.8
Girls < 20 years old	16.3	22.6
Boys in LMIC	8.1	12.9
Girls in LMIC	8.4	13.4

LMIC low- and middle-income countries

This is due to the growth that invalidates the crude BMI (kg/m²) formula used in adults.

Epidemiology. The following data are complementary to those presented in Chap. 2, *Epidemiology*. It is noteworthy how in high-income countries and from 2006 onwards a slowing of this trend is perceived, but this should be welcomed with caution as the specific biases [3] that occur in the epidemiology of obesity may contribute to these variations. Particularly in some countries, including in the Western European (WE) region and with data referring to 2013, the estimated prevalence of overweight and obesity for men is 62.3% (WE 61.3%), for women 46.5% (WE 47.6%), for boys under 20 years of age 27.6% (WE 24.2%), and for girls under 20 years of age 23.8% (WE 22.0%). Spain ranks fourth behind Malta, Greece, and Italy. Another disturbing fact is the increase in the incidence of pediatric obesity [4], if by this term we mean the appearance within a group of a new case of obesity in a child who was not previously obese during a given period of time (1 year). The cumulative incidence over 9 years in 13,614 American schoolchildren was 7.9% for those who were initially (5 years of age) normal weight and 31.8% for those who were overweight. This already raised the question of prevention from this age. To conclude this epidemiological approach, the predictive studies of the WHO and other entities indicate that the global epidemic will continue to increase until the decade 2020–2030 [5] and only after that date will it decline. On the other hand and with data from the CDC [6], the annual incidence rates for the entire North American population would have decreased but will remain at 40%. To these figures should be added the more precise figures from countries that epidemiologically undergo transition from non-communicable to communicable diseases.

In addition to the serious problem posed by this upward trend in prevalence, we must also consider the social burden of obesity [2]. In 1910, and across the world, it was estimated that overweight and obesity caused 3.4 million deaths, 4% of life years lost, and also 4% of life years adjusted for disability. In the pediatric field, the cost of an obese child compared to a normal child is \$20,000 more until adulthood [7]. Finally, and within this far from positive panorama, we must consider the lack of adherence of physicians to the guidelines for the diagnosis and treatment of the comorbidities of pediatric obesity [8], where, for example, at the time and in the German-speaking area, hypertension was only assessed in 88% of cases and dyslipidemia or *screening* for type 2 diabetes in 60%.

Prevalence of Selected Comorbidities

It is difficult to estimate their frequency due to the lack of uniformity in the diagnosis of T2D, CVD, or NAFLD in the pediatric age group. In a valuable non-systematic review [9], an estimate was made for the entire European pediatric population of 20,000 cases of T2D, 400,000 cases of impaired glucose tolerance, and more than one million cases of cardiovascular stigmata. More recently the NHANES study 1999–2008 [10] on more than 3000 participants aged 12–19 years showed a prevalence of 14% according to the terms of that time for prehypertension/hypertension, 22% for pre-/hyper-LDL cholesterolemia, 6% for low HDL cholesterol levels, and 15% for prediabetes/diabetes. In another study [11] cardiometabolic risk factors (CMR) were increased in the case of adolescents and young adults with overweight or obesity especially in the male sex. One of the problems underlying the underdiagnosis of hypertension is the lack of rigor in its measurement: in 2/3 of the cases, it was not measured and sodium intake was ignored [12]. Finally, and within the chapter on hypertension, a systematic review with meta-analysis on more than 50,000 children [13] showed how being overweight or obese implied a systolic pressure of 4.54 mmHg or 7.49 mmHg, respectively, higher than normal controls. According to our own experience [14] and assessing the thickness of the interventricular septum, this was significantly higher in overweight and obese cases that were considered cardiologically *healthy*. It is curious how the figures relating to NAFLD do not appear in these studies, but they will be considered later. The incidence of type 2 diabetes in young people aged 10–19 years experienced an increase of 4/100,000 between 2002 and 2015 [15]. Along with comorbid conditions, it is appropriate to include metabolic syndrome (MS) or perhaps more pragmatically some of the parameters that comprise it because of the precursor nature of comorbidities and hence the consideration of its frequency. With data from the NHANES III study (2003), which assessed nearly 2500 adolescents between 1988 and 1994 through the *National Cholesterol Education Program, NCEP (Adult Treatment Panel III)*, the prevalence of metabolic syndrome was 4.2% in the general adolescent population and 28.7% in cases of overweight. Substantially similar data appear in different studies during the same period. If we take this population as a reference in the last 20 years and using the same definition (NCEP), the prevalence has already doubled [16], even in emerging areas [17]. More recently and in the specific study of systematic review and meta-analysis [18] and circumscribed to hypertension, T2D, non-alcoholic fatty liver disease, and dyslipidemia, the frequency is higher in obese adolescents than in control groups of the same ages.

Causes of Comorbid Conditions

Why these appear is unclear; however, there is an association between them and dietary habits, sedentary lifestyle, and certain socio-environmental factors, but it is clear that these factors are mainly related to obesity. Therefore, some facts that could be more specific to the comorbidities addressed should be analyzed.

Feeding

Continued ingestion of calorie-dense foods is probably the most important cause of pediatric obesity and subsequent cardiometabolic risk, especially if they coincide with a nutrient-poor diet. The Raine study, carried out in Australia [19], showed how increases in glycemic load assessed after a 3-day survey increase the risk of metabolic syndrome. Similar conclusions were reached by a large study in American adolescents [20]. Data from the German nutritional cohort study (GINI) in its most recent and coincident analysis also includes excess animal protein. Increases in plasma uric acid levels in preadolescents, as will be seen later [21], coexist with other cardiometabolic risk factors. Data from the NHANES study 1999–2006 [22] are consistent especially when there is an increase in abdominal circumference. This data is so significant that studies have been undertaken on the specific trend of abdominal obesity in children and adolescents. Factors that could be considered for inclusion in the metabolic syndrome, such as fasting insulinemia, HbA1c, high-sensitivity CRP, or uric acid itself, only increase the predictive level of the syndrome [23], especially if they are accompanied by an increase in abdominal circumference. Moreover, if there is an excessive intake of energy and fat, this constitutes a significant risk factor for the development of comorbidities. Obesity in adolescence is particularly serious as it implies a higher degree of cardiometabolic risk than when it starts in childhood, due mainly to the polygenic contribution to hypertension, even when children are still normotensive [24]. This can be a paradigm for other comorbidities.

Physical Activity

If sedentary lifestyles are considered first, it is clear that screen time in excess of 35 h per week increases the prevalence of metabolic syndrome and comorbidities [25]. Moreover, it has also been shown that when screen time is more than 2 h a day, this widespread habit will continue into adulthood. Interestingly, in the NHANES 2003–2004 study [23], it has been shown as counter-evidence that vigorous exercise is not associated with comorbid conditions. Sleep duration of less than 8 h per day in obese children is also associated with metabolic syndrome. Today, in addition to shorter sleep duration with well-established limits (www.nhs.uk/live-well/sleep-and-tiredness/), the timing of sleep should also be assessed because its interference with circadian rhythms favors an increase in BMI (see below [26]). All these circumstances, when added to mechanization, heating, and fewer safe play areas, will contribute to obesity and, subsequently, to comorbidities.

Mandatory information on cardiometabolic risk factors (CMR) is necessary if they are to be neutralized. This would be possible in the causes mentioned above, but is less feasible, for example, in the case of polygenic hypercholesterolemia or the presence of endothelial microparticles. The list can grow according to the pathology accompanying adult obesity, and pediatricians should take advantage of the resources available as in the case of adolescents, the endothelial dysfunction, the measurement of non-HDL cholesterol, or the thickness of the carotid intima-media [27].

Importance and Stages of Insulin Resistance (IR) in Relation to the Development of Comorbidities

Genomic Bases

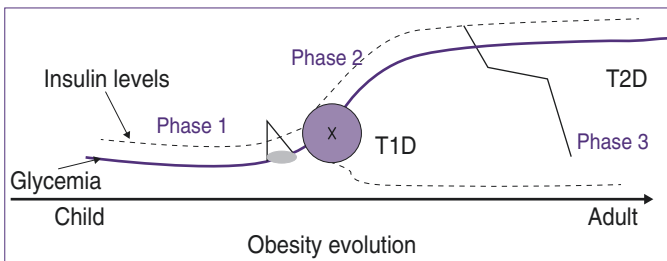
This causal approach is limited, reflects proven facts, and is based on insulin resistance and what it entails. Studies carried out in Mexico in severely obese adolescents [28] show that 13% did not suffer from the metabolic syndrome and neither did a high percentage of obese children with Prader-Willi syndrome [29]. Prevalence studies always show a small proportion of non-overweight boys who have metabolic risk factors or may have comorbidities. In the US/Korea study [30], this proportion was 0.7% in a population aged 12–19 years. This provides a suitable framework for assessing individual predisposition. Following gene and genome sequencing studies [31], preliminary results have shown that certain pleiotropic genes (responsible for different phenotypic traits) are related to their occurrence but with a moderate effect, for example, and in the case of insulin resistance or metabolic syndrome only 10% of their variability is related to gene bases [32]. Haploinsufficiency of the PTEN (*tumor suppressor phosphatase and tensing homologue*) gene leads to a variation in insulin resistance and obesity [33] in cases of Cowden syndrome, but also in patients with a variation in adiponectin or SRBP-1c (*sterol regulatory binding protein 1c*) activity; therefore these different clinical conditions could constitute a model for studying the appearance of different comorbidities. Cox models with or without SNPs (single nucleotide polymorphisms) or even including transcription factors are not giving a significant predictive improvement, but there is no doubt that they will also contribute to the clarification of this greater or lesser predisposition to suffer comorbidities. Epigenetic studies [34] are clarifying this predisposition to IR. In mice, the activity of a specific enzyme (Dnmt3a) plays an important role in the development of resistance through the methylation of a cytosine of a noncoding region of the FGF21 gene. This alters the expression of a hepatic protein capable of modifying the glucose uptake capacity of the cells.

Biochemical Basis

The reserve energy content of the organism and its parallel amount of fat storage have two main regulatory factors. The first is due to the increase in the positivity of the energy balance and belongs to the chapter on the etiology of obesity. The second refers to the endogenous mechanisms of weight control, which are bioenergetic balance, regulatory circuits of energy homeostasis, and adipose tissue. The regulation of these is complex and involves the synergistic action, as far as we know to date, of more than 100 peptides and hormones, with the role of insulin being crucial, as we will see below.

Insulin resistance (IR) is defined as a state of diminished responses to circulating insulin levels. Since insulin has a multiplicity of actions that go beyond the mere maintenance of euglycemia, they may explain certain pathogenic aspects of comorbid states. Normally and schematically, a rise in blood glucose levels, almost always postprandial, stimulates the beta cells of the pancreas to release insulin into the circulation. These higher levels acting on sensitive tissues (muscle, liver, adipose tissue, etc.) will incorporate glucose into their cells, restoring normal blood glucose levels which, in turn, suppress the release of insulin by the beta cells, thus maintaining the usual blood glucose levels of around 90 mg/dl. In an individual with insulin resistance, normal insulin levels do not maintain blood glucose levels, but this situation is reached after three phases. The first is the compensation phase where higher insulin levels maintain normal blood glucose levels. After a normally prolonged period, this phase is followed by another phase where postprandial hyperglycemia is especially prolonged or even apparent during fasting. In the third phase, blood glucose remains elevated throughout the 24 h of the day, leading to type 2 diabetes and the end of the insulin resistance status. In this phase there is a deficient insulin production together with an increase in alpha cells with increased glucagon production (Fig. 6.1).

The oral glucose overload test can identify the state of sensitivity or resistance to insulin but always bearing in mind that this transit is a *continuum* in the different tissues. Classical studies with hyper- and euglycemic *clamps* in normal subjects [37] showed that hyperglycemia decreases beta cell sensitivity to blood glucose concentration variation. There is ample evidence [38] of how the coexistence of insulin resistance (fasting insulinemia >2 SD) increases the risk of other metabolic disorders that are components of the metabolic syndrome and subsequent comorbidities. What are the main mechanisms leading to insulin resistance? The starting point is the chronic positive energy balance in the obese child and the consequent elevation of blood glucose, fatty acids, and other lipids following frequent food

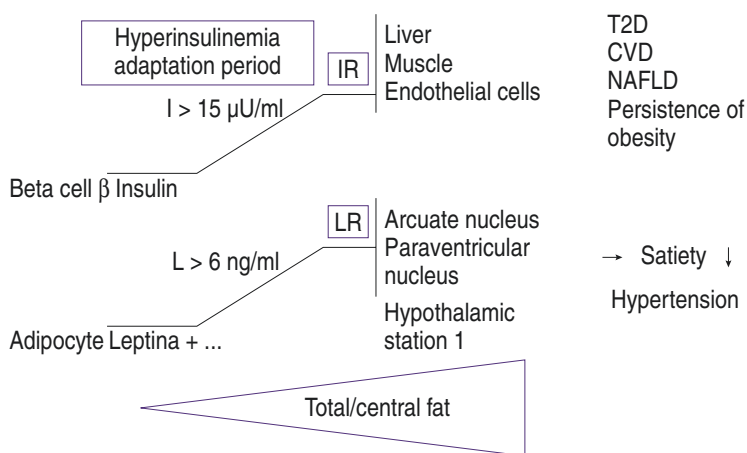


⊗ The starting point can go to an earlier age if genetic predisposition exists

Fig. 6.1 Evolution of insulin resistance during childhood and adolescence. Phase 1 corresponds to normality, phase 2 to prediabetes, and phase 3 to T2D. The transition from phase 1 to phase 2 (gray ellipse) is variable in age and duration [35, 36]

intake. The consequent elevated levels of insulinemia are crucial to increase the fat content of the adipocyte due to the stimulation of lipoprotein lipase activity which facilitates the entry of fatty acids. Insulin also favors the direct entry into the adipocyte of glucose, which is the natural precursor of intracytoplasmic glycerol, so that the synthesis of triacylglycerols, which are almost the only component of cytoplasmic fat guttule, occurs at that rate. When this increase occurs in the fatty tissue of the abdominal cavity, it will have more significant consequences than when it occurs in the subcutaneous adipose tissue, as will be seen later. During the state of insulin resistance, lipolysis in abdominal adipocytes is also increased with a direct release to the portal system and thus to the liver with the consequences we will see below. The rich vagal innervation of perivisceral fat implies a greater facility for lipolysis and increased free fatty acids in the circulation [39]. In connection with abdominal obesity, extensive experience in adults [40] indicates that even when assessed by abdominal girth, it has a higher predictive capacity for comorbid conditions than body mass index (BMI) [41], and this has also been recognized in the pediatric age group [42, 43]. The consequences of visceral fat accumulation are shown in Fig. 6.2 [35].

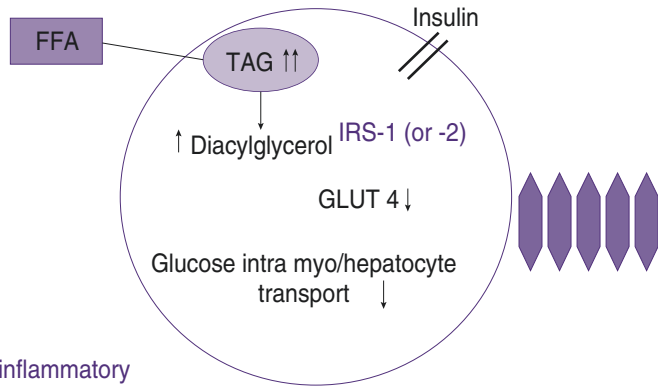
The next step is the cellular insulin mechanism (Fig. 6.3) which is not identical in the hepatocyte, myocyte, or adipocyte. In the hepatocyte and in normal circumstances, the direct arrival through the portal of insulin released by the beta cells binds to its receptor, and, as a consequence, there is a phosphorylation of the Fox O1 protein, which implies a reduction in the expression of the gluconeogenesis genes (GNG) with the consequent limitation of the outflow of glucose from the liver [46].



IR: insulin resistance; LR: leptin resistance.

Fig. 6.2 Clinical consequences of progressive increase in abdominal fat. High insulin levels act on target tissues (liver, muscle, and endothelial cells) that will lead to the comorbidities of the present study, NAFLD, NTD2, and CVD. High leptin levels would contribute to the maintenance of obesity [35]

Origin: additional caloric intake



Origin: adipocyte proinflammatory adipokines > adiponectin <

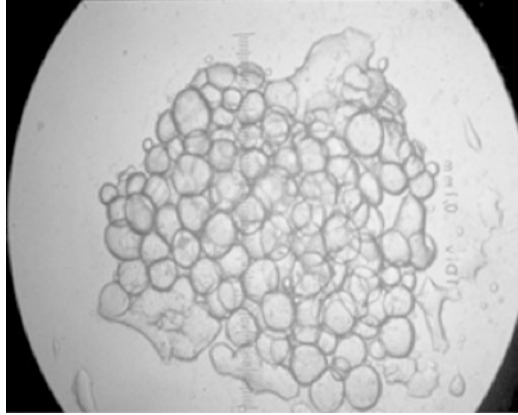
Fig. 6.3 Mechanisms of IR in liver and muscle cells. The increase of endocellular triacylglycerols (TAG) leads to an increase of diacylglycerols (DAG) which through a complex mechanism (see text) causes that the high affinity transporter for glucose (GLUT 4) does not reach the cell membrane of these cells in sufficient proportion, contributing as an important factor to the increase of plasma glucose [44, 45]

In addition to this action, there is another, perhaps more significant one, which is none other than the activation of the *sterol regulatory element binding protein-1c* (SRE BP-1c) which increases the transcription of genes necessary for the synthesis of fatty acids and triglycerides (de novo, lipogenesis), part of which will be bound to lipoprotein B and exported as VLDL which can be used by the muscle or adipose tissue [47]. Conversely, in the case of insulin resistance, the increase of free fatty acids in the hepatocyte, either post-absorptive or by de novo synthesis, impairs the hepatic action of insulin to decrease the rate of gluconeogenesis leading to an increase in fasting blood glucose [48]. It has been shown that obese children have higher blood levels of free fatty acids than controls and that these are usually coincident with the predominant levels in the diet (16:0 and 18:1 *n* – 9). With respect to the fatty component of the hepatocyte, de novo lipogenesis limits the capacity of beta oxidation of the same, due to a relative deficit of carnitine that decreases the incorporation of fatty acids to the mitochondria. The intracellular content of triglycerides increases, and the excess is released in the form of VLDL, which contributes to dyslipidemia that in a significant way supports the definition of metabolic syndrome. It should be made clear here that many of these findings are based on canine models [49, 50]. This, added to post-absorptive input and de novo synthesis, explains the intracellular increase [51], which is a crucial situation for the development of insulin resistance (and T2D) as was indicated more than 20 years ago with the use of magnetic resonance spectroscopy [36, 52]: it is unlikely that inert triacylglycerols are able to alter insulin action; therefore the products of their metabolism such as diacylglycerol (DAG) could be the connecting piece between increased hepatocyte (and myocyte) fat deposition and impaired insulin action [44, 45]. The increase in

DAGs contributes to increased activity of diacylglycerol kinase delta which itself can cause peripheral insulin resistance [53]. Furthermore, this intracellular increase in DAGs acts on one of the isoenzymes of the protein kinase C family, which in turn acts on an endocellular protein, *insulin receptor substrate-1* (IRS-1) and also IRS-2, typical of the liver, resulting in an abnormal phosphorylation of serine/threonine instead of tyrosine. This causes a decrease in plasma glucose transport into the cell because the high affinity transporter for glucose (GLUT 4) does not reach the outer cell membrane in sufficient quantities once insulin binds to its specific receptor in the hepatocyte. In addition, the increase in DAGs decreases the activity of phosphoinositol 3-kinase (PI 3-kinase) which in turn reduces the activity of glycogen synthase and, consequently, glycogen synthesis [44]. Added to this is the increase in GNG [48] with the subsequent export to the circulation of glucose that already had elevated levels due to the reduced activity of GLUT 4 function. The unifying line of thought of the Connecticut group explains the consequences of insulin resistance associated with obesity. In favor of it is the fact of increased GNG in preterm infants under 1000 g and on total parenteral nutrition [54]. In the liver, insulin resistance causes a twofold increase in de novo lipogenesis [50] which increases plasma triglyceride levels by 60% and decreases HDL cholesterol levels by 20%, which is nothing more than atherogenic dyslipemia. In the genesis of insulin resistance and NAFLD, the intracellular increase of a bioactive intermediate such as ceramide or its dihydroxyceramide derivatives is becoming more and more significant [55].

In the myocyte and in a normal situation, blood glucose enters by the action of GLUT 4, is phosphorylated to glucose 6 phosphate (G6P), and can follow two routes: depending on muscle activity, that of being oxidized or that of forming glycogen (glycogen synthase). In this situation of normality and administering a lipid infusion [56] to subjects with a hyperinsulinemic-euglycemic clamp, two things happen: one, a 50% reduction in the incorporation of glucose into the myocyte due to the decrease in G6P formation and decreased glycogen synthesis with the consequent elevation in plasma and, two, an increase in the oxidation of fatty acids [52]. This type of experiment has also shown that the aforementioned increase in fatty acids after infusion also increases endogenous glucose production through GNG [57]. This has recently been tested in the liver by means of the new glycerol-gluconeogenesis pathway [58]. In the case of prolonged insulin resistance and after MRI spectroscopic analysis with different isotopes and different glycemic clamps [50], it can be seen that muscle glycogen is reduced by 30% and its synthesis rate by 50%, including the postprandial rate, which contributes to hyperglycemia. The mechanism of insulin resistance is now better understood following the close correlation between intramyocyte diacylglycerol concentration and clinical severity. The cellular basis [45] is similar to that described in the liver (DAGs and reduced insulin activity), and it is perhaps worth adding that intramyocyte DAGs through their action on protein kinase C family enzymes [59, 60] decrease the activity of diacylglycerol kinase delta (DGK delta) which in itself causes peripheral insulin resistance [45] to which is added that of phosphoinositol 3-kinase which implies a reduction of glycogen synthase activity as noted above [61]. This has opened up new therapeutic possibilities as it is able to act on these enzyme systems.

Fig. 6.4 Fresh view of adipocytes treated with liquid nitrogen and whose size is now known not to follow the patterns of hypertrophy or hyperplasia. (Taken from Moya M, Díaz NM. Obesity. Current histological aspects. Rev Esp Pediatr. 1983; 39: 226–30)



Adipose tissue, especially white adipose tissue (Fig. 6.4), plays an important role in the genesis of insulin resistance as we have just seen, but also through [62] the actions of the various adipokines that it secretes together with other nearby cells (see Chap. 4, *Pathogenesis*). Of these products, leptin and subsequent leptin resistance (Fig. 6.2), probably as a consequence of increased sugar intake [63], it is certain that their elevated levels retain their proinflammatory character [64] which contributes to the development of comorbidities. The study of the mechanisms of insulin resistance has led to therapeutic improvements by optimizing the sensitivity of its receptor [65]. The proinflammatory [66, 67] action of other adipokines and the protective action of adiponectin also have a lesser clinical impact. New factors in the genesis of the insulin resistance are represented by the inhibition of SLC7A10, a soluble carrier from the SLC7 family which implies an increased lipid accumulation in human white adipocytes besides other additional obesogenic actions exerted on the beige and brown adipose tissue [68]. However, in cases of extreme insulin resistance, thyroid nodules must be ruled out, probably due to high leptin and insulin levels.

Pediatric obesity is strongly associated with IR and with T2D [69]. Consequently, it is understood that T2D begins long before it is evident, and the study of leptin and adiponectin variations can contribute to an earlier diagnosis. In the same sense, the study of TNF-alpha and interleukin-6 (IL-6) with a direct action on the liver, varying from fatty infiltration to inflammation and even fibrosis, could contribute to a better approach to this initially silent problem. Once the molecular mechanism through which adipokines act is known, new therapeutic approaches may emerge as has occurred in the case of atopic dermatitis. To conclude this lengthy reference to IR, it is opportune to mention two aspects: first, how the harmful ectopic (epicardial, hepatic) fat deposition together with the visceral would require simpler techniques for its evaluation [70] and, second, and perhaps induced by dietary fats, how ketogenic beverages could increase insulin sensitivity. In this regard, a short study demonstrated that monoester (hydroxybutyl, hydroxybutyrate) is able to reduce significantly the area under the curve in the oral glucose tolerance test in healthy young people [71].

Metabolic Syndrome (MS)

With regard to the comorbid conditions that occur in children and adolescents, two aspects justify the study of MS: the first refers to the growing diagnosis of comorbidities that are increasingly better known and therefore better investigated [70] and the second and of greater interest is their identification in children aged from 6 years and above, especially if they are overweight [72]. Addressing the concept of the metabolic syndrome is perhaps advisable before entering into the description of obesity-related diseases or comorbid conditions (CC) because of its early diagnostic and therefore preventive role in the adult stage of cardiovascular disease (CVD) and type 2 diabetes (T2D) and because of the risk of premature death. Other types of CC cannot be ignored, such as non-alcoholic fatty liver disease [30], hyperuricemia [21], hemostasis disorders [73], or obstructive sleep apnea [74], to mention the most recently described among others already better known. At least in the first three circumstances, insulin resistance is one of the common and determining factors. The metabolic syndrome (MS), as it is currently accepted, is composed of obesity, impaired glucose metabolism, hypertension, and dyslipidemia, and its interest lies in the fact that it is highly predictive of CVD and T2D, particularly when it appears in obese children and adolescents [75] and through mechanisms that are increasingly better known, such as insulin and leptin resistance and adipokines produced in the heart of white adipose tissue.

The MS was first described in 1920 in Sweden and was made known in the English literature in the 1950s [76]. In the 1980s, Reaven [77] linked these early findings to insulin resistance (syndrome X), but it was in 2006 and in England that a consensus was reached as a result of the initiative of the *International Diabetes Federation* [78]. According to this definition, an adult is affected by MS when he or she has an abdominal circumference ≥ 94 cm in the case of European men or ≥ 80 cm for European women and also has one of the following factors: triglycerides ≥ 150 mg/dl; HDL cholesterol ≤ 40 mg/dl or ≤ 50 mg/dl, respectively, depending on male or female gender; blood glucose ≥ 100 mg/dl; and systolic blood pressure ≥ 130 mmHg or diastolic ≥ 85 mmHg. Subsequently, and perhaps with little justification, the abdominal circumference criterion was removed as a requirement [79] although it is still considered a basic *screening* parameter. This is due to evidence showing how visceral adiposity is common to each of the other components of MS. This definition of MS was at that time intended for a unified method of diagnosis in clinical practice that could be used worldwide, allowing comparisons of adults from different countries or areas.

In the case of children and adolescents, there is no clear defining criterion for these situations of cardiometabolic risk. Because of this diversity, among the many existing definitions, we have found 11 different definitions for MS with different cut-off points and even one that directly uses the parameters listed in the case of adults for the pediatric population (Table 6.2). Given this variability, the *International Diabetes Federation* [80] proposed a definition for pediatric ages stratified into age segments (6–10, 10–16, >16 years), and curiously the cut-off points are identical to

Table 6.2 Interest of using a single definition of MS

Number of studies	15
Number of patients	25.433
Number of patients/study	128–13.383
Number of studies using IDF	8
Metabolic syndrome in the total population	2.3–11.5%
Metabolic syndrome prevalence in obese people	6.7–30.8%

Moya M. (2013)

The large variations in prevalence would have been avoided by using the *International Diabetes Federation* definition

Table 6.3 Definition of metabolic syndrome for children and adolescents at risk, according to the *International Diabetes Federation* [80]

Age group (years)	Abdominal circumference (AC)	Triglycerides	HDL-C	Blood pressure	Fasting plasma glucose ^a
6–<10	Percentile ≥ 90				
10–<16	Percentile ≥ 90 th percentile or adult limits	≥ 150 mg/dl	< 40 mg/dl	Systolic blood pressure ≥ 130 or diastolic blood pressure ≥ 85 mmHg	Fasting plasma glucose 100 mg/dl or DT2
>16 (adult criteria)	CA ≥ 94 cm for Caucasian males and ≥ 80 cm for Caucasian females (with ethnicity-specific values for other groups)	≥ 150 mg/dl or specific treatment for high triglycerides	< 40 mg/dl in men and < 50 mg/dl in women or specific treatment for low HDL	Systolic blood pressure ≥ 130 or diastolic blood pressure ≥ 85 mmHg or previously diagnosed treatment Hypertension	Fasting plasma glucose 100 mg/dl ^a or known DT2

^aFor clinical purposes, but not for the diagnosis of metabolic syndrome, if fasting plasma glucose 5.6–6.9 mmol/l (100–125 mg/dl) and you are not known to have diabetes, an oral glucose tolerance test should be performed. Diagnosis of metabolic syndrome requires the presence of central obesity plus two of the other four factors

those for adults, changing only the criterion of obesity, i.e., abdominal circumference greater than 90 centile, and omitting the circumstance of pharmacological treatment (Table 6.3).

This is important because, depending on the definition adopted, the frequency may double [81] or assess parameters that are not significantly predictive (microalbuminuria) of comorbid states. The current situation reflected a slowly growing acceptance (temporary) of the IDF pediatric definition of MS [82]. The diagnosis of MS in these ages requires the presence of abdominal obesity plus two of the other four conditions (TG, HDL, blood pressure, or blood glucose). The cut-off points are expressed in absolute values, as they are easier to apply in a clinical setting. In this definition, which achieved a certain consensus [80], unlike the adult definition of

the same IDF, the obligatory nature of the visceral adiposity criterion is maintained because of its proven action as an independent factor for the development of insulin resistance and probably also because of the change in the distribution of fat that puberty implies. It is also worth remembering how in this document, in one of the recommendations for future research, a proposal was made for specific ethnic studies of abdominal circumference and comparison with those of abdominal fat (truncal) obtained by DXA or magnetic resonance imaging (visceral fat). The current trend is to recognize its value and usefulness in low-income countries as an epidemiological tool (among others), but it continues to raise new definitions with the inclusion of new parameters [83] that in a more pragmatic framework would be integrated into the growing cardiometabolic risk (CMR) factors.

From a conceptual point of view, it can be concluded that MS is nothing more than a set of abnormalities almost always subclinical in pediatric ages but that its presence brings with it an elevated risk of T2D or subsequent CVD and even NAFLD; therefore it should be part of the evaluation of any child who presents not only obesity but also overweight since, even if it is normal, it will always be a reference point in the possibly long evolution of the process. Furthermore, the term metabolic syndrome (with more than 40 different definitions) does not enjoy the same fortune in the medical literature as in the past decade, possibly, and for a more concrete predictive approach, it might be coincident or replaced by that of cardiometabolic risk (if presence of hypertension, hyperglycemia, dyslipemia, and fasting insulinemia) in relation to pediatric obesity [82, 83]. Both the name and the conceptualization of MS have changed [84]. It is now considered a combination of metabolic anomalies fundamentally related to insulin resistance and which represent a growing range of risk factors for T2D and cardiovascular disease (CVD), which are a primary preventive target. Another eventual interference with the term is the new use of metabolic syndrome that has appeared after the spread of COVID-19 and ARDS and its consideration as part of a combination of the two [85].

Non-alcoholic Fatty Liver Disease (NAFLD)

Non-alcoholic fatty liver disease (NAFLD) will be treated with special attention because it is the most common hepatic anomaly in pediatric ages, because it can have a poorly predictable evolution towards steatohepatitis (cirrhosis and hepatocellular carcinoma) and particularly because of the difficulties of an early diagnosis [86–88]. In this area, our patients' results will be included. The onset of NAFLD is closely related to gestational obesity, early obesity and insulin resistance, and factors favoring inflammatory activity. The consequences of these conditions will be evident after the childhood and adolescence phases, and their appearance will also be associated with type 2 diabetes.

NAFLD is more frequent in adulthood, where the clinical features appear with greater amplitude due to the more prolonged metabolic dysfunction. There are excellent reviews among which we can cite the seminar published in *The Lancet*

[89], for its broad coverage of epidemiology and diagnostic and therapeutic advances. NAFLD is a comorbid condition of obesity characterized by a macrovesicular accumulation of fat, triglycerides, in the hepatocyte that worsens with hyperinsulinemia and can have a negative progression towards steatohepatitis and possible subsequent cirrhosis or hepatocellular carcinoma. It was first described in 1952 by Zelman in obese adults and in 1983 in pediatric patients by Morant [90]. Fatty liver develops [91] when the incorporation and de novo synthesis of fatty acids exceed their oxidation and export as VLDL, i.e., triglycerides. Fatty acid incorporation into the hepatocyte has two origins: postprandial and adipose tissue. About 20% of dietary fat goes directly to the liver which in itself constitutes a significant share, but it should also be noted that dietary carbohydrates also promote de novo synthesis of fatty acids from acetyl-coenzyme A and SREBP-1c which are stimulated by higher levels of insulin, as we saw above, and by the stimulation of the *transcription factor carbohydrate responsive element-binding protein* (ChREBP) which also stimulates the aforementioned synthesis. Fructose plays a special role because, unlike circulating glucose, it is only incorporated into the liver [92] and because its phosphorylation at carbon 1 does not allow its access to the metabolic pathway of glycogen synthesis, being converted into glyceraldehyde 3-phosphate which constitutes a suitable substrate for de novo lipogenesis. This fact is significant in light of the progressive sucrose consumption. In perivisceral adipose tissue during fasting, triglyceride hydrolysis is performed by cellular TG hydroxylase, and a fraction of the fatty acids is transported by albumin to the liver. This hepatic fatty deposit has three destinations: oxidation in the mitochondria, re-esterification and storage as TG, or binding to lipoproteins and excretion as VLDL. According to the previous concept, if the incorporation is greater than the sum of the oxidation and export quotas, the deposit will increase. This does not occur in all individuals nor in all obese individuals with positive energy balance; therefore other genetic circumstances or causes [93] must be taken into account. Of lesser significance are the cases of the rare monogenic defects (PNPLA3; Apo A5; etc.) and, more feasibly considered, those derived from gender, ethnicity, or predisposition, which, after the possibility of genome sequencing, may alter the approach to this process. Better understanding of cellular mechanisms [94] reveals how, in humans, hepatic DAG content is the best predictor of insulin resistance, acting through protein kinase epsilon and the subsequent consequences described above and with the more attainable increase in fibrosis.

Prevalence of NAFLD

In adults and high-income countries, NAFLD occurs in 80% of the obese population, although only about 45–60% will develop or coincide with type 2 diabetes and only 10% of simple steatosis will progress to cirrhosis [91]. In children, it varies considerably depending on the method of assessment. If, for example, the criterion is ultrasonography plus aminotransferase elevation, it ranges from 10 to 77% of

pediatric obesity cases, which implies a low specificity. Usually, the prevalence of NAFLD in the general pediatric population is estimated to have doubled in the last two decades and amounts to 9.6% of the population [94]; in the same line, more recent data show a prevalence in a general population of children and adolescents of 7.6%, while in those affected by obesity, it rises to 34.2%. This is consistent with the data of Schwimmer [95], who reviewed 742 autopsies of children and adolescents who had died in accidents, and fatty liver (when 5% of hepatocytes contained a fatty vesicle equal to or larger than the nucleus) was found in 97 cases. It was present in 38% of the overweight and obese young people. This gives perhaps a more realistic idea of prevalence. The Avon Longitudinal Study of Parents and Children (ALSPAC) [96] study based on transient elastography on more than 4000 young people showed that 1 in 5 had steatosis and 1 in 40 had fibrosis, with a clear association with higher BMIs. The same group also revealed that pre-pregnancy maternal obesity triples the risk of fatty liver disease. As the prevalence of obesity has increased, so have the comorbidities, especially NAFLD. This has been considered a common disease in adult obese patients, but now, in the pediatric age group with the new screening methods, it is following an identical path.

HGNA Histology

Steatosis is defined when the hepatic triglyceride content is greater than the 95th percentile (~55 mg/g of liver) in lean, healthy adults [97] or more commonly when more than 5% of hepatocytes contain fatty guttules that are equal to or larger than the cell nucleus [96]. Hepatic steatosis is often self-limiting but can progress to non-alcoholic steatohepatitis (NASH). There are two types of NAFLD [98]. Type I involves degenerative (irregular) ballooning of the hepatocyte with cell damage or death and with an inflammatory infiltrate and perisinusoidal fibrosis. It is the form typical of adults and is rarer in pediatrics and almost always in girls. Type II is the typical form of pediatric obesity and is characterized by a macrovesicular steatosis of regular contour with portal and periportal inflammation and fibrosis. On occasion, but not in the perisinusoidal areas, the cellular infiltration is predominantly mononuclear (Fig. 6.5). We have studied (Hospital Universitario San Juan) a group of 11 obese children and adolescents with NAFLD, 8 of whom presented with type II steatosis, 2 with a steatohepatitis pattern, and 1 with a case (obese) of Wilson's disease. Histology is the gold standard in the evaluation of fatty liver, but also of its severity and fundamentally in differentiating steatohepatitis from simple steatosis and, of course, in ruling out other pathologies (autoimmune hepatitis) that can also increase hepatic fat content. NAFLD presents now new therapeutic possibilities for the adult and young patient; they are normally evaluated as for NAFLD, NASH, and subtle cirrhosis. Liver biopsy allows a classification in five stages on the basis of the extent of fibrosis: F0 no fibrosis, F1 portal fibrosis, F2 periportal fibrosis, F3 bridging fibrosis, and F4 cirrhosis. This point is not at all banal because all-cause mortality increases as the fibrose stage progresses [86]. In the case of adolescents, this

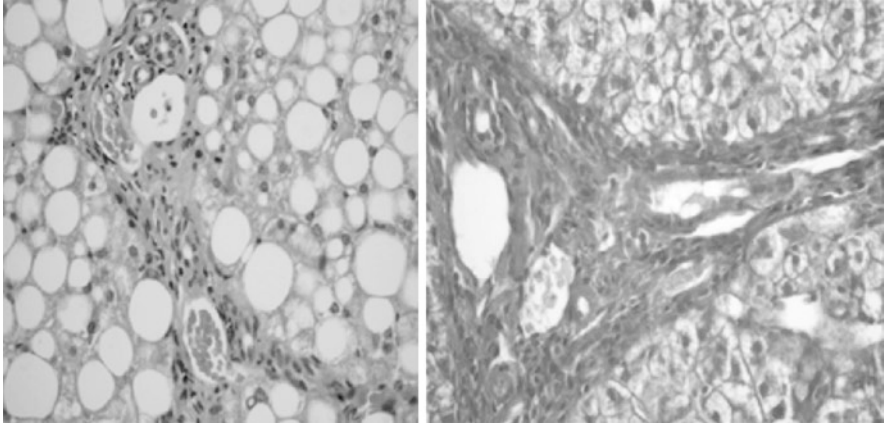


Fig. 6.5 Portal space of one of our patients with typical pediatric pattern: macrovesicular steatosis (without degenerative ballooning) and an inflammatory pattern of mononuclear cells. In the image on the right (Masson's trichrome), an already apparent fibrosis can be observed [35]

requires a close monitoring of the extent of the fibrosis since F3 bridging fibrosis is also associated with hepatocellular carcinoma [88, 99]. However, liver biopsy is an invasive procedure and therefore requires strict criteria for its execution, which in our unit were truncal fat >40% (DXA); elevated AST, ALT, and gamma GT; and fasting insulinemia >15 μ U/ml. The bases and techniques for liver biopsy and evaluation, including safety [95], are already described in greater detail [100].

Clinical Aspects

Despite its prevalence, NAFLD certainly remains underdiagnosed, probably because it is in fact a clinicopathologic diagnosis and most of those affected are asymptomatic. Clinical diagnosis depends on the eventual presence of hepatomegaly and elevated aminotransferases. If the abdominal perimeter is above the 90th percentile or above 2 SD, then suspicion increases, and even liver fibrosis may be suspected [101]. Plasma liver enzyme values or urinary clearance of 1α -microglobulin alone have low sensitivity and specificity when considered against previous biopsy, but are an important aid together with elevated gamma-GT, especially when they appear in obese children over 3 years of age, with increased abdominal circumference and a history of NAFLD in close relatives, although other approaches should be taken into account [102]. The new facility of transjugular liver biopsy would allow a tighter histological control in adolescents [103]. Assessment of NAS histological scores is extremely useful in cases of prediabetes type 2 [104]. Percutaneous liver biopsy, as mentioned above, is the gold standard for assessing the degree of steatosis, the stage of liver fibrosis, and cellular damage, but it involves a certain risk of bleeding and requires experience and short hospitalization. The

clinicopathological correlation is necessary in each case because the histology may be similar regardless of the etiology: drug toxicity (steroids, antiretrovirals), metabolic diseases (Wilson's disease, tyrosinemia, total parenteral nutrition), severe pediatric undernutrition, hepatitis C, autoimmune, or alcohol consumption (in adults). Precisely because of these pros and cons, imaging techniques have been gaining diagnostic space. Magnetic resonance imaging can be used initially as it allows an accurate diagnosis and measurement of the hepatic fat deposit. It is easily performed and interpreted and in adults it has shown a good correlation with histological data. In the pediatric age and using this technique and especially the estimation by proton density, the hepatic fat fraction in both lean and obese children can be measured, and when it is higher than 8.7%, it indicates a medium steatosis [105]. New procedures and the use of contrasts allow the assessment of the degree of fibrosis. Magnetic resonance spectroscopic imaging is capable of detecting minute amounts of liver fat, but its availability in clinical practice is restricted, and MRI-based elastography gives superior results to ultrasonography-based elastography. *Ultrasonic transient elastography*, alone or in conjunction with the pediatric index for NAFLD, is used more for monitoring liver fibrosis in selected chronic patients. Ultrasonography-based techniques, although less accurate, are the most widely used due to their safety, availability, and cost. Their weakest points are that they only detect steatosis above 30%; that there is also an attenuation of the ultrasound beam due to the extrahepatic fat content (>45 mm); the interpretative subjectivity; and the lack of distinction of the degrees of steatosis or the presence of fibrosis. A good correlation with the histological classification is achieved with the use of the ultrasonic *score* (0–3) based on hepatorenal echo contrast, visualization of intrahepatic vessels, and visualization of the hepatic parenchyma and diaphragm [106]. The main problem with imaging studies (and histological studies) is that they do not predict or recognize progression to subsequent cirrhosis [107], but they are undoubtedly gaining certainty as less invasive alternatives. NAFLD, in addition to the hepatic consequences, presents other long-term risks to which we must specifically add type 2 diabetes, arteriosclerosis, and heart disease, especially if it coexists with hypertension, respiratory complications (sleep apnea), and even bone undermineralization. Therefore, when diagnosing this comorbidity, the presence of early features of these conditions in addition to rised soft drink consumption, triglyceride levels and aminotransferases should be monitored [95], including the more rare non-alcoholic fatty pancreas.

Evolution

Although simple steatosis is almost always benign and non-progressive, fatty liver is associated with cardiovascular disease and T2D more than when there is only obesity without this condition. In addition, there is the detail that NAFLD can progress to non-alcoholic steatohepatitis (NASH) and, once this stage is reached, progression to fibrosis or cirrhosis can be a reality [98]. Because of this spectrum of serious chronicity, it is pertinent to consider here that cirrhosis [108] appears in a

proportion of 10–30% after 10 years and that hepatocellular carcinoma after cirrhosis appears in a smaller proportion. This development is related to genomics (certain polymorphisms), to exosomes and RNAs in the case of children, and to ethnic and even environmental factors, the latter being those that can be modified, hence the importance of early treatment of abdominal obesity [109, 110]. In addition to other clinical circumstances, lifestyle changes in adults [109, 110] are able to normalize the triglyceride content in the adipocyte; this is a valuable lesson for pediatric patients. In the case of NAFLD when studied with MRI (fraction $\geq 5.0\%$), they present a prevalence of 1%, 9%, and 25%, respectively, for normal weight, overweight, and obese children and where liver involvement is an independent variable of BMI in its association with subsequent cardiovascular disease [111], which is in agreement with the large European study of 18 million adults [112]. However, in the case of NAFLD and because fat deposition is quantitatively different in individuals with equivalent adiposity, other genetic or inflammatory factors, such as TNF-alpha, IL-6, and endoplasmic reticulum stress, may have a prominent position in the clinical management of obese children and adolescents. This is particularly noteworthy because of the association of NAFLD with cardiovascular disease through proinflammatory mechanisms, increases in carotid intima-media thickness, and hypertension itself. To conclude these clinical aspects, two notions are important: One, the increased risk of severe liver disease and hepatocellular carcinoma, when viewed from the perspective of more than 34 million Swedish adults, lies in the prolonged overweight status [110] and how this risk is attenuated when the obese child ceases to be obese as an adult. The second notion has more of an applied research character and is none other than the development in Japan of an animal model (mouse model STAM) which in 100% of the cases and in 16 weeks develops the sequence of steatosis, steatohepatitis, fibrosis, nodular lesion, and hepatocellular carcinoma.

Cardiovascular Disease

It may be opportunistic to talk about cardiovascular phenotypes, but it is clear that there are currently 66 loci in the human genome that are significantly associated with elevated blood pressure in 50% of hypertensive individuals [113]. However, it should be equally clear that environmental and lifestyle factors are significant in the general increase, where the development in BMI from normal weight to overweight and obesity leads to a moderate elevation of systolic and diastolic blood pressure and increased cardiac output and ventricular mass. The inflammatory component of atheromatous plaques straddles both causal trunks. This is not only the basis of cardiovascular risk for the future but already has clinical implications in young people and adolescents. The *Finns-Study* [114] which also assessed cholesterol levels in a large prospective study shows how blood pressure and lipemia increase as overweight increases and how this increase is maintained in adulthood. It is clear that the presence of dyslipidemia, hypertension, coagulopathy, and chronic inflammation is conducive to the development of cardiovascular disease. Sodium intake

[115] has always been recognized as an important risk factor in adults when it exceeds 2300 mg/day (1 g of salt = 400 mg of sodium), and it has been the *CDC report* (CDC Vital Signs <http://www.cdc.gov/vitalsigns>) who has pointed out that 90% of children between 6 and 18 years of age average a sodium intake of 3.300 mg/day before considering the salt added at the table when the total should be between 2000 and 2300 mg/day and also considering that 40% of this amount comes from the 10 most common precooked foods. This implies the elevation of blood pressure and difficulties in its control through family education and a more precise regulation of the food industry. The presence of two or more cardiovascular risk factors (fasting blood glucose, hypertension, lower HDL cholesterol, or elevated triglycerides) increases it according to the body mass index, as shown by the analysis of data from the NHANES study in the period 2001–2008 [116]. In addition to the known alterations of the left ventricle (posterior wall, septum, and ventricular mass), we must add early diastolic filling, and these alterations are due exclusively to obesity in adolescents, with no metabolic changes in carbohydrates and lipids being involved in their genesis [117], which would retain their capacity to increase them, as shown in the Canadian study [118] with clearly estimated prevalences and where a decrease in cardiorespiratory fitness is already observed. The increase in left ventricular mass must be carefully assessed as it could mask idiopathic hypertrophic heart diseases, some of which already have a known genetic basis [119]. The study of the levels of certain cytokines (adrenomedullin) may be an early marker of ventricular dysfunction.

The interest of subclinical CVD in obese children and adolescents is its continuity into adulthood. The finding of arterial fatty streaks in children and young people who died from trauma initially described by the Bogalusa Heart Study at the turn of the century gave rise to a series of productive studies. In the important Danish study [120], more than 275,000 children and adolescents aged 7–13 were assessed 25 years later according to the persistent risk factor of increased BMI at that stage of life. It shows how and when the BMI-zs increases and when this increase is later, i.e., towards puberty; the risk of coronary heart disease (lethal or not) is significantly increased: for each unit of BMI-zs in the ages 7–13, the risk increases from 1.05 to 1.18. This risk is higher for males and with virtually no influence of birth weight. In another study of similar duration [121] but which also incorporates some of the parameters of the pediatric metabolic syndrome that are actually cardiometabolic risk factors [82], the prediction of adult CVD is more adjusted and with a higher value (OR 6.2; 2.8–13.8; <0.001). Data from the i3C consortium [122] show that pediatric obesity is an important independent factor for the persistence of arterial lesions already present at the age of 9. These initially reversible lesions will be aggravated by the action on the endothelium of proinflammatory adipokines, dyslipidemia, hypertension, left ventricular stiffness, and other factors that will give rise to the broad spectrum of cardiovascular disease. Projection studies indicate a similar trend, but as they are subject to multiple uncertainties, they will not be considered at this time. The advantage of this knowledge is that it allows us to identify a series of patients in the pediatric age group with a real risk of subsequent CVD and therefore worthy of preventive interventions that should be contemplated at the state

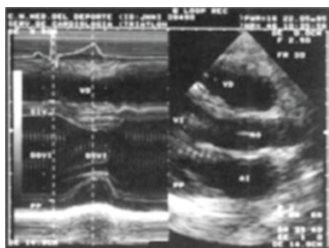
level, given the trajectory that blood pressure also follows. The new special cardiac magnetic resonance on the left ventricle could be of interest, allowing the three-dimensional anatomy of the pediatric heart and its early alterations induced by obesity [85, 123].

Hypertension

This is a highly topical problem because in the case of hypertension, early detection and intervention in children and adolescents lead to normalization, but the studies are of such short duration that the long-term outcome is yet to be determined. This has perhaps contributed to the fact that the *screening* of hypertension in comorbid states does not have the recognition and clinical consideration that it really deserves. Counteracting this attitude was the position of the *US Preventive Services Task Force* of 2013 and especially the complete one of 2017 [124] that introduces new thresholds for blood pressure classification (systolic and diastolic in mmHg): normal <120 and <80; elevated 120–129 and <80; grade 1 hypertension 130–139 or 80–89; grade 2 hypertension >140 or >90. These values along with screening indications are reaffirmed in the USPSTF Reaffirmation Recommendation of 2021. There are other recommendations and thresholds issued by other institutions but with little substantial differences. These levels for adults that are more specific and facilitate clinical follow-up have had an immediate impact on our age segment [125] where hypertension affects 11% of obese children and adolescents, compared to 4% in the general population under 19 years of age [126] with additions such as the elimination of the term prehypertension, replaced by elevated blood pressure, tables referring to weight, which do not invalidate those of the *Fourth Report* and which can be obtained at <http://dites.google.com/a/channing.harvard.edu/bernardrosner/pediatric-blood-press/childhood-blood-pressure>. In addition, in the 2017 guidelines, there is a simplified table for *screening* [125] where if values higher than those given for ages 1–13 were found, this would imply a specific follow-up, according to the guidelines recommended by the same document. The increase in prevalence is closely related to that of obesity, and the importance of elevated blood pressure lies in the fact that there is already organ damage at the time of diagnosis in a considerable number of affected children, for example, in the aforementioned study carried out in our unit [14] shown in Fig. 6.6 where an increase not only in the thickness of the interventricular septum but also in the left ventricular mass is observed.

This is consistent with other similar studies in which hypertension leads to left ventricular hypertrophy, and perhaps most importantly, heart failure, coronary heart disease, and death in people under 55 years of age have been associated with hypertension in the pediatric age group [127]. With this framework, the identification of hypertensive status is essential, and the best contrasted reference frameworks should be used, as seen in the study by Di Bonito [128] where a significant number of obese children and adolescents were classified as non-hypertensive, when re-evaluated with the 2017 AAP standards [125]; not only were 11% classified as hypertensive,

Structural and functional measurements of the left ventricle in obese children



End systolic/ diastolic measurements and left ventricular functions in obese children (n=101) and controls (n= 38)

	Obese	Control	p <
Interventricular septal thickness (mm)	9,1	7,4	0,06
LVED (mm)	43,3	39,4	0,06
Left ventricle mass (g)	38,5	32,8	0,06

Fig. 6.6 Increased thickness of the interventricular septum and left ventricular mass in obese children [14]

but they also already had insulin resistance and increased left ventricular mass, with changes in their mass and geometry. From the clinical point of view, it is necessary to know how systemic hypertension almost always appears in preadolescence, particularly if it coexists with overweight, obesity, and a family history of hypertension. The anamnesis should include, in addition to the dietary survey, sleep habits, physical activity pattern (weekly hours and intensity of physical exercise), and medication that may raise blood pressure, in the case of ADHD or asthma, as well as smoking or consumption of other substances in the case of adolescents. The proven association of hypertension with neurocognitive deficits should be suspected. The examination must be accurate to rule out renal or aortic pathologies that may cause it. The assistance of specialists, including fundus examination, is essential to adequately assess the present impact [129]. In the pediatric age, the normative tables depending on age and growth as well as the 2004 standard of the *Working Group on High Blood Pressure in Children and Adolescents* have been widely accepted and have not been repealed. However, they have been appropriately modified by the *American Academy of Pediatrics* [125], although they initially elicited some comment, because the lowering of thresholds would increase the number of children in the high blood pressure category ($\geq 120/80$ mmHg); stage 1 hypertension ($\geq 130/90$ mmHg); or stage 2 hypertension ($\geq 140/90$ mmHg). The preventive advantages of these new cut-offs are myriad [130], and they also provide a *screening* table that indicates when probands of both genders should be further evaluated (Table 6.4). The general tables refer to the gender and height of the child at the time (rather than age) and the blood pressure obtained, which allows for the 50th, 90th, 95th, and 99th percentile for both systolic and diastolic pressure. It is considered as high blood pressure when it is between the 90th and 95th percentile and as hypertension when it is above the 95th percentile. The technique of blood pressure assessment is important. Traditionally, the auscultatory technique (mercury column or aneroid devices) has been recommended, but the variability of the devices themselves, the subjectivity involved, and the frequent lack of disappearance of the fifth Korotkoff noise have led to the modern automated oscillometers being imposed. This type of electronic instruments has the advantages of their precision (they

Table 6.4 Blood pressure values (mm Hg) above which the following is required more specific research according to the *American Academy of Pediatrics* [125, 130]

Age (years)	Children		Girls	
	Systolic	Diastolic	Systolic	Diastolic
1	98	52	98	54
2	100	55	101	58
3	101	58	102	60
4	102	60	103	62
5	103	63	104	64
6	105	66	105	67
7	106	68	106	68
8	107	69	107	69
9	107	70	108	71
10	108	72	109	72
11	110	74	111	74
12	113	75	114	75
≥ 13	120	80	120	80

measure the oscillations of the arterial wall and, from there, derive the systolic and diastolic pressure) and of avoiding the subjectivity of the observer. That said, few of them have been validated in pediatric patients and deviations of ± 5 mmHg are not uncommon. The next step is the technique itself which, if standardized, would improve the diagnostic and epidemiological quality so necessary today in pediatric hypertension [126]. Different cuffs are required depending on whether the patient is an infant, child, or adolescent, the blood pressure must be taken 3 times during each visit, and the results averaged. The experience of more than 10 years with the use of a program (Seinaptracker) that includes in its software the aforementioned tables has supported these positive results. Finally, it is important to be precise about the technique used to take the blood pressure. Another way that seems to avoid the increase due to the stress of the act itself is that which is carried out on the first visit and after having auscultated the child, it is repeated three times, the first value is discarded, and the second and third are averaged. If the result is high, the patient will be called back in 2 weeks to repeat the measurements on the occasion of a follow-up visit. Sometimes it is necessary to resort to an emotionally calmer environment [131]. It should be noted that the values measured in the right arm may be slightly higher than those in the left arm due to the angle of origin of the subclavian artery. Because of all these factors, the USPSTF (2020) concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for high blood pressure in children and adolescents. Therefore, and although the trend in the last two decades is towards stabilization or even slight decrease for both systolic and diastolic blood pressure in children and adolescents (10 NHANES cycle 1999–2018), screening for pediatric hypertension (primary or secondary) continues its increasing development promoted by medical organizations in the cardiovascular field and irregularly supported by state agencies. The idea of replacing current cross-sectional studies with longitudinal cohort studies would improve the approach

to hypertension in children and, in the longer term, the steadiness of the trajectory to adult hypertension. Literature on salt intake, salt distribution, and even salt sensitivity plus regulatory mechanisms such as filtration or pressure covertly promote a situation of hypertension.

Respiratory Disorders

Because of their relationship and contribution to cardiovascular disease, they deserve a brief analysis since obstructive sleep apnea implies greater cardiomorbidity [74]. This term includes other related aspects such as exercise intolerance, hypoventilation syndrome, and obstructive sleep apnea, among others.

Respiratory alterations derive from the mechanical effects that obesity produces on respiratory dynamics, mainly in the lung but also on the airways, and can be of such magnitude that they can reproduce an asthmatic condition that subsides with weight loss. In the lungs of obese children and adolescents, there is a decrease in residual functional capacity and residual volume [132]. Fat deposits in the thorax and abdomen decrease the movements of the chest wall and diaphragm resulting in decreased chest wall *compliance* and increased work of breathing according to the degree of obesity. This has already been described in classic studies in which the decreases in forced vital capacity and forced expiratory volume occurred as the degree of obesity increased. If we add to this a certain decrease in gaseous diffusion [132] and if obesity is also assessed with the aid of the DXA technique, the harmful effect of obesity in itself can be appreciated, with the positive fact that these alterations are reversible with weight loss, even in adults. The association between asthma and obesity has not been demonstrated, although it is true that the presence of cough and wheezing is more frequent in obese children and adolescents, but neither clinically nor immunologically is asthma confirmed according to the current criteria that define it. Obesity also has negative effects on the airway because, unlike in adults, the larynx is relatively larger, the neck is shorter, the tongue is larger, and in many cases the adenoids and tonsils are larger, all of which creates a relative obstruction of this upper section of the airway, which is clearly increased by the fatty deposits in the muscles of the cervical area and of course makes intubation more difficult if necessary.

Pickwick's Syndrome

Pickwick's syndrome is so named after Charles Dickens' description of Joe (see Chap. 5, Fig. 5.3), the obese boy in *The Pickwick papers*, also known today as obesity hypoventilation syndrome. It is composed of obesity and an arterial pCO₂ above 45 mmHg when awake. Hypersomnolence, fatigue, morning headaches, sleep apnea, chronic hypercapnia and hypoxia, polycythemia, and, finally, pulmonary hypertension are frequently added. It is a condition typical of adults, and descriptions in the pediatric age group are rather scarce and always occur in morbid

obesity with BMI-zs > 5 SD or in syndromic obesity. The cause is related to the aforementioned mechanical overload of the respiratory system where hypoventilation, even during the day, leads to hypoxia-hypercapnia which results in a reduced response of the chemoreceptors and impaired breathing control. Polysomnographic studies have shown how excessive daytime sleepiness in obese children or adolescents may be related [26] to respiratory disturbance during their sleep.

Two aspects, as a clinical corollary, can illustrate the current situation of cardiovascular and respiratory disease in children and adolescents. On the one hand, there is the situation of diagnostic Cinderella within obesity, as is correctly editorialized [133], and, on the other hand new actors hardly controlled at individual level, such as the high ambient NO_2 , hence the chronically exposed adolescents are at risks of developing higher systolic pressure [134]. Finally it should be taken into account the overestimation of prevalence due to a shortened technique in the measurement of blood pressure. These circumstances, unfortunately, are real, and it is precisely the pediatrician who can and should consider both and contribute to a more effective cardiovascular prevention.

Type 2 Diabetes (T2D)

Formerly known as non-insulin-dependent diabetes, type 2 diabetes accounts for 90% of all cases of diabetes in the general population in the current millennium and is also an increasingly detected pediatric disorder. It can be defined as a heterogeneous disorder characterized by peripheral insulin resistance to which, after a period of time, beta cell failure is added, preventing the production of the increased insulin demand (liver, muscle, and adipose tissue). In contrast to T1D, these patients have a relative rather than absolute insulin deficiency and almost no tendency to ketoacidosis. In addition, there is no autoimmune destruction of beta cells and therefore no immune markers characteristic of T1D such as GAD or IA2 autoantibodies. It was also known as adult type diabetes because in 90–95% of cases, its onset is at that stage of life [135], but with the global increase in obesity, its pediatric onset is a fact and when obesity and T2D occur in a type 1 diabetic, the clinical distinction can be complicated, as seen in the 2018 Danish pediatric cohort study. The concept of *prediabetes* is more of an adult one, but with the rise of T2D in the preadolescent, it is of increasing interest here and is assessed by various biomarkers including elevated HbA1c ($>5.8\%$) or fasting blood glucose ($>100\text{mg/dl}$) as well as its clinical development; it would affect either 6% or 15% of obese adolescents depending on the biomarker used. When glucose intolerance and a state of T2D are established, which usually occurs in 10–15% of prediabetes, depending on the gene load and severity of obesity, it is a preliminary step to cardiovascular disease and other comorbidities, including stroke. Prospective multicenter and long-term studies (TODAY, SEARCH, HEALTHY, or the European CARLA or SHIP) with various therapeutic options have undoubtedly increased our knowledge of the problem, although it is not clear the benefits or harms of screening for prediabetes and type 2 diabetes in children and adolescents [136].

From an epidemiological point of view, the data from the CDC could not be more shocking (*CDC Report: More than 100 million Americans have diabetes or prediabetes. Media Relations* <http://www.cdc.gov/media>. Jul 18, 29217). In pediatrics it is worth noting how most studies are done in young people aged between 10 and 20, which indicates the age of onset of T2D. Classical studies such as NHANES 1999–2002 estimate a prevalence of 1.46/1000 for this age group, with more than 5000 new cases per year. This trend is increasing according to the most recent report of the *SEARCH study*, and after the study of 1.7 million young people (aged 10–19) in 2001, the prevalence was 0.24/1000 (95% CI, 0.21–0.37), and in 2009 on a population of 1.8 million, the prevalence was 0.46/1000 (95% CI, 0.43–0.49) with a large accumulation in American Indians, followed by the population of color, Hispanic, and finally white. Unfortunately and in a more recent publication of *SEARCH* [137], the prevalence among people aged 10–19 has increased by 3.4 % (95% CI 3.1–3.7). Prevalence in Europe is highly variable depending on the accuracy of data. In the Swedish study of 1126 overweight 11–13-year-old boys, 2.1% had prediabetes. As a summary of the Global Burden of Disease study on T2D for adolescents and young adults between 1990–2019 [138], it can be said that in this 30-year period there has been an increase in the disability adjusted life years (DALY), in the incidence rate per 100,000 population from 117 to 183 and in the mortality rate (also per 100,000) from 0.74 to 0.77, which indicates a global increase in this age segment and specially in low-middle income countries. The Asian population in general is more prone to develop T2D than the European population for similar body mass indices. Another epidemiological finding from these cohort studies is the fact that the progression to overt diabetes in young people is faster (2.5 years) than in adults (10 years) and that once established, it is possibly a one-way journey. To understand the slower progress in the management of the complications of T2D, it is worth considering Dr Blumenthal's three points (Commonwealth Fund Jul 5 2019, doi: 10.26099/y0ep-ps36): (1) the addition of younger patients to the cohort; (2) the relaxation of glycemic control in the population; and (3) (USA) the recent restricted access to diabetes clinics. The primary cause of T2D is insulin resistance, secondary to chronic hyperglycemia, hyperlipemia, and circulating elevation of pro-inflammatory factors. The location of ectopic fat in the liver and visceral compartment is a reliable predictor of insulin resistance, T2D, and cardiometabolic disease, but not all obese people have the same degree of resistance, nor do all obese people have the same beta cell dysfunction.

Genetic factors have been known for a long time after the concordance of T2D in monozygotic twins, but the reality is that the alterations of a gene are rare; however their number is increasing as in the case of the deletion of 19 base pairs in the *LIPE* gene that encodes the synthesis of *hormone-sensitive lipase* (HSL) and that conditions in the Amish the appearance of T2D and other comorbidities [139]. Similarly, with a larger cohort analyzed by exome sequencing studies, a *missense* mutation in the *HNF 1A* gene produces a protein that is associated with a high prevalence of T2D (OR 5.48, 95% CI 2.8–10.6) [140]. Whole genome sequencing studies, also known as GWAS, allow the identification of genetic variations, also known as genetic polymorphisms, which are statistically associated with increased susceptibility and influence for certain diseases, in our case T2D. Variations in the genomic

locus of transcription factor 7-like 2 (TCF7L2) confer a certain risk for the development of T2D, just as we saw earlier, as do polymorphisms in the FTO gene for overweight and obesity. Previous maturity-onset diabetes of the young (MODY) is almost certainly a monogenic diabetes as the ProDiGY [141] results recently have shown after studying T2D misdiagnosed youths. These variants are responsible for a moderate proportion of predisposition, but as this affects many people, their knowledge could in the future be of preventive interest. The discovery of new variant *loci* has only just begun in this case, but unlike other pathologies where epigenetics and through certain transcription factors can modify the development of the disease, in our case it is no longer a more theoretical approach, and the presence of the Pregnancy And Childhood Epigenetics (PACE) consortium will contribute to fill part of the knowledge gap of this important biological stage. Moreover, the association between food deprivation in children and young people during the Second World War in France and the subsequent development of T2D have been a known fact. Certain ethnic origins (African Americans) are also more predisposed to obesity and T2D.

Environmental factors usually interact with each other, making it difficult to ascribe a direct causality. The important role of positive energy balance in the genesis of insulin resistance has already been analyzed, but this is also the main cause of overweight and obesity, together with physical inactivity. In this regard, it is worth mentioning the Canadian study, due to its greater specificity, conducted in adolescents at risk of T2D, in which abdominal and hepatic fat deposits are quantified, as well as fat and sugar intake by means of a well-known questionnaire [142]. It concludes that excessive fat intake leads to hepatic steatosis while refined sugars lead more to visceral obesity and T2D, all in the context of an evident insulin resistance in adipose tissue with release of triglycerides into the bloodstream and hepatic deposition of fatty acids. Other factors, such as lower socioeconomic status, or low physical activity and sedentary behaviours [143] and belonging to certain ethnic groups, clearly favor T2D (and also obesity). Birth weight is an important factor, and it is known that increased birth weight when assessed by *zs-score* implies significant increases (*hazard ratio*, HR) in the risk of T2D in young adulthood. A multiplicity of causes have also been invoked ranging from maternal smoking, psychosocial stress, and administration of antidepressants (selective serotonin reuptake inhibitors) but may require more informative studies. The well-proven relationship between low 25OHD levels and elevated HbA1c levels in adults [144] is pertinent to mention here, given the frequency of vitamin D insufficiency in pediatric obesity. Other factors that may play a predisposing role are the quality of carbohydrates ingested, i.e., lower intake or poorer quality of whole grain foods is associated with an increased risk of T2D, according to the Harvard prospective studies [145].

From a causal point of view, one can add to the above the lesser incretin effect in the transition from pre- to diabetes or, what may be more interesting, the association with puberty affecting beta cell function and insulin sensitivity (impaired glucose tolerance).

The clinical profile of TD2 is different from that of TD1, as it appears in obese or very obese children or adolescents, with onset at pubertal age, with a positive

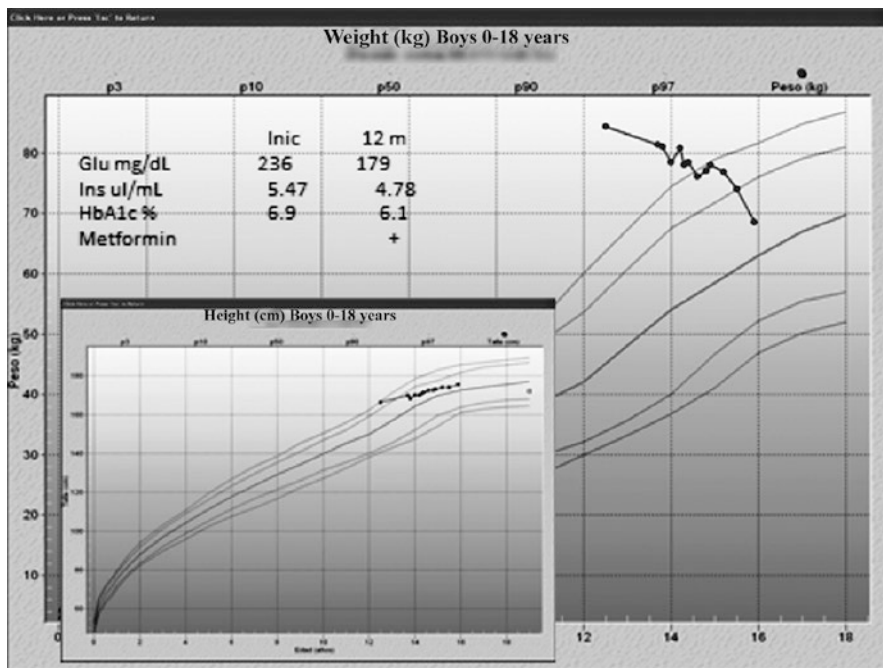


Fig. 6.7 Type 2 diabetes in an obese adolescent. Of note are his family history, the presence of axillary acanthosis, and impaired glucose tolerance. Despite normal BMI and normal growth, type 2 diabetes has been established

first- or second-degree family history or at-risk ethnicity. The diabetic picture is attenuated, of slow onset, with discrete polydipsia-polyuria and rare ketoacidosis, and the presence of acanthosis nigricans and elevated blood pressure is typical. Regarding the latter, a recent meta-analysis [146] shows a prevalence of 25% (95% CI 19–31) in children and young adults at the time of diagnosis of TD2 and a prevalence of proteinuria of 22% (95% CI 17–27) suggesting renal damage that should be investigated. Figure 6.7 shows, on the one hand, the favorable evolution of obesity and growth in an adolescent and the establishment of T2D. This sequence is important because once established, the irreversible phase is reached due to complete beta cell failure.

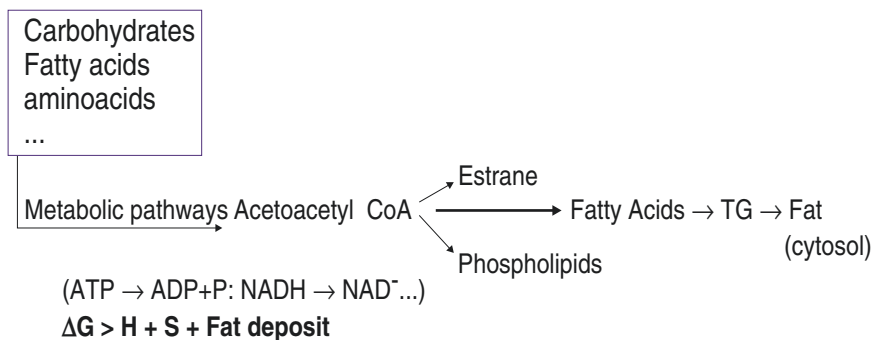
From the biochemical point of view, it is worth noting how glycated hemoglobin levels above 5.7% as established by the *American Diabetes Association* are a better indicator than fasting blood glucose (>100 mg/dl) for performing the oral glucose tolerance test. The 1-h abbreviated form is a good independent predictor of prediabetes progression [147] while indicating a worse metabolic phenotype in adolescents. The degree of insulin resistance is clinically important for prognosis in adults: level 3, the most resistant, is the most prone to severe diabetic nephropathy, while the others are more prone to retinopathy, according to a recent Swedish study [148] and which would complete the previous Swedish findings of frequent prediabetes. In this respect, it is worth considering the eventual *tracking* from mere initial overweight to insulin resistance and T2D and other comorbidities as the former is itself

a risk factor according to the aforementioned Finnish study. The association of TD1 and TD2 during adolescence leads to a higher prevalence of comorbidities than TD2, whereas isolated TD1 has the lowest proportion of comorbidities [149]. Once again the term “metabolically healthy obesity” is misleading to all, and following the UK Biobank’s extensive analysis, it should be avoided.

After the analysis of these comorbidities, it is appropriate to comment on the value of the thickening of the arterial intima-media layers in the pediatric age. By means of a careful ultrasonographic technique applied to both carotid arteries (at 1 cm from the bulb and on the posterior wall of the artery in the longitudinal section), the measurement of this defined distance (0.20–0.60 mm) is obtained. Cholesterol deposition increases the thickness of this part of the artery, which is why in adults it has classically [150] been considered a marker of subclinical atherosclerosis. Risk factors for thickening include familial hypercholesterolemia, obesity, arterial hypertension, and T2D. All of them can also occur in the pediatric age, but they have less impact on the magnitude of the deposit, preventing the interesting identification that would correspond to the lipid striae of the vessel. On the other hand, this thickness can be altered by other circumstances such as *Chlamydia* infection or weight gain in the first year of life. In our experience and using the appropriate transducers, the exploration is complex, and its reproducibility has been variable.

Preventive and Therapeutic Approach to Pediatric Obesity Comorbidities

Taking into account the high percentage in which obesity coexists and precedes the appearance of comorbidities, it is the healthcare system itself that should adopt an approach beyond the pediatric clinical care level. The preventive approach to gain effectiveness should be limited to those clinical situations with a higher cardiometabolic risk: NAFLD, dyslipidemia, dysglycemia, elevated blood pressure, and obstructive sleep apnea. Precisely in this environmental context of the pediatric patient, the Japanese study [151] should be considered, which returns to the conceptual bases of comorbid conditions and where the annual increase in BMI in adults with NAFLD is pointed out, which implies greater complexity and mortality than the alteration of other cardiometabolic risk factors traditionally considered. From the experience of adults with NAFLD, (and T2D) the decrease in the glycemic index and the glycemic load, foods can be taken to pediatric practice due to the improvement of insulin resistance. It is probably premature to use ceramides for this purpose. In general and for this approach, parents and family should be involved, recommendations should be culturally appropriate, and myths should be scientifically debunked [152]. After this step, two preventive principles should be assumed: one, the importance of the first law of thermodynamics, according to which the energy provided by food, if not consumed, will be stored (in fatty tissue), and two, the metabolic facility (Fig. 6.8) with which this excess energy is transformed into lipids [153]. With respect to the first, and in clinical terms, one must consider the



ΔG : free energy; H : enthalpy; S : entropy

Fig. 6.8 Imbalance between nutritional energy supplied and energy used. Anabolic reactions lead to cytoplasmic fat synthesis

energy gap or difference between total energy intake and total energy expenditure (TEE) and how this difference, however subtle, will lead over time to obesity and how it must be adjusted after weight loss. Although exact measurement is not possible, it is possible to have a sufficient approximation at the level of care. With respect to the second, the model borrowed from the Prader-Willi syndrome and in which some comorbidities are less related to insulin resistance than to excess fat in body composition should be taken into account and assessed prospectively, without forgetting the contributions of basic research.

It is worth addressing preventive actions as early as possible to gain effectiveness, hence the interest in controlling the overweight or obese status of the pregnant woman in addition to general preventive rules [154]. It is well documented that obesity in the mother-to-be has adverse consequences for both the mother and her offspring, one of which is extreme preterm birth [155]. In addition, pre-pregnancy weight reduction and moderate weight gain during gestation decrease the number of preterm births and premature rupture of membranes. Maternal obesity in baboon primates involves epigenetic signals (micro RNA, miRNA) which modify the hepatic content of lipids and glycogen in the fetus [156] and open up new fields of research. Optimal fetal growth depends on intrauterine nutrition mediated by the maternal-fetal axis, glucose, insulin, and *insulin-like growth factor-1* (IGF-1). The fact is that both fetal growth restriction and overgrowth (large for gestational age) are associated with the subsequent development of obesity [157]. Epidemiological studies worthy of consideration have shown how this maternal obesity is associated with a high body mass index at the age of 2 [158] and abdominal obesity [159]. Hence the importance of bariatric surgery prior to pregnancy of the obese mother-to-be because of the possibility of favorable effects on the vascular function of her offspring, as shown by preliminary data from an ongoing study [160]. Once birth has occurred, it has classically been said that overweight before the age of 3 does not carry a risk for later obesity, but we now know from long-term epidemiological

studies that, although the onset is usually between 5 and 6 years of age, infants who are overweight between 6 and 12 months are also at increased risk of later obesity [161]. Future appetite/satiety regulation is strongly influenced by two events that occur during gestation: fetal undernutrition (small for gestational age) and in particular maternal obesity on high fat diets, both of which are associated with subsequent hyperphagia that contributes to offspring obesity [162]. Proliferation of the orexigenic neurons of the arcuate nucleus is more difficult to prevent in the first case but clearly can and should be done in the second (maternal obesity) and should be continued after birth and considering the almost invariable projection of pediatric and adolescent obesity into adulthood and thus of comorbidities. It is worth bearing in mind that being overweight at 7 years of age and provided it is maintained until puberty will be associated in adulthood with type 2 diabetes according to the large study [163] which followed more than 62,000 Danes from the age of 7–26 years of age. Changes in behavior and dietary habits, including moderate weight gain of the small for gestational age newborns in the first year of life, should also be considered, particularly if addition of further specific issues such as smoking and alcohol consumption occur in adolescents. Preventive actions stem from the DPPOS study carried out in adult patients [162] where the 3224 patients with prediabetes were randomized to 3 interventions: lifestyle, metformin, and placebo. Lifestyle change (diet and physical exercise) with the addition of metformin was by far the most effective, reducing the conversion to T2D by 60%. Hence, in the pediatric segment, weight control, diet and nutrition, and physical activity are recommended through specific attitudes especially in children at risk of obesity, in practice all those whose BMI is close to overweight (~ 1 SD). It is beyond the scope of this paper to deal with these major sections [164], but it is worth mentioning some aspects because of their interest [165]. Adequate vitamin D repletion [166] is an essential goal. The importance of replacing or not replacing saturated fat and for sure trans fat [167], or the recommendations to eat foods rich in protein after the required physical exercise, questions whether they can be predisposing factors, and they are not well focused in our society. On a more general (state) level, contamination with xenobiotics [134, 168] should be considered, especially in cases of NAFLD due to the progression of the disease that they induce.

The *therapeutic aspects* of the usual comorbid conditions in adults, when applied in the pediatric age, are surrounded by some controversy, especially regarding pharmacological treatment. The general treatment of obesity is probably the most reasonable and safest and to be successful would require a multidisciplinary approach where lifestyle change has adequate support and control. A 10% reduction estimated by relative body mass index (rBMI) is effective even in improving liver histology. The details of this comprehensive program have been discussed previously [154]. Within this general approach, bariatric surgery should be considered which, having demonstrated its efficacy in adults, is starting to be performed in adolescents (see Chap. 9) and which improves not only BMI evolution but also lipid profile, hypertension, and even obstructive sleep apnea [168], adenotonsillectomy was not associated with symptom resolution [169]; in the latter case, the use of personal type II apnea monitors for home use has been shown to be useful. In particular,

surgery should be considered in the treatment of T2D in severely obese adolescents [170] due to its better results compared to intensive medical therapy, which should not be neglected.

With respect to TD2, the appearance of new treatments is incessant, but the use of metformin was unavoidable for the moment, but the positive meta-analyses carried out in adults have demonstrated its safety and efficacy not only in glycemic control (Hb A1c) but also in lower cardiovascular mortality, confirming its position as the first line of therapy. If we add to this its mechanism of action that decreases the availability of glycerol and lactate as precursors of gluconeogenesis in addition to other minor actions [171], its use in pediatric patients should not be limited despite the fact that the initial enthusiasm for metformin use has probably moderated in favor of association with insulin and the availability of new drugs. The new drugs (see Chap. 9) are molecules derived from the naturally occurring 30–31 amino acid glucagon-like peptide-1 (GLP-1) receptor agonist. They have usually been acylated to increase their half-life from 1–2 min to more than 10 h and act primarily on the initially called incretin hormone system exerting a lowering function on postprandial glucose levels. They do this by stimulating beta cells with insulin release, inhibiting the release of glucagon from alpha cells when blood glucose levels are higher than those of fasting. They also cause a certain decrease in the rate of gastric emptying and nutrient absorption which may lead to reduced food intake [172]. The two principles that perform these functions are GLP-1 and to a lesser extent GIP (*gastric inhibitory peptide*), and both are rapidly inactivated by an enzyme, DDP-4 (*dipeptidyl-peptidase-4*). This has given rise to a group of drugs known as “GLP-1 receptor agonists” or simply “GLP-1 agonists” and DDP-4 inhibitors to increase GLP-1 activity and which have a clear and longer lasting insulin secretory and glucagonostatic effect and are of two types: the short- or long-acting GLP-1 AR (liraglutide, dulaglutide, exenatide, semaglutide) [172, 173] for subcutaneous administration or the expected oral one such as semaglutide. A publication in *The Lancet* in 2019 [174] demonstrated the superiority of the oral route of semaglutide [174], or in combination with glucose-dependent insulinotropic polypeptide due to the inhibition of glucagon in states of hyperglycemia [84]. A very practical hint is to keep glycosylated hemoglobin below 6.0 %, then there is a clear reduction of major adverse cardiac events (MACE), this approach would be ideal for obese adolescents [175], these were the initial landmarks in T2D treatment. Efficacy versus subcutaneous liraglutide was not only evident for the reduction of HbA1c levels but also as a reducer of BMI in the adult. Another more varied group of drugs is formed by the empagliflozin (decrease of glucose tubular reabsorption) of increased clinical use or sildenafil, among others. These types of therapies are not applicable at the moment to pediatric T2D, where even long-acting insulin analogues such as detemir, glargine, or degludec may be useful because they reduce the rate of nocturnal hypoglycemia, even the reinstated inhaled insulin could be taken into account, as well as continuous monitoring of blood glucose in real time or not. At this point, it is also important to consider the following non-medicinal points in the management of adolescent T2D: the help provided by the use of low-calorie sweeteners, the isocaloric restriction of fructose in the diet, the practice of even moderate physical exercise, the normalization of overweight during childhood, and that the reversibility

time of the process has a limit marked by the decline of beta cells. Not to forget that an adequate control of T2D in youths will reduce their future cardiovascular risk. In order to increase effective preventive interventions for adults, the US Preventive Services Task Force (USPSTF) [176] has launched a new and interesting recommendation statement for screening of prediabetes and T2D. A more detailed description of this can be found in the pediatric chapter of the American Diabetes Association Standards [163].

With respect to the development of cardiovascular disease, the scientific statement of the *American Heart Association* [177], which clearly defined national goals for the promotion of cardiovascular health and reduction of disease for 2020 and beyond, deserves full consideration. In short, it aims to reduce cardiovascular disease throughout the life cycle and considers it essential to start from the pediatric age. To this end, it establishes seven measurable criteria for three age segments: 2–5 years of age, 6–11 years of age, and 12–19 years of age (Table 6.5), which allow the cardiovascular health status of the population (or of the child) to be classified as poor, intermediate, or ideal, according to easily obtainable cut-off points. The application to a large group of children from one of the NHANES studies could not be more illustrative. The application of this document (and Table 6.5), although designed for the United States, could increase the intermediate and ideal health groups. Interventions on smoking, aimed at the 12–19 age group, BMI, physical activity, and diet are part of lifestyle change (see Chap. 8), but their reinforcement is more than justified at the time when the appearance of a comorbidity is detected, especially in this case because of the possibility of slowing myocardial hypertrophy [178]. The use of drugs is more focused on adults, and it is appropriate to mention here and in the pediatric context how fats are not the primary factor in the obstruction of the arteries, and it is the inflammatory process that is more responsible for coronary artery disease.

Given that pediatric hypertension predisposes to adult hypertension and that this is not frequent [125], treatment follows the indicated guidelines with the use of ACE inhibitors or angiotensin receptor blocking agents, which are the most used and safest in the pediatric age group. With respect to sodium intake (and its urinary monitoring), low sodium intake is not preventive of hypertension, although as is well known high sodium intakes correlate with hypertensive levels and especially how

Table 6.5 Cardiovascular health states applicable to pediatric ages

Measurable parameter	Bad	Intermediate	Ideal
Smoker			No, never
BMI	>95 centile	85–95 centile	<85 centile
Physical activity	None	0–60'/day moderate	>60'/day moderate or vigorous
Healthy diet ^a	0–1 component	2–3 components	4–5 components
Total cholesterol	≥200 mg/dl	170–199 mg/dl	<170 mg/dl
Blood pressure	>95 centile	90–95 centile	<90 centile
Fasting blood glucose	≥126 mg/dl	100–125 mg/dl	<100 mg/dl

^aHealthy diet assessment is based on adherence to the general recommendation of vegetables and fruits ≥150 g × 3/day; fish 120 g/week; Na ≤ 1500 mg/day; sugar-sweetened beverages <1 l/week; fiber foods ≥3 servings/week in the context of a diet of ≤2000 kcal/day [177]

reducing sodium intake linearly reduces both systolic and diastolic pressures [179]. In summary, the population should maintain daily intakes of no less than 500 mg in children and 1500 mg in adults (www.nhs.uk/live-well/eat-well/salt-nutrition/). During the first 6 months of life, repeated exposure to salty foods leads to the development of a later preference for salt-rich foods and beverages, so this early period of life should be adequately monitored [180]. Pediatric hypertension of other (organic) causes has another approach closer to antihypertensive drugs [181]. The traditional advantage of physical exercise in the control of hypertension has perhaps been challenged by the AHEAD study [182] in which more than 5000 adults underwent intensive lifestyle change. Surprisingly, and despite the improvement in other comorbidities, cardiovascular events did not decrease, but this should in no way imply a relaxation of the maintenance of physical exercise. Once again, the early approach to CVD is essential. A study of more than 4400 cases of dilated cardiomyopathy and to a lesser degree hypertrophic cardiomyopathy followed for an average of 37 years [183] showed an association with overweight and obesity suffered in adolescence, and this association was multiplied by 8 when the BMI was greater than 35 kg/m².

With respect to non-alcoholic fatty liver disease (NAFLD), even moderate reductions in BMI lead to improvement in NAFLD. For the above reasons, diets rich in glucose and fructose precursors should be minimized and replaced by diets with low glycemic load and low fat content. Two recent studies [184, 185], although of short duration, show unequivocally how sugar-free diets improve hepatic steatosis in adolescents with NAFLD. The effect of high sugar intake has brought about a revival, albeit timidly, of ketogenic diets, but it does not seem to be the most appropriate in the case of comorbidities or even in the case of overweight. It is important to take into account the possibility of other factors of liver damage that can lead to confusion in obese patients with NAFLD [186] and which include common drugs such as analgesics, diclofenac, amoxicillin-clavulanic acid, antiretroviral drugs, or chemotherapy. In this same context of increased steatosis, it is worth considering a study carried out in more than 700 adults [187] and which relates the high intake of highly cooked red meat to the development of NAFLD (OR 1.92; 1.12–3.30); alcohol consumption in this circumstance favors the development of cirrhosis. Returning to the pediatric age group, the association of takeaway food consumption with risk factors for type 2 diabetes and cardiovascular disease and of course obesity has been demonstrated [188]. The hexose transporters also known as the “GLUT family” include 14 transmembrane proteins of which GLUT 2 and GLUT 8 have a large presence in liver cells carrying out hepatocyte transport of glucose and fructose. The disaccharide trehalose is able to inhibit GLUT transporters and thus exert autophagy by decreasing intrahepatic lipid accumulation in the mouse. This preventive approach, although brilliant, is still far from being applicable to obese children [189]. Because of the long life expectancy of children with NAFLD, early diagnosis is important to reduce complications in their lifetime [190]. The quality of the fat is perhaps less important than initially thought; even the administration of docosahexaenoic acid (22:6 *n* – 3) or other long-chain polyunsaturated fatty acids including conjugated linoleic acid has not been as effective as expected [191, 192].

Drug treatment of NAFLD is rarely used in the pediatric age group [193]; antioxidants including probucol (inhibitor of cholesterol oxidation and, consequently, of foam cell development) have been used in both adults and children with irregular results. The use of insulin sensitizing agents (glitazones, PPAR-gamma agonists) has been limited in pediatrics, and, finally, the use of metformin [194] with or without vitamin E has not been superior to placebo [195]. Liraglutide as a glucagon-like peptide (GLP-1) receptor agonist has experimentally demonstrated a powerful anti-inflammatory action in steatohepatitis, and in humans semaglutide has already shown a high capacity for resolution of the process [196, 197] and may be a therapeutic option in pediatric patients. The therapeutic line is always denser and with a greater number of new contributions than the preventive line. Thus, new drugs such as pentoxifylline (xanthine derivative) with anti-TNF-alpha action [198, 199] or phentermine/topiramate [200] or pegbelfermin, a PEGylated fibroblast growth factor analogue, are possibilities that, at least initially, seem effective. The availability of monoclonal antibodies that bind to various interleukins may represent another therapeutic avenue not far off, but it is necessary to wait for their approval by the Medicines Agencies. Within this aspect of new therapies, it is worth considering that in addition to white adipose tissue (fat deposit) and brown adipose tissue (thermogenic), there is also the so-called beige adipose tissue, which develops within the white adipose tissue after certain stimuli. The interest lies in the fact that in its mitochondria there is *uncoupling protein-1* (UCP1) and, when this is activated instead of synthesis, it stimulates the activity of the respiratory chain and the heat resulting from the combustion of the various substrates is distributed to the rest of the body through the circulation contributing to energy rebalancing and weight loss. Progressive knowledge of the genes responsible for this stimulation (Ucp-1, Cidea, and Pgc1-alpha) would allow new therapeutic targets through increased thermogenesis [201]. Perhaps more promising for slowing the progression from steatosis to steatohepatitis is the assessment of variants in the genome-wide study that are associated with chronic liver pathology [202]. From the experience of adults with NAFLD, the conclusion that the decrease in glycemic index and dietary glycemic load with due improved insulin [203] resistance can be applied to pediatric practice is premature. It is probably also premature to use ceramides [204] for this purpose.

With respect to dyslipidemia in the pediatric age group, LDL-C levels that would indicate treatment with statins in adults are rarely reached, but if this occurs, the administration of ezetimibe, alone or in association with them, is advisable [205] and with adequate time control. This preventive and curative approach could be concluded with a reflection that is none other than its relative efficacy. Systematic reviews [206, 207] can help when considering specific actions in the therapeutic approach which is normally of long duration; again and with the long-term experience it is evident that the general actions taken against obesity within this long period of time, which were mainly dietary, entail a decreased risk for general mortality and particularly that of cardiovascular origin. Perhaps more current approaches such as the relationship between dysglycemia and chronic disease [208] may be useful. It is of clinical interest that when the diagnosis of NAFLD has been

confirmed by biopsy, the occurrence of prediabetes and T2D is not only increased but also interacts negatively with hepatic steatosis, implying a closer follow-up [209]. As regards these comorbid conditions in adolescents, we should consider the good results obtained after bariatric surgery [99]. A complementary information appears at the treatment (Chap. 9).

It could be concluded that obesity, insulin resistance, and a proinflammatory status are the most common basic factors for the subtle development of comorbidities and that the practice of the simple searching clinical task for cardiometabolic risk factors in the overweight or obese pediatric population will contribute to an earlier diagnosis and a prevention perhaps not specific for the moment, but effective through antiobesity actions. To conclude, and in relation to comorbid states and obese children or adolescents, we must always think of the frequent and subtle coexistence of several of these states in a single patient, just as in the case of adults, and act accordingly. In early prevention, the gastrointestinal cancers (of the esophagus, stomach, pancreas, colon, gallbladder, and liver) have not been mentioned, despite their stark impact on the life of the obese adult [210]. This is due to the inexistent relationship in childhood, but it should be a firm argument for early pediatric obesity prevention, within the context of the increasing prevalence of obesity throughout the world and the implications of Dr. Ruth De Bruyne's phrase *Eat now, pay later* for pediatric fatty liver disease.

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Chapter 7

Evolution, Trajectories, and Prognosis of Pediatric Obesity



Introduction

The development of pediatric obesity is difficult to synthesize because unlike other diseases its clinical evolution is varied and erratic due to the multiple external circumstances and multiple interventions that have been carried out; hence the repeated references to studies are a constant. Its natural history is not well known although it could be recognized as a chronic condition. The effects that pediatric obesity will have on the quality of life, lifespan, and the economic cost that it and its comorbidities will cause in adulthood are well outlined in the four global evolutionary phases described by Ludwig in 2007 [1]: increase in pediatric prevalence, appearance of comorbidities in the pediatric age, important consequences in adulthood, and appearance of the state of transgenerational obesity. These phases are not watertight and the overlaps between them are evident. According to Ludwig, the onset of increased frequency in the pediatric age is situated, perhaps belatedly, in the 1970s. The evolution of the weight of children and young people has perhaps not aroused the health interest of other chapters and as is well editorialized [2]. If 23% of a large male population has gained 20 kg between the ages of 18 and 55, the subject is no less relevant than other key factors of obesity. The concept of evolution or *tracking* is supplemented by the perhaps more reasonable concept of trajectories of body mass index (BMI), abdominal circumference, or weight paths.

Of the series of publications of the *Bogalusa Heart Study*, those of 2005 and 2009 [3] concerning the evolution of obesity already showed a strong association between the increase in BMI in children and adults, and clearly less between adiposity (estimated by skinfolds), when assessed after 18 years of development. When it comes to obese adolescents, 86–90% of them will become obese adults. When the *tracking* is carried out according to the *z-score* of the body mass index of a population of 10-year-old boys, it can be seen that in the underweight group (−0.6 SD), 11% become obese, 36% in the normal weight group (+0.5 SD), 59% in the

overweight group (>1.3 SD), and 87% in the obese group (>2.0 SD). These figures speak for themselves in terms of sample size and follow-up time. The important study in Singapore ($n > 12,000$ and follow-up up to 33 years) shows values based on the area under the BMI curve, highly concordant with this path. There is a series of studies carried out in Europe, perhaps of a smaller size, but which undoubtedly show how the existence of poverty or pubertal advancement, especially in the female gender or the level of maternal education, undoubtedly influences *tracking*. One fact that should be highlighted is how in this series of studies analyzed there is no uniformity in the definition of overweight and obesity (different percentiles and cut-off points), which makes it difficult for the different samples to be homogeneous and comparable due to the areas of overlap. This situation deserves to be considered in the context of cancer-associated obesity mortality [4] which remains practically irreducible. Furthermore, the distribution of body fat and its relationship with overall mortality in adults [5] make clinical sense when it is assessed through the waist/height ratio (>0.5), which is being incorporated into pediatric anthropometry.

More recent studies have applied not only the longitudinal criterion (prospective and lasting decades) but also the concept of cohort (a group of people who share a series of characteristics at a given time), which is more informative. Thus, the study by Buscot [6] on a Finnish population of 2717 subjects with 8 staggered measurements between the ages of 3 and 49 years and using the novel Bayesian regression hierarchized by parts determines the existence of two critical periods where BMI trajectories stabilize, a clear and well-defined one, which is before the age of 6 and another around adolescence and young adulthood and where this stabilization has different times depending on the gender of adolescents. The group of obese people who had managed to reshape their BMI by the end of adolescence already had lower BMI values at 6 years of age, and the trajectories stabilized (*plateaus*) from the age of 16 for girls and 21 for boys. Furthermore, when compared with the young people who did not suffer from overweight or obesity and remained so until the end of the study, those who did develop obesity already had a greater increase in BMI from the age of 6 than the control group, and this continued linearly until the age of 30. This allows us to conclude that in order to attempt preventive action against future obesity, we should start before the age of 6 (see Chap. 8, *Prevention*) and that the other period of action should start in adolescence for girls and later for boys, but this would already be secondary prevention. In a practical order and before any case of overweight or obesity, it is always necessary to obtain the weight history or preferably the BMI and waist circumference of the specific child.

Less ambitious studies have also demonstrated points of interest. The 2006 study [7] proposed a specific and longitudinal assessment of BMI in order to detect the increase in percentile (*z-score*, currently) especially before reaching the overweight range in order to moderate this increase. More recently and in another study, we can also appreciate the interest of the assessment of BMI trajectories in students at the University of Vermont [8], where it was observed that from the age of 18 (entry) to 22 (graduation), the percentage of overweight/obesity increased from 23% to 41%. These general outlines show the serious health problem posed by pediatric obesity, especially in terms of its projection into adulthood, and serve as a starting point for the trajectories that follow.

Body Mass Index (BMI) Trajectories

In the pediatric age group, the BMI that identifies obesity in adults requires trajectories whose starting points are becoming well defined thanks to multivariate multiple regression studies and which must be taken into account in the clinical field of obesity. Important clinical data are supporting the next results obtained after the use of trajectories. Following a chronological order, which are not related to the degree of obesity, there are four points in childhood of special risk for the beginning of a trajectory toward a higher BMI later. The first is high birth weight, and according to a study [9] on 750,000 adults, carried out at an average age of 37 years but who had a record of their birth weight, it has been shown that moderate increases in birth weight (<2 SD) do not present greater risks of obesity and/or comorbidities than in newborns of normal weight. However, if this is higher than 2 SD, the association grows and has a maximum value when it exceeds 3 SD; therefore this group of newborns would require preventive measures from birth. The British Birth Cohort 1958 follow-up to the 2019 publication is not as prescriptive with respect to birth weight and subsequent complications. Another large Scottish cohort of over 118,000 mother-newborn pairs does show a clear association between gestational overweight and obesity and increased rates of subsequent type 1 and 2 diabetes in their children. In addition, the sex of large preterm infants (<28 weeks) should be considered as a factor in the rate of weight gain, which is higher in girls, and this should be followed up. Extremely similar large data came recently from the University and Children's Hospital of Wuhan. After these data supported by more generalized studies, it can be assumed that preconceptional obesity is a major risk factor for the complications of pregnancy that double when the BMI is ≥ 40 kg/m², in addition to the appearance of cardiovascular risk factors present in the child and in its evolution to adulthood. At the prenatal period maternal obesity is associated with subtle cardiac structure and function (not congenital heart disease) which entail an increased CVD risk specially if this child develops lately overweight or obesity [10], similarly maternal (not paternal) high cholesterol levels are associated with higher body weight during childhood [11]. These common prenatal situations should be the beginning of pediatric obesity and comorbidities trajectories.

After birth, the second point is the infancy period. A prospective study has shown that excessive weight gain between the 1st and 15th month of life and independently of birth weight will require close follow-up because of the associated risk, especially in those who during these first 15 months maintained consistently high and increasing BMI values and in those whose BMI went from low to high and maintained. The trajectory initiated in this period (up to the second birthday) is not as closely associated with subsequent obesity [12] as the increase of BMI which took place in the 2–6-year period; consequently that is the third point at which to start prevention in childhood (2–6 years). Another, European, study with a follow-up of 50,000 children [13] shows how, in older children and adolescents, the increase in BMI in the preschool stage (and less in school) was 1.4 times greater in overweight children than in children with normal BMI. This preschool stage has not been given the consideration it really deserves from a prognostic point of view. Most obese adolescents had normal BMIs as infants (<1 year), but 22% of them were already

overweight before the age of 5 and 50% if the overweight had appeared before the age of 2. If obesity ($>2DS$) had appeared at 3 years of age, this implied that 90% were still obese in adolescence [13]. The development of the University of Queensland predictive model of obesity [14] based on six of the predictors seen in these three periods provides valid information by the age of 8–9. The fourth and final period is that of preadolescence and adolescence, and a study conducted in China [15] shows how the increase in BMI at puberty and post-puberty with a peak at age 14 years implies a stronger association (OR 3.1) with adult obesity. In short, there are four points, which practically represent the entire pediatric age, where the increase in BMI implies a trajectory towards future obesity and its complications.

In addition to the above, the study of trajectories has the predictive interest of comorbidity. The aforementioned critical periods for trajectories are also endorsed by the important Finnish study [16] which, after an average follow-up of 23 years of almost 7000 subjects who were obese in childhood and adolescence, have an increased and quantified risk (relative risk, 95% confidence intervals are omitted) which was found to be 5.4 for TD2, 2.7 for hypertension, 2.1 for dyslipidemia, and 1.7 for carotid intima-media thickness. When analyzing the trajectories of obese children and adolescents who became overweight, or with normal weight before puberty, the incidence of comorbidities in adulthood is completely comparable to that of individuals who were never obese. Also interesting is the course of non-alcoholic fatty liver disease [17], based in turn on the AVON study of more than 13,000 live newborns sequentially assessed up to the age of 17.8. It can be summarized by expressing that increased adiposity between the first and tenth year of life is consistently associated with adverse hepatic findings: elevated liver enzymes, ultrasonography features, and determination of hepatic fat and hepatic stiffness. Along the same lines but with a shorter duration, the Canadian study *Quality* [18] shows an increase in insulin resistance especially where it coexists with an increase in abdominal circumference. The association between adult type 2 diabetes (T2D) and increased BMI during puberty has also been confirmed in large studies [19]. Metabolic risk, although more closely linked to body fat distribution [20], has provided genetic support for the greater or lesser clinical expression of these complications. Similarly, in the study of the four evolutionary trajectories of BMI (decreasing, normal, moderately increasing, and sharply increasing) during the first decade of life in a cohort of 17,000 children and young people, those in the increasing categories had a higher frequency of emotional symptoms. It is important to note the socioeconomic and household educational levels, when they are low (Federal Poverty Level $< 138\%$) the prevalence of obesity in adolescents went up from 17.3% in 1999 to 27.1% in 2018, these social conditions help the prolonged uprising trajectories for pediatric obesity [21]. Aspects of shortening and worsening of the life cycle will be discussed in the section on prognosis.

Beyond the routine monitoring of BMI in adolescence [22], there are few data on interventions for trajectories of increasing BMI, whether moderate or sharp. The study based on the CDC's WIC (*Women, Infants and Children*) and cross-sectional assessment of 22.6 million children between 2000 and 2014 shows that 2% of that population is obese ($>2 SD$, $>120\%$) and shows a stable or even slightly declining trend over the last 5 years, but not in children from low-income families with increasing trajectories, but provided they are cared for at younger ages [23]. Other risk

factors in this study will not be considered here because of their etiological profile. It is worth mentioning how improved dietary patterns attenuate the genetic predisposition to increased BMI [24]; again this extensive experience from the adult has pediatric implications. To conclude these aspects concerning BMI trajectories, two reflections are as follows: The first is the importance of having studies with a high number of observations to which we must add the criterion of precision which has recently been perfectly editorialized [25]. The second, with a more care-oriented profile for professionals dealing with overweight in children, is that they should be aware that the quality of life perceived as normal at that time will be lower when they reach adolescence [26]. The varied BMI evolution has propitiated new polygenic studies on the obesity genetic predisposition. The Norwegian study of 900 single nucleotide polymorphisms firmly associated to (polygenic) obesity in both parents and in their offspring showed a weaker risk for those SNPs in comparison to the obesogenic environment [26]. Therefore, one should not be fatalistic with respect both to the trajectory assigned to the child in the first two or three visits, as this can be influenced both in terms of moderating BMI, as occurs in environments where food is easily purchased, especially if it is ultra-processed (according to the NOVA classification of food, BMJ Editorial 2019; 365: 12299), or applying therapeutic actions.

Excess Weight Maintenance

In these development evolutionary aspects, it must be considered that, once obesity is established, the return and maintenance of adequate weight in the long term are laborious and infrequent due to the recovery of previous habits (and weight) that often occurs. In order to obtain a realistic framework for the treatment of obese pediatric patients in our environment, it is worth considering the experience of the Nutrition, Growth and Metabolism Unit of this Hospital in which 439 obese children and adolescents have been followed for a period of 11 years, with a minimum study duration of 24 months [27]. None was premature, and 13 were diagnosed with syndromic obesity and were therefore excluded from the evolutionary study shown in Figs. 7.1 and 7.2. There is a group with a favorable evolution ($n = 88$), where the *skewness* in the representation of excess weight indicates the difficulty and effort to maintain the relative body mass index (rBMI) below 120% during the more than 7 years of follow-up. A favorable evolution can be considered as the fact that at the end the median rBMI is 117%. The second group ($n = 260$) with unfavorable evolution exceptionally reached a level below this border of 120%, not even in the honeymoon period that usually occurs in the first months of treatment. After this same long period of evolution, the rBMI is exactly the same as at the beginning. There is also a third group that we call of uncertain evolution ($n = 78$), because they were lost after the first visit, probably because their expectation was that the initial care would be easier; their relative body mass index was 135%. Direct analysis of this population indicates that the group with favorable evolution came to this obesity consultation earlier (median age 4 years) and with an initial rBMI of $130\% \pm 12$, while the group with unfavorable evolution came later (median 8.7 years) and with a rBMI of 143.7%. The treatment for both groups was identical, and despite having

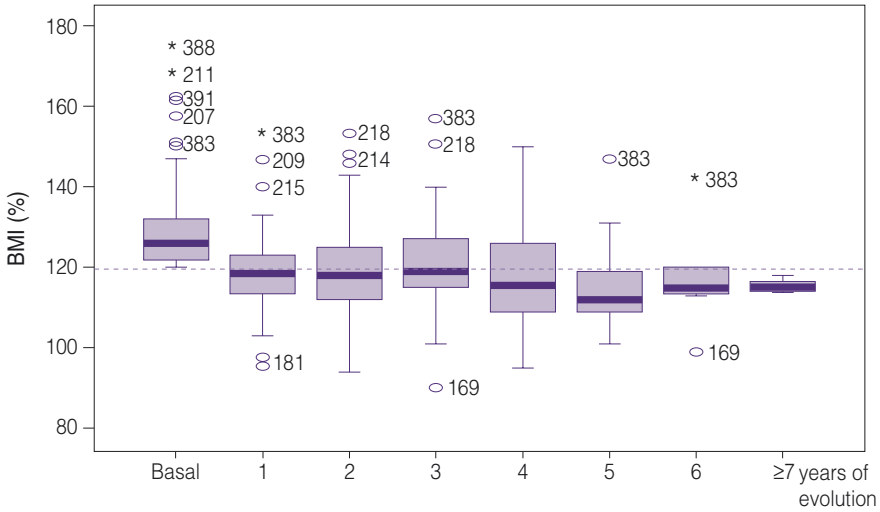


Fig. 7.1 Obesity. Favorable evolution (n = 88)

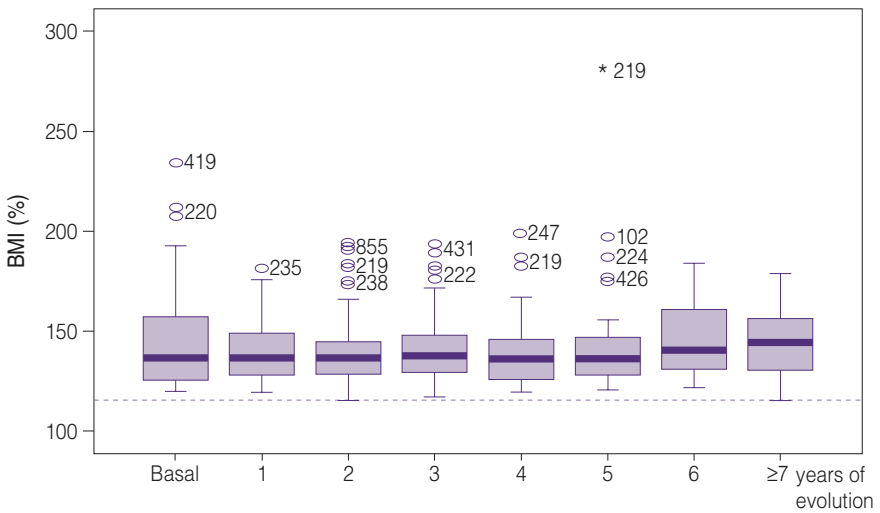


Fig. 7.2 Obesity. Unfavorable evolution (n = 260)

covered the medical and dietary aspects, exercise guidelines, lifestyle, absence of drug treatment, and free access to consultation, the results considered as a whole were not effective. In general, in this weight maintenance, the decrease in physical activity that occurs at that age and the frequent obesogenic environment also play a certain role [28]. There is also a predisposition of certain ethnic groups (Hindus) to visceral fat deposits when measured by volumetric magnetic resonance imaging. The fact of weight regain after any therapeutic plan has been studied in adults and probably this regain is more related to the achieved lower weight loss that was not at the expense of fat mass [29].

Prognosis

With respect to prognosis itself, it could be said that the most relevant data on the health interest of obesity is precisely the risk of death, and it is obvious that practically all deaths occur in adults. The first relevant studies [30] began with data from the *American Cancer Society* in 1998, which studied mortality in 300,000 people without cancer, heart disease, or previous cerebrovascular accidents followed for 12 years and reached the unequivocal conclusion that death from any cause and from cardiovascular disease is associated with the risk implied by a higher body mass index. Similar conclusions were reached by the European study that included more than 350,000 participants from 9 countries, including ours and with adequate regional representation. However, it is the study conducted by the University of Oxford [31] with a prospective analysis of almost one million participants of whom 66,000 died at 67 ± 10 years of age. In both sexes the lowest mortality was in the group with a BMI between 22.5 and 25 kg/m², and as for every 5 kg/m² increase in BMI, there was a 30% increase in total mortality (hazard ratio (HR) 1.29 (95% CI 1.27–1.32), and as within intervals between 30 and 35 kg/m², the average survival was reduced by 2–4 years, and between 40 and 45 kg/m², this reduction in survival was 8–10 years. In this line, it is pertinent to mention the results of the *GBD collaboration report* [32] based on data from 65 million people and of which 4 million deaths coincided with high BMI. The “Countdown to 2030 for non-communicable diseases” (NCD countdown 2030), published in *Lancet* [33] and where 80% of the 32.2 million deaths are caused by cancers, cardiovascular disease, diabetes, and chronic respiratory diseases, all associated with obesity, reaches concordant conclusions. Furthermore, when considering all nations of the world, the mortality reduction target for 2030 would only be reached in 19% for women and 16% for men. Similar conclusions are provided by the *Framingham Heart Study* [34]. At this moment the existing bias when assessing mortality associated to BMI are known [35].

A study carried out in China through an analysis of more than 10,000 deaths in adults whose nutritional history was known shows that, in addition to the usual data already seen previously, a new factor appears, which is that of prevention established from the beginning of adulthood, which they estimate at 25 years. This leads to a reduction in the rate of premature deaths, although the preventive aspects carried out in childhood and adolescence were not considered. However, this study has the interest of providing data from emerging countries and that until now had only been carried out in what is known as the westernized world.

Another aspect to consider is what was rather unfortunately called the “obesity paradox” and which was pointed out in the Oxford study [36]; this term leads to confusion, given that what it really assesses is the J-curve of mortality that favors undernutrition (BMI < 22 kg/m²) and overnutrition [37]. This fact has no clear explanation but is possibly due to (confounding) variables not taken into account, such as cardiorespiratory problems due to smoking [38]. A study covering near 200 countries show unequivocally how high BMI is associated to musculoskeletal disorders [39], not threatening life but creating significant discomfort and limitations to the obese patient. Here we must consider the comorbidities of obesity that favor mortality in adults which are, in order of frequency, the following: vascular [40]; the

13 types of cancer including liver cancer which appear more frequently in the obese adult [41] or the stimulus of metastasis in established cancers [42]; the aforementioned insulin resistance; the decrease in glomerular filtration rate as BMI increases, especially in individuals who are in terminal stages before they die [43]; and respiratory alterations, where the development of strictly diagnosed asthma must be added to the mechanical ones [44]. In children this association is more difficult to demonstrate, firstly because wheezing is not synonymous with asthma and, secondly, because the actual diagnosis of asthma requires objective measures that even in themselves can give rise to interpretative biases. In addition, and among various other causes, we must take into account the loneliness frequently experienced by obese adults ($>30 \text{ kg/m}^2$), which increases over time [45] and to which the chronic feeling of not feeling well contributes, as has recently been seen in the Aarhus study (Denmark). The suggested protective effect of moderate overweight on mortality has not been demonstrated. Besides mortality, other consequences must be taken into account, such as the decrease in life expectancy from 78.9 to 78.8 years in the United States from 2014 to 2015 (The Commonwealth Fund 2017 on Shortening American Lifespan). The study carried out in Finland [46] in a large adult cohort showed the association of obesity with 21 non-overlapping cardiometabolic, digestive, infectious, and other common diseases such as gestational diabetes, this would entail the subsequent appearance of CVD for herself. All together constituted a burden with significant consequences, such as long-term mortality, as demonstrated in another study in Denmark [47]. The impact on quality of life and professional success which appeared in a well-conducted journalistic investigation (Huffingtonpost 2017) refers to the case of weight discrimination especially in women candidates for high posts. The study carried out in 26 European countries and with the innovative technologies of the *Population Research Centre* of Groningen [48] has been able to calculate, apart from the mortality attributable to obesity, the potential gains for life expectancy at birth in 2012 by eliminating obesity-attributable mortality from all-cause mortality, and that have resulted in 0.86 to 1.67 years for men and 0.66 to 1.54 years for women. This, in contrast to the US data, represents about 0.78 years more than those born in 1975. The studies on life expectancy tend to be normally of great scale and not always separating groups of different socioeconomic levels [49], and then comparing life expectancy of obesity with that of a general population may offer a certain bias. Versus this advantage for nonobese people, some new and positive aspects concerning undue discrimination came from countries with a high educational level [50].

Obesity in the pediatric age is not usually a common cause of death, because although the process begins at that time, it takes time for the consequent pathology (cardiovascular, diabetic, hepatic, respiratory, etc.) to be established, which shortens the life of the obese person. A factor of interest in this regard is that pediatric obesity is not in itself a predictor of cardiovascular disease in adults, since if it is cured, it will not have major consequences, but the maintenance of high *z-scores will*, hence the interest in its prevention.

Prognosis of Pediatric Obesity

Two aspects must be considered: the immediate and the long-term prognosis, which has a complementary approach to what has been discussed above and occurs in adulthood.

The long-term prognosis, when viewed from the complications of obesity in adulthood, is clearly associated with obesity that occurred during childhood and adolescence. Large studies show how overweight and especially obesity during adolescence are strongly associated (HR ~ 5) with cardiovascular causation in more than 3000 adult deaths [51]. The same is true of the association between pediatric obesity and the presence of ischemic strokes ($n = 8000$) according to the study carried out in Denmark or the study carried out in Sweden [52] on 41,359 children aged 3–18 years who presented a mortality rate three times higher from the beginning of adulthood than the comparative group, both for any cause and for the usual ones associated with obesity which include suicide. One of the most striking and serious associations is that of severe adolescent obesity, not overweight, with the subsequent appearance of colorectal cancer (HR 1.95) and, to a lesser extent, pancreatic cancer, according to the study carried out by Tel Aviv University on 1.8 million adults [53]. In addition to the unfavorable prognosis of continuing obesity into adulthood, the i3C study was conducted on a population of 12,142 children and adolescents assessed between the ages of 3–19 years and again between 28 and 38 years. Those who suffered from obesity in the first phase presented in the second phase with severe adult obesity (class II/III) in 80% of cases, again confirming the tenacity of tracking. In the i3C analysis of fatal cardiovascular events that occurred in 38,589 participants for the evaluation of childhood risk factors (BMI, elevated systolic blood pressure, total cholesterol and triglycerides, and youthful smoking), said factors were associated with cardiovascular events in the third decade of life [54]. The association of high BMIs with the onset of type 2 diabetes in adults has been firmly established [55] in almost 300,000 children aged 10 years, although there remains a school of thought that the presence of metabolic syndrome in childhood and adolescence is not a good predictor of cardiovascular disease and other adult comorbidities, based on data from low-income countries.

On a more positive preventive level, Mendelian randomization is beginning to bear fruit, as in relation to cardiovascular disease in obese adults, due to the presence of certain SNPs favoring weight gain, according to the UK Biobank studies [56]. The reason probably lies in the analyzed trajectory in which obese children are at high risk of becoming obese adults, following an upward BMI trajectory. However, this may also be related to negative dietary habits, given that the pattern of meals with animal proteins, excessive salt, and a decrease in vegetables (especially those rich in fiber) is associated with dysglycemia and hypertension without forgetting the impact of gonadal hormones that together with obesity and the urinary Na:K ratio have on the elevation of blood pressure [57] and with possible damage to microvascular endothelial function. In this sense and with preventive and therapeutic

potential, there are some markers that in the moments prior to the onset of overweight would indicate a possible resolution upon reaching adolescence [58], the most significant of these being the level of education of the mother (OR 1.92); this circumstance should be considered at the level of general prevention due to the time required for its application to the mass of the population. A study from the Environmental influences Child Health Outcomes (ECHO) program points out how higher opportunity and lower vulnerability neighborhoods, were associated with lower mean BMI trajectory and lower risk of obesity at adolescence [59]. In the opposite neighborhoods a summatory factor could be the possible presence of an altered cognitive development, nowadays also traceable by imaging procedures [60] new long-term prognostic finding comes from the study [61] of 2.6 million healthy young men (16–19 years) who were candidates for the Israeli army and who were followed over time. Those who were hypertensive during their adolescence and who were also mostly overweight or obese developed end-stage renal disease in 27% (HR 5.07) this proportion is clearly higher than that of the hypertensive peers with normal weight. This cardiovascular risk status has been updated by the *American Heart Association* and when the obese adult has not been overweight during childhood and adolescence, this link is weak. There are also trajectories for carotid intima-media thickness (cIMT) values that are associated with frequent subclinical atherosclerosis and that aggravate the cardiovascular future of the obese if present. Unfortunately, the follow-up of trajectories is not usually present in these prognostic studies that start with adequate and precise measurements in youth, and from there they move on to the assessment of adult pathology without a full consideration of factors that may have been operative for several decades, such as discrete overweight. Within this long-term approach, it is appropriate to mention the cost of overweight and obesity with onset in the pediatric stage; after this meta-analysis [62] based on 13 studies shows a notable variability due to the inclusion or not of the usual costs of the individual health program and/or productivity, but the negative impact of overweight on health expenditure compared to subjects of normal weight is evident.

Immediate or Present Prognosis

In this section the degree of clinical suspicion is fundamental given that the pathologies associated with pediatric obesity are mostly subclinical or can be considered as not directly related to future obesity. Chronologically, the earliest and still underestimated prognostic indicator is, as seen above [9], that of high birth weight and the presence of an increasing BMI trajectory during the first 6 months of life [63], both of which have a moderate predictive value for obesity and subsequent comorbidities. Monitoring of the growth of extreme preterm infants may provide important data regarding BMI increase when they reach preschool age [64], especially if certain biomarkers are determined in cord blood [65]. Also typical of this period is the risk of type 1 diabetes (HR 1.24 for every 1 SD increase in BMI-zs) at 8.6 years of age for infants who gain more than 6 kg during the first year of life, according to the Scandinavian prospective study of more than 100,000 children [66]. This risk situation is also increased for T2D in the case of preterm birth. The association of high

BMI in adolescence with elevated blood glucose (OR 2.76) and elevated blood pressure (OR 3.72) is also found in low-income countries [67].

There are other areas of immediate prognosis, the first of which could be cardiovascular. The presence of cardiovascular risk factors in a pediatric population of 8500 overweight and obese children and adolescents from the NHANES study [68] shows the occurrence of decreased HDL-cholesterol and elevated systolic and diastolic blood pressure in addition to other components of dyslipidemia and other causes of early heart disease [69]. See in this regard our study of increased left ventricular mass and interventricular septal thickness, as described in more detail in Chap. 6 *Comorbid conditions*. In this way, and as a significant complement [70] to the Israeli national study and with a follow-up of more than 230,000 overweight, obese and severely obese adolescents for an average of 4 years, this study shows how obesity (and not overweight) is associated with hypertension in both girls (OR 2.13) and boys (OR 2.60) and how the association is less strong with respect to type 2 diabetes. Interestingly, the Canadian FAMILY study [71] shows that elevation of all anthropometric measures for childhood obesity (BMI and abdominal circumference ($>P 90$), $z\text{-score} > 2$ SD, and abdominal circumference/height ratio > 0.5) is associated with the occurrence of risk factors (elevated blood pressure and dyslipidemia) at age 5. We should now reflect on the association between shorter night time sleep duration and cardiometabolic risk [72] and consider that persuading obese adolescents to sleep more may contribute to improving their prognosis. Perhaps related to these cardiovascular factors is the increased risk of mortality in patients admitted to pediatric intensive care units, according to a *PICU system database* that includes 127,000 admissions [73] and with a U-curve in relation to BMI. Post-surgical complications are reported in another study of 1400 cases [74] of surgical wound infection (superficial, abdominal, or thoracic) in overweight or obese pediatric patients (odds ratio, OR 1.23 and 1.43, respectively) compared to children of normal weight, which should be taken into account in the preoperative period. In the traumatological aspect, the incidence of any type of fracture in 4-year-old children is 4% higher in those who are overweight and obese than in those who are not, and there is also a predominance of fractures in the lower limbs [75].

To conclude these aspects of the immediate prognosis of pediatric obesity, it is necessary to refer to the possible decrease in IQ; studies so far have been short [76] but show a lower evaluation of cognitive tests at 5–8 years of age in those children who were overweight between the first 1–2 years of life. The study [77] in which no association between elevated BMI-SD values and cognitive function was observed may be destigmatizing. This could be indicative for further studies on this basis in pediatric patients. The cognitive dimensions include, among other functions, the so-called working memory that plays an important role in the development of language, especially written language, sensitivity to reward, and inhibitory control that, in obese children when altered by the expectation of food, may be an important factor in the maintenance of obesity. These cognitive functions are located in the prefrontal cortex, and the recent finding of bilateral thinning of the cortex in several areas (rostral, medial, and superior) has already been demonstrated in obese children [78]. Brain imaging studies that also cover the white matter are giving objective support to certain behavioral changes including psychosis, associated not only

with BMI but also with fasting insulinemia rates [79], which is an important advance with potential therapeutic repercussions; it should be remembered at this time the increased risk of dementia in adults suffering from (abdominal) obesity. There is an association between adiposity and cognitive function in adolescents after ABCD Study on episodic memory and executive function with an altered volume in the lateral prefrontal cortex [80]. Also this relationship was more evident in adults as the Health and Retirement Survey has just shown. The prognostic situation in the motor, personal-social, and problem-solving areas may worsen if the parents are obese and with small differences in the odds *ratio* (OR) depending on whether the obesity is paternal or maternal and with an additive effect in the case that it occurs in both [81]. In the study [82] assessing school and social performance, boys with obesity have less chance of success than those of normal weight according to these preliminary data. When the severely obese boy approaches puberty, another important problem appears, and that is the marginalization they suffer from the point of view of romantic and sexual relationships compared to their peers of normal BMI [82, 83]. From the point of view of functional prognosis, in addition to the aspects seen in clinical practice, mention should be made of the social and economic consequences of overweight and obesity in adolescents. Another study [84] shows that this essentially distressing situation in the 1800 adolescents assessed at baseline (14 years of age) does not subsequently improve given the lower number of university degrees (OR 0.32), salaries of less than \$50,000/year (OR 0.52), or marriages/stable cohabitation (OR 0.45). This would confirm more classic studies (although not so drastically, low OR). In one of these classic comparative studies with other chronic diseases (asthma, muscular, etc.), obese adolescents, 8 years later, have completed fewer years of school, marry less, earn less money, and have a higher rate of poverty. Given the increased prevalence, tracking, and shortened lifespan trend of obese people, it would not be too pessimistic to say that the present generation of children may live shorter lives than their parents.

The earlier growth spurt, and thus earlier puberty, so closely linked to high BMIs entails all the undesirable consequences of earlier puberty (M. Bygdell, University of Gothenburg 2019). To this, male hypogonadism should be added, secondary to obesity with a complex basis but which could already affect adolescents [85], as well as premenstrual disorders [86]. The well-established and proven link between obesity and cancer in adulthood is now justified by the almost inexorable chain of maternal obesity, pediatric obesity, adolescent obesity, and adult obesity [87]. If it were reduced, it would also be a way of reducing cancer, since in a study with almost 2300 adolescents perfectly grouped according to their BMI, the obese group showed, at the age of 42, a higher proportion of cancers, HRs of 1.26 for males and 1.27 for females [88]. We are also aware of the higher risk of mortality already in obese children suffering from acute lymphoblastic leukemia [89]. Also of interest is the new situation in which maternal obesity (BMI > 40 kg/m²) and obesity during pregnancy are associated (HR 2.51) with colorectal cancer in their offspring when they are 50 years old [90]. This is a further contribution to the excess of deaths associated with overweight and obesity [91]. The interaction of cancer and obesity has been known for a long time, but a new threat has been found at the Turku University (Finland): in a large cohort, childhood obesity remained as an independent predictor of cancer mortality after adjustment for adult BMI [92].

Final Considerations

In this chapter large sample numbers of adult, child, and adolescent patients have been analyzed, and due to their epidemiological nature, the concepts of *hazard ratio* (HR) for immediate studies and *odds ratio* (OR) for more cross-sectional studies appear; in general in both situations the 95% confidence intervals have been omitted, which have been within the appropriate limits as can be seen in the references of these publications. It is time to recall that association is not causation.

The pooled studies that are so frequent and perhaps necessary in cases of large samples have enjoyed less recognition than those based on systematic reviews, but this does not limit their value. Such is the case of the possible cognitive deficit [84] or latest data from the Bogalusa study [93] on the association of cardiovascular risk factors with the subsequent appearance of T2D or the two examples of obese adolescents: the study using magnetic resonance imaging with more than 12,000 participants shows that obesity is associated with a lower volume of subcortical gray matter and possible microstructural alteration of the white matter [94] or the possible risk of suffering from pediatric multiple sclerosis [95]. Also the finding of a lower immune response of obese children against the usual vaccines [96] would show, along with the above, that there are necessary avenues of applied research in this evolving field of pediatric obesity. The epidemiological evidence in our case undoubtedly has some weaknesses, such as the different cut-off points to determine normal weight, overweight, and obesity, as has been repeated in previous chapters, or the real or indirect assessment of adiposity, but especially in our age group, there is an almost present impossibility of the application of Mendelian randomization [97] which would allow us to address the gene function in the object of the study, but this is being remedied as shown by the study on the prediction of multinational obesity with a reasonable mathematical application [98]. Nevertheless, from adult obesity and with reasonable levels of certainty as mentioned above, the association with common diseases [46, 50] leading to higher mortality rates [47] has been established. In animals, in this case elephants, [99] we understand the natural history of weight gain and even the trajectories according to sex. This is an advantage over humans in the case of obesity studies. The importance of the trajectory concept has gone beyond overweight, the case of anorexia nervosa evolution and levels of ghrelin can improve obesity prevention in these patients [100] or the overweight and obesity in adult patients with phenylketonuria [101] and its relationship with the mechanism of protein leverage [102]. Therefore, and agreeing with Dr. West [103], we would say that it is time to renew our vows for evidence-based medicine, which allows us to undo the great promises of scientific ignorance and misinformation from ineffective or erroneous medical actions.

Perhaps these studies on big numbers should go beyond the purely clinical setting to that of the industry in general [104] or certain industries since, despite the negative data on supplements, their sales are not decreasing. But with the conjunction of new data and increased family awareness of the obesity problem, it is to be hoped that the problem can be reduced.

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Chapter 8

Prevention



Praestat cautela quam medela (prevention is better than cure).

Edward Coke, 1628

Introduction

Why is the prevention of obesity necessary in childhood? There are four factors: prevalence, clinical impact (comorbidities already in pediatric age), *tracking*, and general poor therapeutic results. In this human and preventive context, the fundamental reason is that 30% of all obese adults became obese before adolescence [1]. As a reference point, it could be said that when one considers that at the beginning of past century there were 2.5 billion overweight and obese people (>18 years of age) in the world [2] and presently 7.9 billion according to the World Population worldometer, these figures provide sufficient motive in the context of prevention. In addition, the report of the *International Obesity Task Force* (IOTF) [3] already indicated that 10% of children and young people aged 5–17 years are overweight and 2–3% are obese, which is equivalent to 155 million and 45 million affected children, respectively, in absolute figures for the year 2000. The proportion of children under 5 years of age (<5 years), following the classic WHO analysis, follows similar trends with 42 million in 2013 [2]. The consideration of the double burden malnutrition (DBM) has meant a new source of obesity in areas theoretically free of overweight and with wide international health resonance [4]. Moreover, from 1980 to the present decade, the prevalence of pediatric obesity has tripled in many parts of the world, even in low- and middle-income countries (L-MICs) [4]. These figures are globally representative and are generally consistent with those provided by the WHO today (but still refer to 2016), although they show an increase, for example, in the 5–19 years age group. In 2016 there were 340 million overweight and obese children and adolescents in the world. This does not imply that in certain areas as in

the case of some countries in Europe or America, these quotas are higher; see Chaps. 2 and 3. In southern Europe, for example, Spain, the National Health Survey in its latest edition in 2017 (ENSE 17) and in the population aged 2 to 17 indicates the existence of 28.7% overweight and 10.2% obese, percentages higher than those of 1987, the date on which the first ENSE survey was published. Finally, once obesity is established, a long, painful, costly, and often unsuccessful path to overweight and, more rarely, to normality begins. Consistent with these circumstances, the WHO, at the *70th World Health Assembly* (Geneva 2017), recognized a preventive approach to obesity across the life course that specifically encompasses the stages of preconception, pregnancy, the first 2 years of life, childhood, and adolescence at the 70th edition, and the *International Pediatric Association* (IPA) reaffirmed its commitment.

A very particular phenomenon of obesity, derived from the four reasons mentioned above, is the varied scientific response to the prevention and treatment of obesity, to which we should add the (e-) extended shamanic or miraculous proposals. This has motivated the growing reaction through the graduation of evidence, which is nothing more than a defined and solid process for the search and analysis of the literature that objectively covers from the causes to the most recent preventive or therapeutic actions. There are several methods to assess the degree of evidence and subsequent recommendation of systematic reviews, randomized trials (RCT), and observational studies. The results are graded as A, B, C, or D and more recently through the GRADE methodology that assesses the quality of the evidence (high, medium, or low) and the strength of the recommendation (strong or weak). These requirements are sometimes responsible for a lack of fresh data.

Another reason for effective prevention in pediatric ages is the homogenization of anthropometric measures: body mass index (kg/m^2) and abdominal circumference and waist/height ratio or other estimators assessed by the *z-score* method are probably the most appropriate in the clinical setting, but their evaluation is also highly desirable through a general graphic method such as Cole's or CDC's. The WHO method would be the third option due to its design (see Chap. 1). The relative body mass index (rBMI) expressed as a percentage [5, 6] is a very simple method that is well understood by families and older children. Recently, and due to the increasing trend of overweight, the 95th percentile has been shifted upward so that children and adolescents who are not extremely obese may remain unidentified, hence the advantage of the *z-score*. In general the Health Care policies in the world are considering new preventive approaches as a recent editorial from the American Medical Association points out. In a more practical ground the preventive and treatment of obesity when delivered at primary care level has been beneficial [7].

Types of Prevention

From a theoretical point of view and in order to be more effective, prevention in general has been subdivided into three levels: primary prevention (before the disease appears), secondary prevention (latent disease), and tertiary prevention (in the

face of the consequences of the disease). In addition, there is a fourth level, holistic prevention, which encompasses the three previous levels and which is desirable for the prevention of pediatric obesity. The preventive pathway starts at the global/national guidelines and reaches the community organizations where it bifurcates towards actions on the social environment and especially towards the individual preventive set formed by the child, his/her family, the pediatrician, nurse, social worker, and other collaborators. Normally this flow should be smooth, but there are certain obstacles between the three levels, especially when it comes to the individual level which is the final interface. The blockage at this level was precisely described in the 1970s [8], and 50 years later health professionals cannot apply the appropriate knowledge emanating from scientific organizations [9] as will also be seen later with regard to specific aspects.

In relation to this slow progress, we reviewed 56 obesity prevention plans published from 2010 to 2016, of which 11 came from global agencies, 20 from national health authorities, and 25 from scientific societies or groups. The information resulting from this non-systematic review can be summarized as follows: preventive plans for adults can be a good model for the prevention of pediatric obesity and were also the ones that most frequently contained specific guidelines; the plans of global agencies presented complete contents including practical, updated aspects as is the case of the WHO report [3]. Results on preventive effectiveness were scarce and offered almost exclusively by scientific societies. The individual preventive approach was also rare. Perhaps it could be said that the main preventive lines have not changed much from those of 50 years ago. In the not very frequent cases in which vertical integration has taken place, it has been useful, especially when there has also been a horizontal integration of the different institutions related to pediatric health.

Implementation of the Prevention of Pediatric Obesity

The classic questions raised by *Population Health Promotion* [10], what approach (general or individual); to whom (the child); and how prevention will be carried out (actions), are applicable here, although aspects of the second and third questions will be dealt with on an individual basis.

General Approach

The general approach is the competence of health authorities as in the following examples: the recent WHO *Commission on Ending Child Obesity* or the FAO *HLPE Nutrition and Food System* for malnutrition in its three forms; the WHO *European Food and Nutrition Action Plan 2015–2020 (5-color nutrition label)*; the projects of the European Union: *EU Action Plan on Childhood Obesity 2014–2020*; the *EU EATWELL*; and the USPSTF for children and adolescents of 2017. All are aimed at

member states, to develop policies against childhood obesity. One of the most veteran programs with the longest follow-up is that of the general prevention program of the European Union through the *European Commission on Public Health* [11]. It includes three levels: primary care (doctors, effectiveness, barriers), school and community programs (education, diet, exercise), and government programs (sports fields, energy regulation of food, TV, etc.), which effectively cannot be carried out without state support. In Europe, the evolution of prevalence in children aged 7 years between 2015 and 2017 is fairly stable in the various countries, except for the increase in Italy, Greece, and Spain [12]. Due to the social discovery of obesity and its evolution, national and regional programs have appeared, and even programs by various scientific societies, which will surely bear fruit in the medium term. However, at the present time, in addition to a certain confusion on the actions to be taken, they may create undesirable competition, especially in terms of resource management. In fact, the large preventive plans are giving way to more specific plans (USPSTF Primary CVD prevention; Obesity in pregnancy; Dietary guidelines; Leisure time physical activity, etc.). Even WHO has joined this trend in its Global report on the high cost of physical inactivity [13].

As noted, evidence policies are needed to clarify this dense preventive landscape. A *Cochrane* systematic review of randomized studies showed that only ten studies were of sufficient quality in terms of design, measurement accuracy, and duration, but the results extracted from them were inconsistent on the main preventive actions. Ten years later, another *Cochrane* review of randomized clinical trials to analyze the effectiveness and duration of the preventive effect on pediatric obesity [14] showed an improvement in quality although out of 93 reviews only 37 (279,946 children) could be included in the meta-analysis. They conclude that the programs would be effective in reducing adiposity, but the individual interventions were not all equally successful, and this heterogeneity was not clearly explained. They also point out that current obesity prevention efforts need to build a reliable foundation: sufficient numbers of participants, adequate follow-up, and rigorous measurement. Only in this way will the cost/benefit ratio of health strategies to ensure adequate weight for all children and young people be known. It is pertinent to mention in this section of clinical studies the opinion of the WHO [15] that adds the modifications of the children's behaviors, of the environmental conditions, as well as the homogenization of the results obtained (BMI-zs, rBMI). The size and duration required probably do not make it advisable to carry out small, randomized studies. Moreover, in this type of studies, it is not easy to establish comparable controls. It is difficult to determine whether they represent the population; and specifically, whether in this case there is also a crucial factor: the absolute impossibility of quantifying the energy balance. Hence, the design(s) must be generous in terms of number and time and also take into account qualitative aspects. These precautions must be present when the studies collect data obtained from preventive (and therapeutic) actions at the individual level.

The implementation of preventive programs is not straightforward. Hence the variety of recent national preventive studies in high-income countries where the importance of socioeconomic status or place of residence (urban or rural), racial disparity, or the clinical relevance of abdominal obesity have been shown to be

significant and, at present they have provide solid knowledge but unfortunately less preventive results. For example, the New South Wales (Australia) program [16], despite reasonable support, has not achieved the government's stated objective. The same can be said of the specific program for Victoria in the same country, although this is still under development [17] (see *Results* section below). Within this complexity, certain potentially effective actions, such as the high energy content of restaurant meals [18], or the implementation of a specific tax on sugary drinks (New Zealand), or the careful legislation for school canteens [19], have not progressed to the implementation stage. Other general actions with specific individual aspects, such as reducing BMI before pregnancy [20, 21] or during pregnancy [22], require the strong involvement of health authorities and national healthcare networks to be successful. The social and environmental components and perhaps certain genetic aspects of the illness require a special approach, at least in the medium term, with general actions (on food, physical activity, health education among others) by specific institutions. In our case, if the target is the general population, the first might be the school. In high-income countries, these general programs have frequently failed to achieve the desired results. Therefore, it is necessary to turn to more specific but regulated actions [23] (e.g., the well-structured vaccination calendars) with simultaneous support from the health system, which would provide greater efficacy to the general obesity prevention approach.

Individual Approach

The individual approach, on the contrary, is much more concrete since it affects simultaneously the physician and health team and the child at risk of developing obesity. Individual prevention can and should be carried out by a specific pediatrician on any child with an increasing tendency in BMI and especially if he/she is already overweight and has come to the consultation for this or any other reason. For prevention to be effective, the practitioner must be motivated and have a minimum knowledge about the prevention and management of childhood obesity. The involvement of the primary healthcare provider, in this case the pediatrician, has led in some countries or states, with a liberal healthcare system, to the creation of certain projects (ACO) which have a group of physicians who can care for patients with complex, prolonged, or costly diseases [24]. This initiative could be tested in the case of pediatric obesity. The next questions are to whom and how will they be analyzed from this individual proposal?

Who?

The answer to this question has changed due to the concept of early prevention [25] and according to which prevention should start preconceptionally [26]. Morbid obesity (>40 kg/m²) in women before pregnancy carries risks of gestational

hypertension and diabetes, extreme prematurity, increased inflammatory markers in the newborn (CRP, IL-6, TNF alpha), low cord iron levels, and increased risk of non-alcoholic fatty liver disease in their future children with high postnatal weight gain who later develop significant obesity. The first step of early prevention is precisely in this population group, informing the obese mother-to-be that she should lose weight before conception. The retrospective study of nine million pairs (mother and child) carried out between 2016 and 2018 [26] demonstrates the association between overweight and particularly periconceptional obesity, and not only preterm birth but also neonatal macrosomia, and maternal overweight (OR 1.18) and above all severe obesity (OR 1.47). These values (OR), with reasonable confidence intervals (95%), increase considerably if the infant is large for gestational age (LGA). Once gestation has occurred, excessive gestational weight gain and breastfeeding preparation (6 months minimum) must be controlled. This has been the subject of a study of more than 15,000 mothers and their newborns by the research department of the *Kaiser Permanente Southern California* (Pasadena) confirming an association with overweight/obesity at 2 years of life. This fact, increasingly well known, has led the health authorities in Trondheim (Norway) to launch a physical exercise program for pregnant women to reduce excess weight gain. Father weight should also be considered as a risk for offspring obesity, specially if both progenitors are obese [27].

This type of action is positive although does not produce spectacular results due to the epi- and genetic component of obesity. This has been determined after the analysis of 32 gene variants assessed in mother and child in an exemplary study [28], and, whether the mother has lost weight or not, the genetic predisposition may be passed on to her offspring. However, it is already known that the hereditary associative component of BMI in this study ranges between 40 and 70% [28]. High genetic susceptibility implies 2.09 kg/m² (95%CI 1.90–2.22) more, and also in these subjects, environmental factors continue to influence and add up [28]. The next [29, 30] is the reduction of excessive gestational weight gain, better control of gestational diabetes, and therefore large for gestational age newborns (>4.0 kg in terms). These circumstances are associated with obesity and adult onset comorbidities [26, 31]. A systematic review carried out in South Africa [32], appropriately designed to show the preventive effectiveness of the various actions carried out during gestation, gives less brilliant results than expected: only five actions, all of them related to diet and physical activity, can be labelled as beneficial or possibly beneficial. Lifestyle, medical, or psychosocial factors (DT2, smoking, or depression among others) lead to fetal exposure to glucocorticoids that would act through transcription without altering the nucleotide sequence of the DNA gene causing specific DNA methylations, which have been found in umbilical cord and placental tissues. Specifically, and following the adult experience [32], screening for pre-diabetes in the obese child (impaired fasting glucose, glucose tolerance, or elevated HbA1c) and strengthening care implementation will decrease adult mortality for this cause. Among the various factors (BMI, T2D, systolic hypertension, lipid profile, vitamin D, and adiponectin levels) studied in 30,487 mother-child pairs, increased BMI and elevated blood glucose levels were most associated with high birth weight and also later development of obesity [32]. Also, in interpregnancy weight gain (between first and

second), the second child has a higher risk for obesity at 4 years of age [33]. Increasing genome and perhaps exome sequencing (WES) will undoubtedly contribute to a better understanding of the relationship of genotypes to the development of obesity, as well as more specific risk markers or treatments such as certain gene variants (DRD 7) that influence subsequent food choices [34]. Monogenic forms almost always involve morbid obesity but account for only 2–5% of pediatric cases, e.g., heterozygosity of the melanocortin receptor 4 gene.

Early prevention should include the newborn with exclusive breastfeeding up to 6 months of age. It is worth considering the CDC study [35], where the policy of initiation of breastfeeding in maternity wards achieves a longer duration of breastfeeding than other more traditional initiatives. On the other hand, the introduction of complementary feeding, even when it follows generally accepted feeding guidelines, is often excessive and leads to early overweight and eventual subsequent obesity [36], which requires continuous and certainly critical evaluation. We now know [37] from the study of two breastfed cohorts that the introduction of infant formulas at 6 months (rather than during the 0–3 months stage) is associated with a lower BMI at 1–3 years of age. Prevention must also continue later because a number of environmental factors are influential from the outset. Environmental factors at this early stage are already framed by the per capita increase in the availability and consumption of appetizing, high-calorie, generously portioned food and by the decrease in physical activity due to the present mechanization and increase in sedentary lifestyles (time in front of small or large screens). Other factors to consider are lack of sleep or the use of certain medications.

All this occurs in a context of acceptable control of infectious diseases and where chronic non-communicable diseases have increased. Therefore, after birth, prevention should focus on weight gain during the first 3–6 months of life and ensure that breastfeeding is maintained during the first 6 months. It should be remembered here how solid food intake unfortunately starts very early in large parts of society throughout the world. It is advisable to read the extensive WHO document [38] which recommends a limit to the inappropriate promotion of complementary foods for children from 6 to 36 months of age and offers a guide for adequate feeding. At the same time, it refers to another no less important document (*WHO 2019 Commercial foods for infants and young children in the WHO European Region*) which, after the analysis of 1328 products on the European market, analyzes the inappropriacy of some contents and especially the generalization for these ages of foods excessively enriched with sugars. Therefore, the classic recommendation to establish prevention between the ages of 4–6 years should be reviewed, especially if there is an *early rebound* of BMI at any previous age, given the risks involved: in the case of an obese mother, the association with an obese offspring is greater than if the father were obese, and this association is more evident the older the child gets [32]. Furthermore, the earlier the adipose rebound occurs and the faster the weight gain develops before the age of 5 years, the greater the risk of obesity. In an extensive study (3930 children) carried out by the *Cincinnati Children's Hospital* [39], it has been demonstrated how severely obese children at the age of 6 years presented a BMI already above p 99 before the age of 2 years. This has led to the initiation of preventive programs in nursery schools in some countries, such as China. It is not

well known whether this early rebound is due to some mechanism favoring weight gain, or on the contrary it is purely secondary to genetic or environmental factors; therefore it is essential to educate the general population about the well-known risk factors for obesity such as those mentioned above and to which should be added large for gestational age and low socioeconomic status. Unfortunately for preschool children [40], there are none of the preventive programs which are somewhat more widespread among school children (>6 years) [41]. Therefore, they depend on the interventions of family and primary healthcare.

Regardless of the chronological approach, prevention should be implemented at any age of the child in which a progressive increase in BMI is detected even without reaching the threshold of overweight, and even more so for those with overweight (BMI-zs 1–1.9 SD; rBMI 110–119%; centile 85–95), whether or not assessed by the family. This is especially relevant in the case of adolescents since, if they are obese at the end of this period, 80% of them will continue as obese adults. The overweight child should be included in the preventive program especially if the aforementioned circumstances are present. In addition, there are two risk factors that should be taken into account to reinforce preventive action. One is ethnicity. Therefore, non-Caucasian children and adolescents living in Westernized areas are at increased risk for obesity [42] although certain cultural burdens may also contribute to this. The children of diabetic mothers, even if they normalize their weight by the end of the first year, later have a higher risk of obesity and lower glucose tolerance at later ages according to the extensive study of more than 24,000 mothers and their offspring conducted by the *Kaiser Permanente Center* [29, 43] which also highlights the epigenetic possibility. Another situation to consider is insufficient growth (*stunting*) or reduction in height with respect to age, mostly related to prolonged non-optimal nutrition. When the energy intake situation is resolved, the appearance of obesity is frequent, and this tends to occur more in developing countries or in depressed communities in developed countries. Despite recent interest in nutrition in the first 1000 days of life (conception to second birthday), only a small percentage of interventions are effective [44], which would imply the need for greater awareness of this period. Small for gestational age children, although often on a poor growth path, especially if there is no catch-up before the first 18 months of life, are more prone to hypertension or ischemic heart disease for this intrauterine growth retardation than for obesity, as can be seen in the recommendations for reducing cardiovascular risks [45]. The exemplary cohort study conducted in Finland [46] identifies genetic predisposition to obesity based on genome-wide analysis (GWA) after a long period of study of mothers and their newborns.

How Prevention Can Be Carried Out at the Individual Level

At the primary care level and despite the preventive habit of the pediatrician, in the field of obesity, there are still some points to be systematized and incorporated into clinical practice. The physician can play a decisive role by providing the family and the child with basic information while promoting behavioral, dietary, and exercise/

leisure measures in this important and sustained healthcare action [47, 48] that will be discussed below. This preventive incorporation is especially important in rural areas, even in high-income countries, where obesity prevention programs are more difficult to access. The first point is to provide basic knowledge to pediatricians or physicians dealing with these children, but also, if feasible, to teachers and school tutors. The concise information on this subject given by the WHO [49] may be sufficient. For the time being, the most important thing is the knowledge and understanding of the first principle of thermodynamic equilibrium. According to this principle, if the energy intake through food exceeds the energy consumed through oxidation, it will be stored in the only way that living beings can store it, i.e., in the form of fatty deposits. It is even advisable to provide them with a diagram of this concept that is simple and can be understood by the parents and by the child or young person him or herself. In this way, and provided that it is followed, excess weight (fat) can be reduced more comfortably and effectively by reducing food intake and increasing energy expenditure through exercise and physical activity. The information for the professional should be completed with the management of body mass index and abdominal circumference, preferably z-score for the advantages mentioned above. The family dietary pattern or usual food intake [50] should also be obtained, which is simpler than a nutritional survey, and the pattern of physical exercise. The next notion is that of accuracy in anthropometric parameters. Accuracy in the measurements of height, weight, and waist circumference is fundamental, not only for subsequent and scheduled visits but for any clinical study that may arise. At the individual preventive level and to avoid fat deposition from initial overweight or obesity, the following actions can and should be carried out:

Reduced Dietary Intake

The reduction will be implemented through a balanced diet and adapted to family and school standards, but we must ensure that the following five points are raised and understood:

Reduce foods rich in fat. Selecting low-fat milk and dairy products and less fatty meats and fish and using oils and butters sparingly are relatively simple and effective. One forum (NationalObesityForum.org.uk) recommended eating more fats and fewer carbohydrates to reduce calorie intake. This caused a strong controversy in the *media* but also in the scientific arena where the evidence (see Chap. 9, *Treatment*) shows that there was excessive negativity against saturated fats and there will still be support (although more tenuous) for the initial recommendations for unsaturated fats until there is more evidence to the contrary [51]. The protein overeating of the past makes no dietary sense. Moreover, a possible treatment could be based on decreasing the intake of branched-chain amino acids.

With regard to carbohydrates, which in principle should provide 60% of energy, the criterion is to change the concept of low carbohydrates to slow carbohydrates [52], thus a significant reduction in foods rich in refined sugars that are so readily available today (desserts, candies, ice creams, etc.). It is therefore probably useful to know the glycemic index (GI), which is beginning to appear on labels in some

countries. Low GI products (<55) are recommended, while high GI products (>70) should be avoided [53], and the real importance of the glycemic load and its association with cardiovascular disease and death should be taken into account [54]. The incorporation of whole grains and legumes [55] as an important part of a daily meal with vegetables (~150 g) and fruit (~150 g) is an acceptable form of nutrition and of GI. They should be varied as much as possible because this avoids food neophobia. The preventive action of dietary fiber towards adult cardiovascular disease should induce its use at pediatric ages, but it should be clear that true cardiovascular prevention rests on a healthy diet in its quantitative and qualitative aspects. For more information see Chapter 3 Macronutrients-energy intake and Chapter 9 Modification of eating habits.

Reduction of sugary drinks These have added caloric sweeteners, and it has been seen how their consumption is associated with a noticeable weight gain within a few weeks of starting this habit [56]. The president of the *European Association for the Study of Obesity* (EASO) expressed the same opinion almost two decades later with regard to the situation in Europe, and the same has occurred in other regions (Southeast Asia) where the consumption of these beverages spread later. In children aged 2–5 years, as in other age groups, their consumption is clearly associated with an increase in BMI [57]. The replacement of sucrose by fructose-rich corn syrup [58], which is widely used not only for soft drinks but also for dairy products, represents a non-negligible caloric intake and is also associated with an increased risk of insulin resistance and comorbidities [59]. It is important to note the increase in adult mortality from any cause in those individuals who consume sugar-sweetened beverages in a proportion equal to or greater than 10% of total daily calorie intake [60]. The ideal solution is the substitution of water for these soft drinks and, failing that, those with non-caloric sweeteners. The rationale for this reduction is well expressed in the joint document of the American Academy of Pediatrics (AAP) and the American Heart Association (AHA) [61], which report that they are particularly harmful as they are subsequently associated with cardiovascular disease, type 2 diabetes, non-alcoholic fatty liver disease, and increased overall mortality. In addition, the AHA, in pursuit of its objective of preventing cardiovascular disease, through the Healthy Drinks-Healthy Kids website, recommends, for infants aged 0–6 months, exclusive breastfeeding; from 6 to 12 months, water with solid foods; from 12 to 24 months, in addition to the basic and necessary water, whole milk should be preferred to 100% natural fruit juices, bearing in mind that these do not offer any advantage over natural fruit; and from 2 to 5 years, water and whole milk should predominate over other types of drinks, including flavored milks. Reduced-fat milk in childhood may not reduce obesity risk. The battle against vitaminized juices, sweetened beverages, and so on will be a long one. Given the large increase in consumption of these drinks in the last decade, reaching 200% in the USA, it must be taken into account, in the light of certain recent studies, that children who consume drinks with these types of sweeteners ingest more calories than those who drink water. This point is more complex to resolve because of the industry's counteroffensive (with data on hydration, the importance of physical exercise, etc., or

even by supporting controversial research) which has led the WHO to publish a specific document on the health impact of sugar-sweetened beverages [62]. The standard given by the *American Heart Association* (AHA) [63] for children aged 2–18 years for sugar intakes of less than 25 g/day (~6 teaspoons), for sugar-sweetened beverages of 250 ml/week, and no sugar intake for children under 2 years is simple and effective. The recent UK Government's Sugar Reduction Programme (UK Government's Sugar Reduction Programme) is along the same lines, and its follow-up would suggest a reduction of 25 kcal/day in children of 4–10 years of age. With regard to the multiplicity of sugar-sweetened beverages, it is worth remembering that in the areas where the tax increase on these drinks has been implemented [64], there has been a decrease in their consumption in favor of a greater consumption of water, especially, according to sales in large supermarkets, where the price increase is 20%. The results in Mexico in research on more than 12,000 adolescents have shown how price rises through tax increases on sugary drinks (SSB) and soda have produced a reduction in weight excess, especially in young people [65]. These results have also been observed in ten countries of the European Union, where studies have been carried out on measures designed to generalize tax rates on this type of drink [66]. Given that this is not easy in older children, the New Zealand initiative to reformulate packaged foods and beverages with a reduced sugar content should be considered, as should the addition of alternative flavors (bitter, sour, etc.). However, there are still no results as to whether this is an effective preventive measure. Despite all these actions against SSB, the stubborn reality is that the consumption by children and adolescents has increased globally most likely do to the targeted marketing of these products [67]. Still on this subject, it should be noted that publications warning about the risks of consuming non-sugar sweeteners require longer and more numerous studies to give them the necessary credence [68]. Therefore, the well-conducted meta-analysis [69] on low- and no-calorie sweetened beverages and cardiometabolic risk indicates that, over a moderate term, these types of beverages are a viable alternative to water, which is helpful in obese child management. The popular fruit juice intake in infancy requires a more precise analysis, not only for the additional energy supply but also for the fructose content, a well-known promoter of visceral adiposity [70].

Attitudes during meals Breakfast deserves some considerations since it has sometimes been overlooked. It should not be rushed, nor should it be small, and much less should it be skipped, since the erroneous thought that the child is being spared a caloric intake can have other consequences with precisely the opposite effect [71]. A contemporary editorial (16 May 2019) in the *American Journal of Clinical Nutrition* defines breakfast as “the most important meal of the day” in its title. Parents should modify the pattern of meals whenever necessary; an atmosphere of friendly conversation should be sought, with muted screens and also avoid any coercive attitude (eat up! I want to see a clean plate!) in the face of the physiological feeling of satiety. Do not eat between the classically accepted four meals a day (or five, in some countries, there is the questionable mid-morning snack); this measure considerably reduces caloric intake. Also avoid as much as possible food, snacks,

and appetizers as a reward or celebration. When these are prepared, fruits should replace biscuits, chocolates, and nuts, although we should bear in mind that all of them are available for the child in the corner shop. Recent studies carried out in the United States and Australia show that snacking between meals has grown significantly in all socio-demographic groups in the last 30 years. In addition and in a study, snacking linked to motivational factors is not associated by either the child or the family as promoting weight gain [72]. In some countries these attitudes have been regulated in schools, but in the variable energy content of school catering, excess tends to predominate. Nor should it be forgotten how, for example, the initiative of some US states, (unlike Kentucky or Florida), with programs to guarantee at least one meal at school for children at risk of undernutrition, can be obesogenic for the whole or how the SNAP (*Supplemental Nutrition Assistance Program*), which has updated the old *food stamps*, has the collateral effect of increasing the purchase of sugary drinks [73]. It should also not be forgotten that an intake of more than 1 g of sodium (equivalent to ~3 g salt)/day in children (<https://www.nhs.uk/live-well/eat-well/tips-for-a-lower-salt-diet/>) leads to higher energy consumption. Attempts to reduce sodium on menus in restaurants and fast-food chains have been addressed and the estimated results for 2030 are worth to take into account [74], but at present it is difficult to measure the effectiveness of this. The educational program initiative for primary schools and families on the reduction in the consumption of salt [75] has been especially effective in the case of adults. It is highly recommended that as far as possible, reductions should be implemented in the consumption of ultra-processed foods (fourth group in the 2018 NOVA classification), which are almost always formulated ready-to-eat meals, with high palatability and including pâtés, pizzas, new sausages, new pastries, etc. Their regular consumption leads to weight gain in adults and, above all, an increase in all-cause mortality according to a study conducted in Europe with 20,000 participants [76]. A similar pattern occurs in the United States [77].

Finally, reducing portion sizes of both solid foods (decreasing the diameter of plates), packaged food, and sugar-sweetened beverages [78]. This policy of smaller portion sizes is probably useful from the period of infancy, where larger bottles are associated with higher BMI values and larger portions and at ages 2–4 years have the added problem that these children are not able to adjust their dietary intake to these contributions when they are prolonged [79]. Following more recent experiences in Japan in adults [80], where the increased speed of food intake (gulping), the onset of metabolic syndrome and obesity, and the promotion of slow eating have become more widespread, in pediatrics it has been seen how smaller bites or slow eating (up to 30 s between initiation of bites) can help the essential fact of promoting a healthy eating pattern for all members of the family. The erroneous family belief in the maxim that leads to making children eat all the food on their plate, including those with higher BMIs, must be addressed.

Specific diets, as we have been repeating, have little preventive value and low adherence; nonetheless there are preventive measures against overweight, such as healthy eating patterns, especially those with a large epidemiological basis [81], such as in the prospective PURE study (more than 130,000 adults), which is of great

interest here. A family diet with a rotation of the following foods, fruits, nuts, vegetables, legumes, dairy (skimmed), fish, and unprocessed red meat, can constitute with its sensible quantitative use a safe and probably effective basis for the prevention of pediatric obesity. The problem with the prevention of pediatric obesity is that it always clashes with what is offered to the child, so family diets must be improved and made more flexible and palatable to achieve long-term adherence. The nutritional labeling of foods, the raising of prices of undesirable sugars (including drinks), or recommendations towards the consumption of fresh fruit are worthwhile initiatives, even though their acceptance by the population is rather limited at the moment. Improving the level of education will undoubtedly lead to greater effectiveness of these dietary measures.

Increased Physical Activity (PA)

In the preventive or therapeutic evolution of obesity, there are three phases [82]: initial weight gained, weight loss, and maintenance of weight loss. In the first two, the variation of ingested energy is the basis, but in the maintenance of weight loss, the regular and systematized practice of physical exercise is critical. Female children are less active than boys, thus encouraging physical activity (e. g. games with no elimination or additional time) is positive not only at school [83]. We should bear in mind that physical exercise is a small part of the total energy expenditure as a result of daily physical activity [84]. This should be increased [85] as much as possible and consequently decrease sedentary lifestyles, and this activity varies, among other things, depending on whether the child lives in an urban or rural area.

The advantages of regular physical activity have long been well known through adult preventive programs, but in pediatric stages the most recent meta-analysis studies have shown how PA in overweight or obese children improves the rate of preclinical arteriosclerosis estimated by non-invasive methods and, more generally, the cardiometabolic risk when compared also with an ad hoc, but sedentary, population [86]. PA and the muscular contraction it entails contribute to the acquisition of bone mass and resistance in healthy boys and girls or those affected by bone pathology [87]. In the same vein, it has been shown that upward trajectories of BMI compared to normal in adolescents are associated with sedentary behavior [88]. A new aspect of regular exercise has been published by a Harvard group working on mice, i.e., the positive regulation of cognitive function related to higher levels of irisin [89].

The Canadian study AHKGA [90] and with data from 49 countries, with European participation, shows how PA in children and young people is a cause for concern throughout the world due to its low level, which is determined by the “report cards” which include nine physical activities and then ten indicators, reaching the conclusion that general actions are necessary to improve them. In this sense, there are various recommendations, but it is worth pointing out the guidelines of the North American Ministry of Health, HHS [91], which indicate, as noted before, that children between 3 and 5 years of age should be physically active throughout the day, those between 6 and 17 years of age should do 60 minutes or more of moderate

or vigorous exercise a day, and adults should do 150–300 min a week. Given that 80% of adults and adolescents do not meet these PA minimums, this guide states that both health professionals and health authorities should strongly support all procedures and practices that increase PA. The Director General of the WHO also deals with the globalization of this situation in a plan for 2018–2030 to increase PA in all ages, taking into account that they are not looking for elite athletes but simply active children/adults. This plan was ratified and completed 1 year later [92] and in greater detail for children under 5 years of age. The importance of sleep duration is also specified, and recommendations are offered so that in high-income countries, children under 3–4 years of age spend as much time as possible outdoors and, for older children, their incorporation into regulated sports is facilitated, all with the aim of increasing PA from an earlier age. On the other hand, the study of this activity is gaining biochemical precision, which includes the compensation that exercise exerts on individuals FTO, Allele A, among other assessments.

Measures to increase physical activity

Physical (in)activity is conditioned not only by the child's desire to be (in)active but also by the environment, and the guidelines should be focused on these poles. PA at school should be a state measure for investment in the short and medium term. The study of more than 11,000 children belonging to the *UK National Child Measurement Program* and followed for more than 6 years shows that in schools with less time dedicated to physical education, this is associated with higher levels of BMI-zs [93]. At school it is necessary to separate physical education (PE) from physical activity (PA). The former should have a formative capacity in children so that they understand the need to incorporate the latter into their way of life, in the same way that they are trained to acquire knowledge. This implies new offers beyond classical gymnastics, from which they can choose and which, if we follow the Swedish example [94], include games, dance, and PA in sports facilities. In addition, the notion of intensity should be instilled from the outset; all PA should be categorized as *moderate* or *vigorous*. PE should not consume the time allocated to PA at school. Another problem in the school setting is not only to eliminate barriers but also to facilitate them [95]. In addition to the physical barriers, there are the functional ones and the issue of how academic work relegates PA to undesirable levels. What type of activities would be ideal? If a few, well-systematized activities are offered, such as football, basketball, and dance, the possibilities of success are greater. In the case of aerobics and with experience from adults [96, 97], a randomized study (including oxygen consumption) showed that aerobic exercise significantly reduced BMI compared to resistance exercise. Perhaps even more importantly, in a study of aerobic exercise in 1.3 million adolescents followed for 29 years [98], those in the top quintile of activity had the lowest risk of death from any cause, and this is repeated when the sample is adjusted for weight. Although aerobics requires a monitor to be effective, there are videos in the *media* that allow you to do it at home. Because of the preventive importance of PA, any effective method can be used when common offers are not available. Therefore even small intervals of high intensity physical activity (e.g., running) are associated with decreased adiposity and cardiometabolic improvement [99].

From within the core of the family, regulated physical exercise at school should be taken seriously, including the times, which in our country are usually 2 h a week. This is because it is well known how three 30' sessions of intense exercise per week are able to prevent and compensate for the other adverse factors. Longer times are reported in the literature between 45 and 60 min (x3 weekly sessions), but the intensity of PA is a basic factor in assessing the effect of PA and not only the time. In the home environment, physical activity should be considered as a key element of the child's lifestyle, especially if the child is overweight. In the clinical field, the pediatrician should play an important role not only by unconditionally supporting PA for physiological and leisure motives but also as a means to quantify it (time and intensity) by virtue of simple guidelines [100] and taking into account that accelerometry has made it possible to quantify with a certain precision which games involve greater physical activity and that outdoor games are clearly more effective than games in playgrounds or indoors. It is a constant that prevention must be early, and this affects the activity of the child who is already walking, and, whether in school or not, outdoor games or staying outdoors, being in contact with other children, and good interaction with the mother have been shown by accelerometry to be the most effective [101]. Aerobic exercise, muscle strengthening, and bone strengthening are the three headings which cover the wide possibilities of physical exercise for children and adolescents [102], but for adherence gain, parents should set an example. Furthermore, accelerometry not only determines the overall activity which is increasing up to the age of 5 years but also indicates that it is lower in girls [103]. From the domestic point of view, two recommendations are important: As the child grows in age (from 5 to 9 years), his physical activity decreases, and this must be taken into account to counteract the problem, involving him in household chores when indicated by the pediatrician is an effective way of combating inactivity. The other notion is perhaps more difficult to carry out, to stabilize a moderate or vigorous PA in addition to the positive attitude of the child; the physical habits of the parents are fundamental. The control of PA should be taken into account, since the correlation between what is programmed and what is carried out is variable, being greater in high-income populations. Planning for walking and using stairs whenever possible are a simple option and are generally well accepted. Planning and facilitating physical activity after leaving school but on a sustainable basis: effective formal sport should be to the child's liking and affordable for the family and should be made possible and should at least include walking (or running) as it does not require special support. Cycling is a way of increasing PA that is well accepted by many children, unlike walking, which is preferred by adults. Cycling has the advantage of greater efficacy than walking (both of which are regulated) in weight control, even with shorter weekly times, according to adult data [104]. However, cycling requires safe spaces, as the number of minor, serious, or even fatal accidents has increased, for example, in the UK, although they are still lower than those related to the car. The duration of a session should be at least 30'. The same could be said with regard to weekends, which should be separated from other days as here, if family collaboration exists, the possibility of energy use can be contributory. A study was carried out in our department on 96 schoolchildren (Fig. 8.1 and

Table 8.1), in which it is evident from the analysis of accelerometry data that physical activity is clearly higher at school than on weekends when they stayed at home.

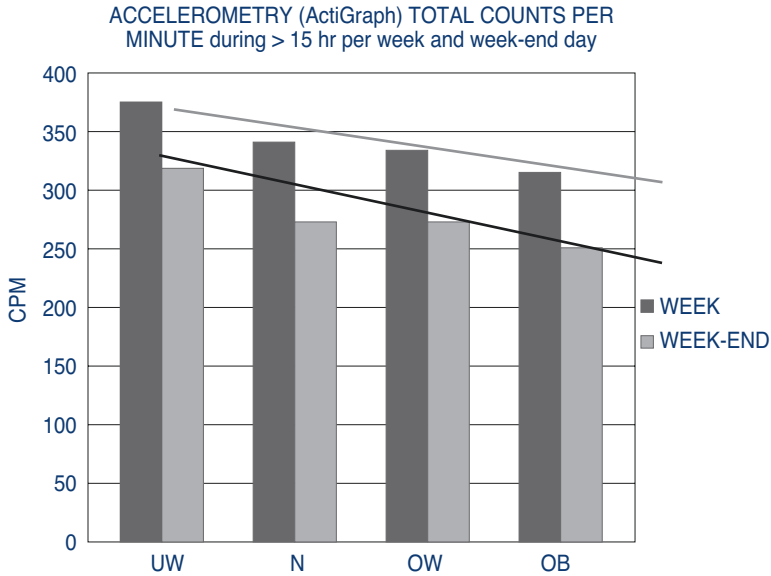


Fig. 8.1 Total accelerometry count (ActiGraph) per minute for >15 h per day in week and week-end days. There is a decreasing trend in the CPM count during the weekend and as BMI-Zs increase, especially in the obese group

Table 8.1 Physical activity assessed by accelerometry during 2 days of normal school attendance and compared with that of weekends

Nutritional groups, BMI (%) >, range, <	n=	BMI (%)	BMI-Zs	WC-Zs	DIASTOLIC BP mm Hg	Weekdays (CPM)	Weekend (CPM)
		mean(SD)	mean(SD)	mean(SD)	mean(SD)	mean(SD)	mean(SD)
Obesity >121	22	138.94 (17.9)	2.98 (0.52)	3.23 (1.43)	66.5 (8.7)	322 (105.73)	249 (98.8)
Overweight >111	17	114.35 (3.53)	1.11 (0.30)	1.81 (0.94)	62.47 (7.81)	337.25 (91.8)	279.3 95.02
Normal weight 90–110	44	99.54 (6.23)	−0.01 (0.48)	0.78 (1.04)	60.33 (8.37)	342.69 (84.84)	278.69 (114.42)
Underweight <90	13	86.34 (3.24)	−1.06 (0.31)	−0.26 (0.46)	57.6 (4.37)	369.69 (155.03)	324.92 (86.67)

Abbreviations: OB, obesity; SP, overweight; rBMI, relative body mass index; WC, waist circumference; DIAST, diastolic BP; mmHg; cpm, counts per minute

Physical Inactivity and Sedentary Lifestyle

The definition of physical inactivity is not precise due to the difficulty of obtaining exact data on it, given that it is considered as that state where physical involvement in habitual activities does not reach the various recommendations established as healthy for different ages. This is a serious and widespread problem as shown by the study [105] analyzing 298 population-based surveys with 1.6 million participants, where physical inactivity affects 80% of adolescents with a higher incidence in the case of girls and in both LMIC and HIC. We will probably know its projected progressiveness in its future edition (2030 Sustainable Development Goals). In the classic WHO approach [106] and with limits designed for adults, two levels are established: level 1 (inactive) is that in which no or little physical activity is carried out at work, at home, in transport, or during leisure time, and level 2 (insufficient activity) is when less than 150' of moderate physical activity or 60' of moderate/vigorous physical activity is carried out per week. Once again, quantifying the intensity is another weak point, especially in the case of children. Sedentary behavior is of a more general nature and is popularly reflected in the phrase "he is a quiet child," but it can be assessed by the number of hours spent sitting (>6 h) or when PA performed is less than 10% of resting energy expenditure. In this sense, accelerometry (see Chap. 5 Clinical) provides greater precision, but does not usually reach individual studies. It is therefore essential to reduce sedentary time and physical inactivity [103]. Using these thresholds and in adults, it has been shown [99] that inactivity is associated with increased cardiovascular risk, stroke, diabetes, colon and breast cancer, and increased risk of death even when there is not too much time sitting [107]. In the pediatric age group, sedentary leisure time in this country and in the 5–14 age group affects 10.8% of boys and 17.4% of girls (ENSE 17), worrying figures in the current context of overweight.

In adults, global physical activity (leisure time, transport, domestic, and work) has been systematized and quantified by determining *metabolic equivalents* (METs) from measurements of oxygen consumption at rest (VO_2 rest) and during a defined exercise (VO_2 max). In this way, tables [108] of physical activities defined by their level of intensity have been obtained: light <3 METs; moderate 3–6 METs; and vigorous >6 METs. This would allow estimation of the energy expended (exercise of 5 METs \times 60' = 300 kcal/hour). Unfortunately, these tables have not been developed for children, and the use of adult tables, even for children's activities, adds variability to the estimation, in addition to the difficulty implied by age, the diversity of games, and domestic activities. Simulation studies with this MET-h/day technique in children have a theoretical character. The estimation of vigorous intensity in pediatric ages is sometimes considered by whether or not they end up tired and sweating after exercise. This aspect, although highly subjective, is within the reach of anyone, and it should be taken into account that regular vigorous exercise is associated with normal weight.

The problem is that the inactivity gap is often filled by screen time. In high-income countries, the 2-h daily limit recommended by many scientific societies [109] is exceeded by 30% of North American adolescents aged 12 to 15, and, in the case of overweight adolescents, the percentage is 70%, with some minor differences according to race or gender. There are many studies on physical inactivity and sedentary behavior. Among them we should take into account that of the *American Heart Association*, AHA [110], because in addition to the prognostic approach already indicated, it points out that the average American boy aged 8–18 spends more than 7 hours a day in front of his screens, and another study, no less interesting [111], concludes that between 0 and 2 years of age, the time in front of screens has been increasing since 1997 to reach 3.05 h/day in 2014, figures that are probably worthy of valuing in our media. A recent study by the University of Calgary (Canada) reveals that 79% of 2-year-olds and 95% of 3-year-olds exceed the limit set by the WHO of 1 hour a day in front of quality programs for those ages. In Spain, screen time in excess of 1 h a day (ENSE 17) on weekdays occurs in 60% of children aged 1 to 4; in 76% of those aged 5 to 9; and in 83% of those aged 10 to 14. This interesting data should be completed at least with the limit of 2 h/day (more obesogenic) and also during the weekend. The risks of screen time should be considered, in addition to what has been mentioned in adults; in children the ALSPAC study [112], carried out in the United Kingdom on more than 4500 young people aged 11–12, did not show a link between sedentary time and adverse cardiometabolic consequences but did show how moderate-vigorous PA (adjusted to 10') was associated with better indicators of adiposity, greater lean mass, and better cardiometabolic markers. In the same vein, the association of reduced carotid and femoral intima-media thickness in 11- to 13-year-olds who participated in specifically organized sports could be considered, and perhaps more interesting is the association in preschoolers between screen time and reduced white matter microstructural integrity [113]. The large prospective ECLS-K study [114] shows how in children aged 6–9 an additional hour a day of TV for 10 years implies an increase of 0.4 SD in BMI-Zs. Data collected by the major North American information networks show how screen time decreases the time devoted to study and school work and creates a certain addiction to the Internet. In addition, children aged 6 to 24 months who are exposed to large or small screens show moderate language delays. Minor consequences of prolonged screen time are sleep problems (terrors, nightmares) following the viewing of certain evening programs. After considering these extensive series of data, from any point of care for children at risk of overweight or obesity, inactivity should be evaluated, and an attempt should be made to compensate for it with increased PA, always on an individual basis and always being flexible, especially in terms of time [115].

After this analysis of energy intake and expenditure, certain facts must be taken into account. The first is the metabolic adaptation of the organism to the negative balance which in itself leads to a greater activity of the orexigenic peptides (see Chap. 4), which leads to a greater food intake [116] and which subtly makes this intervention less effective. In addition, there is the clinically proven fact that the

child after exercise which he or she subjectively considers as vigorous feels justified to eat more for what he has already consumed. Contributing to the latter situation are certain media reports where x hours of exercise equals “burning” y kilocalories (e.g., *TIME Health*, 12 Sep 2018). These three circumstances should be taken into account when planning the PA program with the patient. The other aspect that impacts negatively on this balance is that it is easier to successfully intervene on dietary restriction than on increasing physical activity, both in school time and in the home setting [117]. Again, school remains underutilized in both respects; it is well known how in low-income countries after school education nutrition improves despite no modification of food resources, and this is true for both forms of malnutrition. However, to return specifically to obesity, a study in Denmark [118] shows how increasing physical activity from 1.5 to 4.5 hours/week for 5 years significantly reduced the percentage of overweight and obesity. This would be worth considering by the various westernized governments.

Inadequate Sleep

It is well known that in childhood, shorter sleep duration is associated with obesity, both in high-income countries [119, 120] and in low- and middle-income countries [121]. We will now consider only shorter sleep duration and not the more difficult to assess quality of sleep or its pathology: insomnia, light sleep, or fragmented sleep. The exact mechanism of this interaction is not known, and alterations in leptin, ghrelin, and insulin levels, thermoregulation, greater opportunities to eat, less physical activity due to previous fatigue, etc. have been postulated [122] to try to explain it. The reality is that prospective studies initiated in the first year of life [123, 124] and evaluated after 1 year show a moderate protection of longer sleep duration against obesity (OR 0.54, 95%CI: 0.35–0.82). Children aged 5 and assessed at 15 according to the time they normally go to bed (<20:00; 20–21:00 and >21:00) resulted in a prevalence of obesity of 10.16 and 23%, respectively [125], and the same trend has been demonstrated in adolescents. Variability and timing (early wake) imply gains in adiposity [126]. Furthermore, it has recently been shown that shorter sleep duration in preadolescence is associated with subsequent cardiometabolic risk [127]. It is important that sleep, in addition to its regular duration, covers the night, as interference with circadian rhythms favors overweight. Daylight saving time has cardiovascular consequences in a large number of adult patients [128].

The framework for estimating the duration of sleep is given by the *National Sleep Foundation*, which can be summarized as follows: for children under 1 year of age 12–15 h/day (h/d), from 1 to 2 years of age 11–14 h/day, from 2 to 5 years of age 10–13 h/day, from 6 to 10 years of age 9–11 h/day, and adolescents 8–10 h/day. How to achieve these times is not always simple, and the parental (maternal) attitude of encouraging these times must replace that of respecting the child’s desires and especially hostility. From a practical point of view, the following four points can help:

Recognize signs of tiredness in the child to put him/her to sleep while awake.
Do not associate sleep with special behaviors (meals).
Quiet and darkened room.
Follow safe sleep guidelines.

Interventions, either through health visits or mobile phone apps, have shown positive results in the areas where they have been implemented. An integrated sleep model for families with vulnerable children who are also prone to overweight seems particularly useful, but its implementation requires for the moment a pioneering spirit (*The Sheffield Children and Young Sleeping Well Project*) and state action, perhaps simpler, because vulnerability in children and young people is already more considered and it would essentially be a 2 for 1.

Involving Parents and the Family Environment

Parents should be educated to know and be aware of the future of obesity, as well as the measures to be taken at home, even if they are untreatably obese parents. It is worth positively emphasizing family lifestyles that can contribute not only to weight control but also to the child's improved emotional state. The situation of the adolescent who prefers to get involved himself/herself rather than his/her family should be understood and supported [129]. Two articles published in *JAMA* clearly illustrate what can be expected from preventive parent education. The first [130] concludes that an intensive behavioral intervention, both for parents and child, with face-to-face sessions and telephone monitoring, did not result in a greater change in BMI trajectory after 3 years of follow-up than in the control group. In the second [131] and for a similar age group, with a lower intensity intervention, this did have a moderating effect, although discreet compared to the control group. An education given to the family in friendly terms and not only informative of the process [132, 133] but also practical (no acquisition of sugary drinks, *snacks* never in sight, certain flexibility with screens, etc.) can probably make parents have a more objective conception of their children's overweight or obesity. Parental education, even in adverse family situations, if carried out well, can perhaps be as effective as standard preventive action itself [134]. In any case, the interview with parents should make them aware of the chronicity of the sometimes small factors responsible for excessive weight gain or weight regain once the period of trust has been entered. Particularly important here are the little apparent changes in food intake. Parents should know the school policies are frequently weak for making a possible home compensation if necessary [135]. Present and future risks are a special section. Parents are more familiar with the late consequences especially if they are obese adults. However, new data such as both the stagnation and even paradoxical shortening of life expectancy (see also Chap. 7), which in 2015 declined for the first time in two decades in the United States [136] (where the increase of overeating and obesity has been significant) [137]. This parameter should be discussed in all developed countries. The alterations present (hyperinsulinism, hypertension, sleep disturbance, final size, acanthosis nigricans etc.) must be explained in the same way. The active

participation of parents in the preventive process has been shown to be effective whether they were obese or not. One of the concepts that parents should incorporate is the importance of adequate nutrition in the first 1000 days in the genesis of obesity, especially in families at risk, and how some interventions in this period improve the weight trajectories of these children [138], perhaps the most effective being the prolongation of breastfeeding, where every month counts, as shown by the EPOCH Collaboration and the InFANT Program studies, also conducted in Australia. Finally, and as a separate and basic aspect, we should consider the knowledge of the benefits of permanent physical exercise and how parents should create a favorable environment for it and monitor progress [139]. Given that adherence to PA is generally far from prolonged, this aspect is important since the determinants of adherence throughout life are not known. Barriers to family PA behavior change include low motivation; social, economic, or environmental pressures; lack of time; physical or health limitations; lack of knowledge; and boredom with exercise [140]. The existence of any of these barriers together with unrealistic weight loss expectations is an early indicator of non-adherence.

It must be taken into account that there are children and adolescents (and parents) who are capable of making these behavioral changes and others who are not and consequently obtain worse preventive results. In no case should they be reproached for this because, in addition to their ineffectiveness, additional suffering is inflicted on them, which is considered unethical by the institutions of medical ethics.

The child himself/herself. Finally, the child him-/herself and especially the older he/she is and with the utmost delicacy and tact must understand the physical consequences and particularly the progressive isolation he will be thrown into in the immediate future. Bullying in general can be better accepted than further isolation. The results [141, 142] following action on this specific and complex aspect would indicate the need for further research, especially considering that the number of adolescents who are overweight or obese and do not try to lose weight is increasing [142].

Results

With regard to prevention outcomes, it is difficult to provide representative figures especially in the long term. The Catalan study [143] has a good design although a follow-up of only 15 months; surely its longer-term results can be more informative. The Chilean study [144], with assessments at 5, 10, 15, and 21 years of age, has the weakness of four groups with different BMIs which means that confounding variables need to be accurately assessed, although it seems that lack of adequate family and home support are associated with higher BMI values. The list of publications on positive preventive outcomes of pediatric obesity is extensive, with added assessments such as insulin resistance, metabolic syndrome, elevated blood pressure, school success, and a long etcetera, but, in general, they require greater size, duration, and better follow-up standards. There are some studies with positive preventive outcomes (WIC) in preschoolers but not completed [145] along with some other

also positive studies (Net-Works Randomized Clinical Trial 2012–17) but with a follow-up of only 3 years. A specific designed meta-analysis on adults [146] concludes that ‘larger reductions to portion size resulted in larger decreases in daily energy intake’. Some rigorous models [147] with a duration of 20 years and biannual nutritional controls show cardiometabolic improvement and how the dietary adequacy introduced in childhood persists into adulthood. This same design applied by the same Finnish group but applied to the different calcium intake shows its scarce relevance with respect to the appearance of cardiocirculatory risk. On the opposite side of negative preventive outcomes, the studies are more numerous, and in the “commentary” by William Dietz [147], and modifying his own 2015 article, he concludes that there are no differences between the novel intervention groups and those who took the usual standard prevention. The idea that prevention should start in the home is perceived in European literature, along with another positive fact, prevention before the age of 2 years of life. In this section of the results, the intervention of superior organizations is surely necessary and with operative capacity to know the evident bases of prevention.

Final Considerations

The way in which the prevention of pediatric obesity is carried out is a large and widely studied chapter [147–151]. The four (or five) points discussed here are not complicated, though they are time-consuming for the pediatrician practicing prevention at the individual level. Note that neither special examinations nor psychiatry is required, but regular follow-up is necessary. We have to be aware that small-scale preventive activities only achieve small-scale effects, but as long as general prevention is not established, it is the only method we have and cannot be underestimated from any angle as the results of treatment once the obesity picture is established are disappointing.

As a preventive balance, it could be questioned that if there are good programs emanating from institutions and agencies of recognized prestige, then why has obesity in the world continued to grow until now and will probably continue until 2030 or perhaps more realistically until 2060 [148, 152, 153]? The European Commission launched the *EU Action Plan on Childhood Obesity 2014–2020* coinciding with that of the WHO *European Food and Action Plan 2015–2020*, but the impact on member states is not especially visible at the moment. This does not mean that there have not been positive developments such as the decrease of the trend in certain communities or a better anti-obesogenic education and a social dimension of the problem beyond the classic medical approach. In our country, the NAOS strategy and through the Spanish Agency of Consumption, Safety, Nutrition (AECOSAN) of the Ministry of Health has launched a program in addition to the existing ones coming from autonomous communities and scientific societies, where early and general preventive advice can reach the general population through the media. Another positive example is that of the aforementioned WIC [145, 154, 155] in which and after a

cross-sectional study of 22.4 million children from 50 US states and territories, a significant reduction in the prevalence of obesity appears for the first time during the period 2010–2014 thanks to the modifications of the food package offered. However, the subsequent commentary from the CDC itself (CDC Newsroom 21 Nov 2019) is not so flattering, as on the same population only seven state agencies (out of 41 states analyzed) have achieved a decrease in obesity of 3% in those children aged 2–4. Moreover, in three states (Alabama, North Carolina, and West Virginia), the prevalence has increased significantly (2.2%).

In general this has allowed early detection of risk situations and eventual action and even treatment of comorbidities so unapparent in pediatric obesity. The influence of television cannot be ignored, and the self-regulation of food and beverage companies for responsible advertising is rather utopian, and the reality is that preschoolers in the United States already see 3.2 ads for sugary foods/drinks per day and the rate is higher in schoolchildren [156]; these ads increase children's preferences for certain brands and foods. The situation in Spain is not more optimistic; the excellent work of León-Flández [157] shows how the PAOS code (advertising, activity, obesity, health) when evaluated by means of TV advertisements has the same low compliance in 2012 as in 2008, both with respect to high- and low-calorie products. The food industry's consideration and response are slow and limited, for example, the current elimination of trans fat [158] or the persistent contrived promotion of fast food [159] and hydration drinks [160] or the resistance to improve the ideal dietary percentage in school canteens [161].

Two new aspects are worthy of attention. One is the lower awareness of overweight or, in many cases, obesity in children in primary care and practically nonexistent in emergency pediatrics [162], when the preventive efficacy at these levels has been well proven [163]. The second would be related to the education of the general population that acts as a protective factor against obesity [164]; the best level of education when it reaches the family, the school and nursery, and the community is effective [165]. More ambitious projects such as regulatory laws for energy content information in vending machines or restaurants (*US Affordable Care Act* approach), changes in food crops, and food chains need more time to show their effectiveness. An editorial in the *BMJ* [166, 167] reports the effectiveness of calorie labeling on the menu and that it is effective in reducing 60 kcal per service over a whole year; however, over time this reduction is decreased by the individual's own choice. They conclude that, although the reduction is modest, it should be considered by decision makers (sic). We should bear in mind that not all preventive projects against obesity are the same, and so, for example, the one concerning blood pressure elevation [168] seems easier to carry out because of a more concrete clinical management; however, the number of hypertensives has altered little. Probably the idea of increasing synergies among countries may be useful [169]. These aspects are not of minor importance, due to the fact that food marketing is associated with demand and increased intake in children and adolescents [67].

On the darker side of prevention, apart from minor failures (*Fat letters* to parents or the more than 50 food pyramids or plans that stigmatize obesity), the following facts deserve to be considered: the difficulty of applying evidence criteria to assess

preventive effectiveness, this is not a health characteristic, for example, it happens also in conflict prevention. There are too many plans and guidelines, not all with the desirable quality or coverage. The flow from global guidelines stalls before reaching the child at risk even in high-income countries with inclusive programs. Continued evaluation of applied processes such as labeling (Flabel in the EU), taxation of sugar-sweetened beverages, or school menus, among others, have an unknown impact on obesity reduction. In addition, the possibility that some guidelines for the introduction of solid foods may increase BMI after 1 year should be taken into account [170]. Improving the translation of behavioral patterns to the home environment is likely to be an urgent goal [171]. It is probably time to address the failures in the preventive system: insufficient evidence, shortcomings in downstream communication, and especially prevention research and strict monitoring [172, 173]. In low- and middle-income countries, nothing has been done except for small, ad hoc actions, and within a few decades, obesity will be just another problem in the backlog of care in these regions. The initiatives of IFT, *Feeding the minds that feed the world* (19 Jun 2019) or the more media-friendly one of *The Guardian* in its issue of 20 April 2019, with the suggestive headline breastfeeding reduce the risk of pediatric obesity by 25% and, together with the simple recommendations it offers, are something that should surely be extended. One reason for this difficult preventive success could be the lack of long-term external for the obese individuals, and then the idea of semi-structured interviews by a public health specific organization in preventive results (BMI, WC, and cardiometabolic red flags) would help. There are initiatives in that sense mostly for adults [174, 175] but also for children [176]; their results should be analyzed. For the moment ‘An ounce of Prevention is Worth a Pound of Cure’ [177] would not apply to obesity.

Finally, I would like to add one of Albert Einstein’s thoughts against foolishness: “Foolishness is doing the same thing over and over again expecting different results.” If the classic binomial restriction of intake/increase of energy expenditure has led to an increase in global obesity, surely other actions or variations should be explored.

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Chapter 9

General Treatment of Pediatric Obesity



Introduction

The treatment of pediatric obesity deserves full clinical and research attention and support as it is slow and arduous and its efficacy is far from desirable. In some high-income countries, life expectancy declined in 2017 [1], both in the United States and in some European countries (UK in 2021), and overweight, obesity, extreme or not, and comorbidities are increasingly prevalent, with an association between both circumstances. Precisely because of this lower efficacy, therapeutic actions should be based on their strength (recommendation or suggestion) and the quality of evidence, especially in the current scenario where certain publications of systematic reviews and meta-analyses lack the required rigor. In addition, a few years ago, the need for a team to provide treatment was established, generally with the required hospital base, but today a continuous vision is also contemplated according to the evolutionary stages of the process: prevention, initial treatment, follow-up with structured weight control coinciding with therapeutic intervention (multidisciplinary or not), and finally a tertiary approach if severe obesity is reached. During these four stages, actions on lifestyle modification, pharmacotherapy, or even bariatric surgery should be implemented, as will be discussed below. But this should not undermine the primary therapeutic capacity, as it would leave a large group of patients without control, incurring an ethical problem. We need to know how to take advantage of, and encourage, family cooperation with the health visitor, an important emerging figure [2], and take into account that in the medium- and long-term treatment all actions add up, while when they are isolated (motivational interventions, the important collaboration of parents, etc.), they are less effective. The excellent therapeutic guide for pediatric obesity issued by the *Task Force* [3]) of the European and American endocrinological societies addresses the fields of lifestyle, eating habits, inactivity, pharmacotherapy, and bariatric surgery in the aforementioned rigorous terms. In the face of therapeutic failure, the existence of models

(SMART, MOST) that facilitate new, more complex and perhaps more decisive approaches must be taken into account. In the same way and from the studies coming from adult obesity [4], it is worth considering some of these aspects of clear pediatric implication. Finally, in the treatment of pediatric obesity, the chapter on prevention should not be overlooked and will continue to be valid, especially in lifestyle aspects.

Initial Approach (See Also Chaps. 5 and 6)

The clinical approach to the child to be treated requires knowledge and a receptive attitude on the part of the team or the pediatrician or the physician in charge. First of all, it must be established that there is no underlying endocrinological or monogenic pathology in severe cases ($BMI > 3 SD$), as is usually the case. Predisposing genetic factors, such as gene variants (SNPs, *FTO* gene, etc.), are typical of epidemiological studies applied to population masses, although genome sequencing is bringing this possibility closer to individualized studies and the same could be said of the epigenetic [5]. With regard to the existence of comorbidities, one of the most important factors is the accurate diagnosis and management of insulin resistance syndrome (IRS), preferably through the assessment of fasting insulinemia rate or alternatively through glucose tolerance tests (oral or IV) or ideally the hyperinsulinemic-euglycemic clamp. The latter should always be performed after the age of 5 years [6], since those performed at a younger age usually give inconclusive results regardless of the degree of obesity. Perhaps the applications of the classic indices (more than 20) of insulin resistance have not met initial expectations. It should not be forgotten that the insulin resistance syndrome or status should include assessment of blood pressure and dyslipidemia in addition to impaired glucose homeostasis.

The exhaustive evaluation of the clinical condition prior treatment decisions has been recommended by the American Academy of Pediatrics through two valuable publications [7, 8]. Some predisposing circumstances must be taken into account here: birth weight regardless of gestational age and whether or not they have received macronutrient supplementation will probably require further studies before considering them as real risk factors for later obesity. The next cause for concern within the medical remit is the presence of non-alcoholic fatty liver disease, which is being diagnosed with increasing frequency and is always a further uncertainty in this prolonged clinical course [9–11]. Other aspects requiring medical attention, although long known, are no less important, such as thyroid dysfunction, accelerated pubertal development, and sleep duration and quality. Pubertal advancement should be assessed by means of bone age, testosterone, DHEAS, and gonadotrophin levels as well as secondary traits. It is best controlled by weight reduction since LHRH analogs, as expected, are less useful in controlling pubertal advancement. The same could be said of abnormal sleep patterns and disturbed breathing during sleep, mainly its duration and quality and the presence of sleep apneas, the negative consequences of which have been identified after the generalization of polysomnographic studies. The treatment of this situation is mainly weight reduction, and if

this is not achieved, nasal continuous positive airway pressure is highly effective in improving nocturnal gas exchange. Adenoidectomy is sometimes indicated here. Finally, within the medical work, variations in height, especially where below average, the presence of dysmorphic findings, and reduced learning capacity should all be studied and evaluated, in addition to the endocrinological study that comes with consolidated obesity. The presence of monogenic obesity requires the study of the hereditary pattern and enzymatic and/or genetic evaluations.

The second task within the medical approach is undoubtedly weight control, which should be unified and based on standards as universal as possible. The BMI-zs, as well as the assessment of the zs of the abdominal circumference or the derived indices (waist/height ratio and relative fat mass pediatric RFMp), are mandatory and require the same precision in their successive evaluations. In this context, treatment should be initiated when the values of the former are equal to or greater than 2 SD (~ 95th percentile). If the child is growing, the most useful and endurable policy is not to gain weight as he/she gets taller. Rapid weight loss by means of a strict diet is not appropriate because of the slowing of the growth rate in addition to the frequent return to the initial BMI. If the degree of obesity is severe and there are complications, then a maximum weight loss target of 0.5 kg/month can be considered, and in the case of adolescents who have finished growing, then the loss could be targeted up to 0.5 kg/week [12], but with close monitoring in both cases. If the child and the family agree to significant energy restrictions in order to improve BMI (and physical appearance and shape), then the opportunity should not be missed, as the adverse effects on body composition are not relevant when dietary intake is balanced. Moreover, this incorporation of the family into the treatment at least slows down or stops the upward trajectory of the BMI. Other medical aspects, although less important (mammary fat deposit, stretch marks, etc.), should not be neglected because of the impact they have on boys and hypertrichosis in girls. Finally, and from the beginning, the objectives to be achieved and the estimated time should be agreed upon. If this series of previous actions are not fully available, this should not be an obstacle to starting the treatment and planning the most possible and the most appropriate type of follow-up. At the same time, the lengthy duration of the treatment in inveterate cases and how the actions do not always improve the anthropometry should be reported.

Non-drug Therapeutic Approach

Lifestyle Change

Interventions in this sense should be aimed at modifying the family attitude or behavior towards obesity, specially directed at eating habits and physical activity. The reasons are, firstly, the efficacy of its implementation and, secondly, its low economic cost and safety. In the case of not having or not using a support team, the family or at least a member ideally should provide emotional support and

therapeutic support and commit to keeping a simple record of food intake and physical activity as well as adherence to the evolutionary controls that would involve an initial fortnightly visit and then monthly for the next 6 months. All available resources should be used, from simple programs well proven in adults [13] to mobile phones with accelerometry (physical activity) and food intake applications to obtain an approximation of the energy balance. From the moment the patient is included in a weight reduction program, two notions should be clear: one is the lengthy duration of the treatment and the other is the frequent relapses. No matter how many ups and downs the patient has, the patient should not be reproached, nor should the family be threatened with the stigmas of obesity.

Behavioral intervention when carried out by a team and with an intensive character (more and longer sessions) may offer better results than when it has a normal level, but it has not been as positive as expected in obese adults. In children and adolescents, this type of intervention provides inferior results [14], as we saw in Chap. 8 *Prevention*, and improves when the family is involved as a priority [15]. Recently the focus has also been on community actions (training, cultural activities, sports, etc.).

The family, especially the parents, should be involved in the treatment, and if they are obese, they should be advised to lose weight, follow the same diet and physical activity regime, and create an anti-obesogenic climate. Collaboration in at least one is essential. During childhood (5–11 years) behavioral interventions are much less structured and yet effective [16]; therefore parents can have an important influence on eating (see below) and exercise habits, which has been accepted after or through studies on long-term weight maintenance. The incorporation and adherence of parents to the program are not easy, especially if they involve separate sessions, either individually or with other parents. Cultural and personal perceptions and family stability mentioned in the prevention part are other non-facilitating factors. When there is family incorporation, the reduction that usually occurs during the first year is more intense, and, although some BMI_r is later recovered, it always remains at significantly lower levels than when there is none [17] and often for a prolonged period of time. When the parental attitude-based program works well and sustainably as in some studies [18], it does so effectively. However, the effectiveness of parental action is not always as effective as one might think. According to a study of nearly 500 families [19], it lasts for the first 12 months, but the differences with the control group disappear by the time the second year of follow-up is reached. Another study carried out in the United Kingdom shows that despite having a special design (“families for health”) after 1 year, there are no differences in the degree of obesity with the group that received the standard treatment [20]. Family fatigue in the face of daily behavioral change is a significant factor, to which should be added the fact that the father’s involvement in this clearly parental task is almost nonexistent, as demonstrated in a large systematic review [21]. These parental behavioral modifications are more difficult when dealing with obese preschoolers. The USPSTF (*US Preventive Services Task Force*), after a systematic review, concludes, among other things, that at least 26 h of contact with the family is required for weight reduction in adolescents and adults [22]. It should not be forgotten that

well-controlled actions, although numerically smaller, do achieve significant reductions in BMI. Furthermore, we should not lose sight of the fact that the earlier (pre-school) the intervention on lifestyle is started, the more effective it will be [23]. Within the lifestyle, routines are important; from the preschool stage, regularity at bedtime, mealtimes, and screen time contribute better to self-regulation and therefore lower risk of obesity when evaluated at 12 years of age [12]. A sedentary lifestyle as a tendency or habit has been dealt with in the section on physical (in)activity in Chap. 8. Another aspect worth mentioning is how the child should not be confined to the family environment, must have an adequate social life, and must be taught how to restrict his or her own intake when outside the family environment and in any case compensate in the next meal for any previous energy excess.

When it comes to adolescents, ideally they should be encouraged to promote changes in eating habits and lifestyle, probably through individual sessions and leaving them free to come or phone even on a weekly basis. At this age it is always better to understand the improvement in image that being slim means, rather than the fact of being healthier, and to know how to take advantage of these circumstances. The change of behavior decided by adolescents themselves is probably the most important factor in the treatment [24] either through group sessions or individually. This psychological support is important at this age, although as it is not always available, and should be stressed during the training of residents. For the modification of eating behavior, the following sequence is used: analysis (described by the children themselves) of the act of eating and the circumstances surrounding it; frequency of meals; analysis of the rhythm and size of the mouthful; and analysis of the sensitive response to the act of eating (i.e., if they are really hungry and if they like what they eat). The aim is to change the obesogenic behavior, which will also include physical exercise, as we will see below. It is important that they themselves recognize these signs that precede weight gain. The role of the family is completed with concrete agreements for the achievement of a goal and maintained verbal support, one of which is adequate sleep.

The change in lifestyle approach has drawbacks that are difficult to solve. Circadian and seasonal rhythms influence the BMI of pre- and schoolchildren [25] due to the longer duration of the day and less sleep time. The metabolic dysregulation that this entails will not be compensated by the possible longer duration of sleep during the weekend [26]. Another imponderable today is the evident association between poverty and pediatric obesity [27], in addition, the sometimes paradoxical fact that conventional interventions can have counterproductive effects when applied to children aged 3–5 years [28].

It should not be forgotten that nutritionally insecure and especially neglected children have a ninefold increased risk of becoming obese adults [29]. In this regard, a study in adults from Europe, Australia, and New Zealand [30] shows how a fixed but low-energy diet (800 kcal/day) produces rapid weight loss and metabolic improvement, but this differs according to gender. These data demonstrate, once again, that the different individual responses are difficult to assess at the beginning of treatment and yet will modify the therapeutic outcome, which must be taken into

account in pediatric patients. A study of 1000 adults shows the importance of correct lifestyle intervention and how this overrides genetic susceptibility [31].

If there is low self-esteem or bullying by peers, this should also be addressed as part of the specific treatment [32]. It should not be forgotten that there is some psychological research into the quality of life of the obese that suggests that in some cases they improve their quality of life despite continuing to gain weight.

Modification of Eating Habits

The therapeutic dietary approach is based on the aforementioned thermodynamic balance described in prevention, and this section will deal with caloric restriction (CR). CR involves a reduction in energy intake, but with adequate nutrition. Caloric restriction has been shown to be effective in prolonging life span and improving health status in both overweight and normal weight in both animal and human studies. Moreover, CR has an additional advantage in that it reduces craving or compulsive ingestion of certain foods in both adults [33] and possibly in children [34], due to the predominance of observational studies as opposed to randomized studies. Within this section of CR, self-regulation of appetite, which has genetic, biological, and psychological bases, but which is influenced by dietary and especially family policies from preschool age, plays an important role [35]. These influences lie in the better taste of certain foods or beverages (soft drinks vs water), greater accessibility (home pantry, vending machines), and marketing with advertising aimed at children. In addition to state regulations, it is at the family level that proper nutrition and nutritional education, including knowledge of the feeling of satiety, will be established to counteract these circumstances. The inhibitory control of the hedonistic response to food intake is a subject with a broad psychological basis and in which adult experiences do not yet have a clear application in childhood [36] and the same could be said of “food addiction” [37], but these are aspects that should be assessed. From a general point of view, it should be added that variations in the rhythm of meals (fasting every other day or at certain times or for 16 h at a time) and energy-labelled menus or pre-loading with water before meals, among many other varied recommendations, have not produced the predicted adherence or reduction in BMI [38–40]. To a common question, “I want to lose weight. Which diet is best?” the adequate reply [41] implies a triple response, probably neither expected nor wanted: Decrease caloric intake. Increase physical activity. Set diet-exercise-related goals.

Dietary Treatment No medical situation has given rise to such a number of dietary programs as obesity, and this is because of their promoters and followers, without any conclusive results so far. It is true that this motley collection of dietary measures does not exist in pediatrics, where there are carefully designed plans with broad state support, some of them seen in the chapter on prevention, and whose results are worth noting. For example, *Let's Go 5210* is one of the most widely disseminated school-based healthy habit implementation plans in the United States, but when its

results were analyzed 2 years after its implementation [41, 42], it was clear that there was no improvement in eating habits, physical activity, or BMI. A similar outcome was also detected in the traffic light diet [42, 43], and there are even paradoxical facts such as the case of children with adequate and balanced diets who increased their BMI-zs [44]. In another study, in which fast food and “snacking” predominated, the BMI surprisingly improved [45]. The reason for these paradoxical results can be attributed to the design and especially the duration of the studies, but especially to the fact that preschoolers already have access to and choose obesogenic foods in quantities not easily detectable, as has been demonstrated even in low-income communities. The problem with diets is the real adherence level even in the short term, exceptional in the long term (> 12 months) [46]; that is, the fault lies not with the menu but with the increased intake.

Saturated Fats The controversy about their dietary use began in the 1960s [47] when dietary guidelines appeared recommending a significant reduction in saturated fats as part of the prevention of coronary heart disease. This was followed by a series of studies in the 1970s, including those of the Minnesota School of Nutrition, which showed that reducing saturated fats in the diet reduced plasma cholesterol. This idea was taken up and sponsored by the prestigious DGA, *Dietary Guidelines for Americans*, and even the US Department of Agriculture (USDA) caused them to be displaced from the base of the food pyramid in favor of carbohydrates [48], which enjoyed wide medical and social acceptance. The real problem is that these recommendations were not supported by adequate studies. It was in the last decade and with the advent of evidence-based studies [49, 50] that no association was established between the consumption of saturated fats and the risk of coronary heart disease. From this point on, a series of studies and a movement against the demonization of saturated fats in the diet began to emerge, given that, coinciding with this nutritional trend, obesity increased significantly. Despite these facts and the need for more extensive and longer studies, for example, the action of heptadecanoic fatty acid (17:0) or ketogenic diets, the exclusion of saturated fats continues to be supported by the American National Institutes of Health (NIH) [51], by the American Heart Association (AHA), and by the DGA itself [52], although not with the previous persistence [53]. Even the DGA itself has proposed a redesign of its previous recommendations, and also reports from the financial sector warn about this plausible change in diet. In this same line, the scientific group led by Astrup [54] rightly expresses that for the 2018 WHO guideline on saturated fats and trans fats, perhaps the time has come to give it a new approach. In this exculpatory sense, the prospective PURE study [55], based on a cohort of over 130,000 adults that concludes that increased carbohydrate intake is associated with increased mortality risk while total or unsaturated fat intake is associated with decreased mortality, should be taken very much into account. In summary, on this argument which, although it occurs more in adult territory, also affects the pediatric one, it can be concluded that fats are important in the nutrition of the obese child and that, far from being replaced by carbohydrates, they should be adjusted to the normal quota of their energy intake or reduced with respect to their previous dietary intake.

It is worth considering how hypocaloric diets at the expense of an immediate principle, in the end, are compensated by the organism [56] through gluconeogenesis from amino acids and by an increase in free fatty acids, mostly unsaturated. It should also be noted that some dietary restrictions do have value in certain comorbid conditions, such as the reduction of fructose intake in the case of metabolic syndrome and more specifically in the case of non-alcoholic fatty liver disease [57], not to mention the questionable meal replacement, which consists of replacing one meal a day with soups, shakes, or bars and, if in adults it has given a small result, perhaps it could also be applied to adolescents. This should not be confused with intermittent fasting guidelines for the treatment of adult obesity, which has had some positive results [58] not found when strict randomization has been carried out [59]. This aspect is unlikely to be applicable in pediatrics, as prolonged fasting for several hours or even a day has not produced conclusive results with respect to BMI, insulin resistance, and other metabolic parameters such as TEE (total energy expenditure). There is also an ongoing study [60] that shows the resistance of abdominal fat to alternate-day fasting.

Dietary treatment (diets) has been considered as the most important and has generated a multiplicity of varied diets both in their composition and in the amount of energy, which, when evaluated in the long term, have shown relatively little efficacy [61]. We must take into account that specific circumstances related to correct prevention strategies [62] may encourage such excessive eating behaviors as eating when one is not hungry. It is also known that strict diets have had a number of negative consequences [63], such as loss of lean mass, decreased longitudinal growth, binge eating, and anorexia. Despite some occasional positive results [64, 65] in pediatrics with low-carbohydrate diets, the reasons noted above have led to their decline. This is not the case with ketogenic diets, where animal experimentation may open new therapeutic avenues by acting on mTORC1 [66]. However, we need to consider the known risks after ketogenic diets used in certain epilepsies and which involve, among issues, insulin resistance, edema, renal lithiasis, hyperuricemia, acidosis, and hypercalciuria. This means that, for the present, well-controlled studies are required, especially over time, before endorsing diets which until now have only been recommended for obese adults with TD2. Regarding the protein content in the diet, there have been different points of view, some more passionate than rational. The rationale for its increase rests on its satiety-inducing capacity, as was seen in Ch 4 (protein-leverage), which decreases energy intake [67]; conversely, its reduction leads to a compensatory increase in energy intake through other macronutrients. However, studies of precise design and with strict intakes are not conclusive; therefore caution dictates maintaining the classic protein intakes at around 8% of total energy. Perhaps it should be kept in mind that the low-protein component of the diet leads to higher carbohydrate intakes and potential risk of obesity, especially topical because of the exaggerated crusade against red meat consumption that has transcended the general population as shrewdly editorialized in *Annals of Internal Medicine* (1 Nov 2019).

In general, it can be said that diets are not very durable in the pediatric age, and perhaps it is more effective to give concise information to the family just on foods.

The healthiest and most effective foods against overweight that involve eating vegetables, fish, and more fruit; avoiding cold cuts and other processed meats and the refined sugars that are so visible in supermarkets; reducing portion sizes; replacing snacks with fresh fruit; using foods that require more effort (wholemeal bread, fruits that have to be peeled); and baking, grilling, or boiling foods, without adding extra oil, instead of frying. In short, it would be a return to more traditional diets, which is not so easy because they require more complex and prolonged cooking and in some cases involve a higher cost. However, and when possible, one should try minimally processed foods or group 1 of NOVA Food Groups [68], Processed foods and culinary ingredients, or group 2 foods (bread, homemade cakes, cheeses, olive or palm oils, salt, sausages) should be used with precaution. Of course ultra-processed foods or group 4, including industrialized sweets; sugar-sweetened beverages; industrialized cereal flours; fast-food, fried, or baked snacks; lasagna; hotdogs; and cereal bars, should be avoided, because of their high energy density, also reducing portions to what is known as normal-small size, since this is effective in the medium term (Cambridge University Press, 06/08/2019). There are approaches that in theory may be useful such as alpha-glucosidase inhibitors originally found in green apples, beta-glucan from oats and its increase in viscosity, or resistant starch from potato, or L-theanine from mango sorbet, or replacing one serving of food with 25 g of nuts, among many other recommendations, all of which may be reasonable, but require better designed and longer studies.

Condiments. Salt consumption deserves separate mention; we should not overlook the fact that it promotes the consumption of fats, or even that of other macronutrients, by reducing the feeling of satiety that they produce [69], and the lack of awareness of parents and the environment about their overuse. It is also time to consider non-nutritive sweeteners (aspartame, acesulfame, sucralose, allulose of natural origin, among others), since they have a significant role in desserts and soft drinks and in the case of adults as a substitute for sugar. Of particular interest is the use of sucralose (trichlorosucrose), which is labelled in our media as E995 because of its sweetening power (600 times higher than sucrose) and because it is not metabolizable and therefore caloric and superior to the previous ones when it comes to maintaining BMI [70] and as we will see below when dealing with soft drinks and juices. The effectiveness of these sweeteners in reducing BMI is unclear, and, because of their improbable long-term association with type 2 diabetes [71], their use in pediatric patients is probably not widespread; although they are approved by international and national health organizations (*Stevia* sweetener has been approved at the lower GRAS level), their long-term effects are not fully known. Their use, however, is understandable because the alternative would be the use of sugar, both caloric and containing fructose, which facilitates the progression of obesity and comorbidities. For all these reasons, more attention should be paid to changing eating behaviors and negative factors in the food environment, which is still obesogenic, as noted in Dr. Ayton's letter to the *BMJ* (05/08/ 2019), where she discusses the dramatic increase in ultra-processed food. From a qualitative point of view, diet should be balanced, avoiding the bias which is so typical of the variegated diets of obese adults.

Soft Drinks and Juices Perhaps the emerging concept of sugar-sweetened beverages or sugary drinks is justified as it includes soft drinks (mostly carbonated), fruit juices with added sugar, nectars, energy drinks, *horchata*, and sweetened coffees or teas. Diet drinks (if >40 kcal/250 ml), 100% natural fruit juices, flavored/chocolate milks, and naturally alcoholic beverages are not included in this concept [72]. Particular mention should be made of flavored milks with a reputed nutritional balance when in reality they often have a high sugar content. The consumption of sugary drinks according to data from the *National Center for Health Statistics* [73] of the US Department of Health based on several NHANES studies concludes that on a typical day, two thirds of children and adolescents consume at least one sugary drink and that this consumption increases with age and more so among men. But what is important is that the average consumption of sugary drinks is 164 kcal/day (120 in girls), which represents 7% of the total caloric intake (Table 9.1) and entails a risk of overweight and a lower efficacy in the treatment of obese children. With regard to the effects or risks of sugary drinks, they have been associated with obesity, metabolic syndrome, T2D, hypertension, and other comorbidities [75]. This is due, in addition to the energy intake, to the fact that the other monosaccharide—fructose—does not stimulate insulin secretion and is a fast substrate for lipid synthesis and a possible stimulus for the synthesis of products with an inflammatory profile. During childhood and adolescence, consumption of sugar-sweetened beverages is associated with obesity [76], and so the WHO strongly recommends [77] reducing sugar intake to 10% (or better 5%) of total energy intake (Table 9.1). However, it is not easy to reduce the consumption of sugar-sweetened beverages in the present social context; therefore the idea of education should be considered both at school and especially within the

Table 9.1 Energy requirements according to age and sex [74]

Guys/boys			Age (years)	Girls		
Weight (kg)	Energy requirements			Weight (kg)	Energy requirements	
	Kcal/day	Kcal/kg/day	Kcal/day		Kcal/kg/day	
11.4	948	82.4	1–2	10.8	865	80.1
13.5	1.129	83.6	2–3	13.0	1.047	80.6
15.7	1.252	79.7	3–4	15.1	1.156	76.5
17.7	1.360	76.8	4–5	16.8	1.241	73.9
19.7	1.467	74.5	5–6	18.6	1.330	71.5
21.7	1.573	72.5	6–7	20.6	1.428	69.3
24.0	1.692	70.5	7–8	23.3	1.554	66.7
26.7	1.830	68.5	8–9	26.6	1.698	63.8
29.7	1.978	66.6	9–10	30.5	1.854	60.8
33.3	2.150	64.6	10–11	34.7	2.006	57.8
37.5	2.341	62.4	11–12	39.2	2.149	54.8
42.3	2.548	60.2	12–13	43.8	2.276	52.0
47.8	2.770	57.9	13–14	48.3	2.379	49.3
53.8	2.990	55.6	14–15	52.1	2.449	47.0
59.5	3.178	53.4	15–16	55.0	2.491	45.3
64.4	3.322	51.6	16–17	56.4	2.503	44.4
67.8	3.410	50.3	17–18	56.7	2.503	44.1

family with the aim of substituting water for sugar-sweetened beverages; obviously any initiative in this direction is always positive because it is well founded scientifically [78, 79]. In Europe, some National Health Departments are providing growing insights into this problem. In Spain the National Health Survey (ENSE 17) made an overall assessment of the entire population in this regard which showed that the consumption of these drinks increases the higher the social class and is always higher among men. Once again, it is necessary to insist on nutritional education in the family and institutional environment that leads to an appreciation of the taste of non-sweetened beverages [80] (carbonated or non-carbonated water with lemon or lime, iced tea, etc.) which can also be prepared at home. We must also take into account that although they may have a high glycemic index, it is essential that the total sugar intake be “Slow Carbs” [81, 82]. However, we need stronger policy measures in this respect as we now know the taxation of sugar-sweetened beverages reduces their sales [83]. The modern nonnutritive sweeteners probably will increase their presence in soft drinks due to their lack of effect on glycemia and on appetite scores [84].

Within the current food scene, it is worth mentioning how food companies, and at the behest of the legislation of each country, are striving to improve and decrease the caloric density of certain foods, how labeling is increasingly informative, and how it would be desirable that, as mentioned above, the glycemic index and glyce-mic load appear. However, there has been a firm refusal almost since its launch to use the traffic light diet system in labeling: green, go ahead; orange, reduce; and red, stop. Unlike in the case of adults, in pediatrics the labeling of physical activity (walking time to burn the kcal of the product) is not useful because of the variety of exercise. The dietary recommendations are the same as those for prevention. Perhaps we should now add that the balanced and low-calorie diet should be in accordance with the economic status and accepted by the whole family; mealtimes should be regular; there should only be water on the table; smaller portions should be served; snacks and eating between meals should be avoided; and fresh fruit should replace snacks, as we have just seen. As we have already seen in Chap. 8 on Prevention, the importance of breakfast should also be considered in the dietary treatment. To the above we should add the study carried out on more than 300,000 children [85] where the first thing that is evident is that between 10 and 30% do not eat breakfast and precisely this population of morning fasters suffers from overweight or obesity in 90% of cases and also has a worse lipid profile, higher blood pressure, and higher levels of insulinemia. In those countries where breakfast contains a higher amount of fiber (oatmeal, 7 g/100 g), it produces a greater and longer lasting feeling of satiety than in those whose cereals are corn, which contains 0.1 g of fiber/100 g. In relation to satiation, and based on data from adults [86], they should continue eating until they state that they do not want more; this is a signal that should be respected. Eating quickly is another factor which should be discouraged. When both circumstances coincide, the association with overweight increases (OR 3.21). Although with a smaller sample size, this has also been shown in pediatrics [87]. It should be clear that dietary changes alone have little long-term effect. Nordic diet or Mediterranean diet (high polyphenols content) are both similar and correct, but irrelevant as regards obesity treatment and the same could be said for certain foods (watermelon, premeal almond) that will require pending appropriate studies.

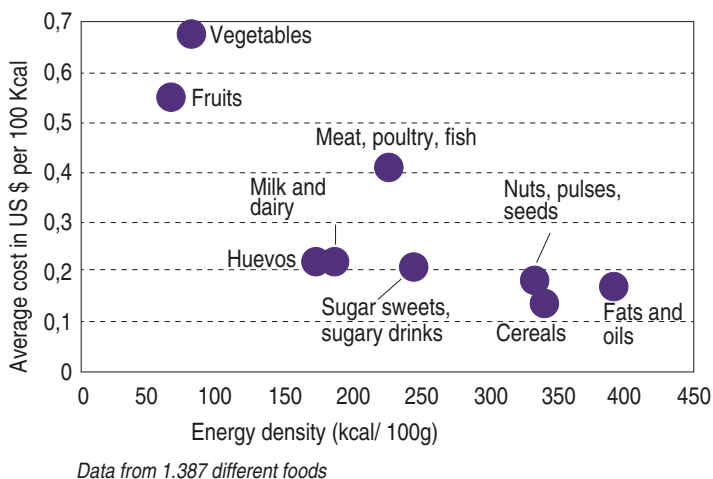


Fig. 9.1 Relationship between energy density (kcal/100 g) and its economic cost (\$/100 kcal) in nine most common food groups (Drennowski 2010) [89]

The aspects of nutritional recommendations are complex due to the variety and the large number of their origins and because other than the purely scientific interests are tempting even though they are sometimes based on pseudo-results; this should lead us to look for those supported by evidence. In this sense and by way of conclusion of this section, the treatment in adults, which is clearly applicable to the pediatric sphere [88], shows how the essential factor is the reduction of caloric intake and how the variation or exchange of macronutrients is irrelevant. The next complexity is given by the price of food [89], since at the present time, the most economical foods are those with the highest energy density (Fig. 9.1).

Physical Activity (PA)

It has come to play a greater role in the treatment of the obese individual and is currently based on less empirical grounds. Before going into the therapeutic actions themselves, everything set out in the chapter on Prevention (fundamentals, measures to implement PA, sleep, and inactivity) should be taken into account. The scientific and quantifiable bases provided by the FAO for human energy requirements [74] at various ages offer a baseline for considering increased physical exercise. Table 9.1 shows the energy requirements in order to have a reference for the PAL (*physical activity level*) on the understanding that it is applicable to adults in normal situation and activities. The problem is that of the half million adults surveyed, only 20% meet the minimum aerobic and muscle strengthening requirements [90]; and in the pediatric age group, in the previous CDC study [91], 61% do not participate in any physical activity outside school. This situation is generalizable to

pediatric populations in high-income countries and has motivated various governments and health agencies to promote a series of recommendations in a large part of these countries where the promotion of exercise is clear (NAOS, *Movimento Sport Organizzato*, *Trim and fit*, etc.) and always promoted in general prevention actions. Chapter 7 of the 2018 physical activity guidelines of the American Ministry of Health [92], which replace the previous ones of 2008, provides guidelines for children under 6 years old, for children older than that age, for adolescents, and for sedentary people with evidence-based data. These facilities should be promoted and taken full advantage of.

At the individual level, the family and especially the adolescent should be informed, making them aware that exercise, even in cases where it does not significantly reduce BMI, improves central and peripheral vascular adaptation in a highly positive way, such as the improvement of metabolic function of white and brown/beige adipose tissues [93], in addition to reducing comorbidities, one of which is high blood pressure. One should be aware that in a large genome-wide study (> 200,000 adults), the obesogenic effect of 11 genetic variants of the FTO gene is attenuated by 30% with PA [94], and this has also been demonstrated recently by the Taiwan Biobank in more than 18,000 participants. It should be explained to the family and the child that the response to exercise is not uniform for all living beings. Precision medicine [95] has identified the dependent variables with respect to the best cardiorespiratory fitness background, and these have been grouped into three components: ethnic, individual, and those attributed to random error. Despite advances in all three areas, there are still major limitations in attributing causality in this heterogeneous response. Furthermore, it should be explained that the effect of PA with respect to the reduction of BMI in children and adolescents [96] is moderate and that it alone would not be capable of achieving reductions that would lead to normal weight and, above all, that moderate daily activity (overcoming inactivity) can be even more effective than drastic gym sessions, but always assessing in each case the possibilities and preferences of the child and his or her environment. In this sense, and in the case of vigorous physical activity sessions, both the child and his family should be reminded that the energy drinks so often recommended in these circles and sometimes by monitors induce undesirable acute cardiovascular and metabolic changes, as the Pan-European case-cohort analysis has shown. Furthermore, exercise when combined with Liraglutide improves and maintains healthy weight loss in adults [97].

Finally, the child and his or her circle must be made aware that the “fat but healthy” subpopulation is a myth and that a pan-European study from the Imperial College (London) has clearly shown that this situation does not exist [98]. One of the most important problems is the child’s refractory attitude to exercise, but if he or she comes to accept it, they will maintain better weight control in the long term. Regular sports, games, swimming, cycling, etc. if accepted, have a more lasting effect than aerobics regulated from the beginning [99]. The bicycle can be a safe and acceptable means; in this sense it is worth considering the Danish experience in which inactive adults exchanged the suburban train for the bicycle, and where, after 6 months, they showed an improvement in insulin sensitivity, better

cardiorespiratory endurance, as well as a discreet decrease in intra-abdominal fat [100]. This does not imply that initially aerobics does not have a clear indication, as it can be done with some privacy and is well accepted especially by girls. Competitive and team sports are not the most suitable, since not performing well and changing in the locker room are additional reasons for quitting the activity.

The collaboration of the family in supporting the practice and allowing the child to choose a sport is essential, despite the effort involved [101]. Another aspect to be considered and accepted naturally is the greater fatigue of obese people when faced with a given physical exercise, since they probably expend twice as much energy as a thinner companion. It is necessary to dose physical activity in such a way that severely obese people (BMIr >180–200%) limit themselves to walking, swimming, and gentle static cycling, while the more moderately obese can do aerobics or programmed gymnastic exercises. However, as recognized since ancient times, flexibility and individualization should be maximized. In order to increase physical activity, the use of electronic monitors has proved moderately effective in adults [102]. The technique can be used in children and adolescents by means of accelerometers. In the case of scheduled physical exercises, the presence of a person acting as monitor is also positive. The cooperation of schools with regard to better designed and controlled physical education is effective in the treatment of obesity [103]. As with adherence to less energetic eating patterns in the obese, positive changes occur during the intervention, but after 1 year the differences with the control group are not very striking [104].

At the same time that these activities are programmed, it is necessary to establish an attitude against sedentary lifestyles. Children who are not sedentary are more interested in things, and their activity tends to be more progressive [74]. Perhaps the fact of watching television or a smart phone screen for long hours is the most criticized, not only because of the inactivity it implies but also because of the advertising that induces viewers to eat snacks almost always with a high content of refined sugars and fats. This reduction in sedentary time together with video games has already demonstrated favorable results [105]. The sedentary lifestyle should be replaced by a lifestyle in which any physical activity is adopted because it will help substantially: walking, cycling, using stairs, helping with household chores, etc., not only on a daily basis, such as going to school, but also during the weekend, for which the family should adopt this new lifestyle. The problem of increasing physical activity has not been solved satisfactorily or massively anywhere. The experience of the state of Texas [106], which has involved gathering information on the present situation, and which after its analysis proposed a series of resources for increasing physical activity outside the home and recommendations for screen time, may be a good model, and it will be interesting to see its results in the medium and long term. Quantitatively, PA is more effective than reducing sedentary lifestyles [107].

There are questionnaires to measure physical activity during leisure time through metabolic equivalences, which are laborious to calculate but which can more reliably estimate physical activity, as when this is reported by the obese person themselves, it tends to be overestimated [108]. Although it is known that prolonged sedentary time is associated, independently of physical activity, with cardiovascular

disease [109], and that the norms and recommendations against it have been known for more than a decade, their application to obese children is not widespread. The preventive precocity of PA is already evident when it is established in the pregnancy of the obese mother; the implementation of a comprehensive program, but with special dedication to her, has been associated with a significant reduction in adiposity in newborns [110].

The results of increased physical exercise should be known in order not to create false expectations. Results usually take several months to manifest themselves and require a minimum of 30 minutes three times a week. It is necessary to convince children to take school sports/fitness seriously; otherwise the scheduled hours are far removed from reality. It is also wrong to think that the exercise that an obese person can perform can counterbalance the caloric intake of a large portion of fast food (≈ 700 kcal), as this would require 2 h of vigorous exercise (elite). Finally, and in a positive sense, PA contributes to the stability of BMI after bariatric surgery.

Drug Treatment

This section was previously almost exclusively valid for the treatment of adult obesity; in some countries [111] regulations restricted drug treatment to adults with BMI > 27 kg/m², and there is still a certain reluctance to offer prescriptions even for adults. Presently the basis for pediatric pharmacotherapy are well established [112, 113]. This gives a base for treatment versus the care required in the prescription of the three groups of drugs that were initially used in non-syndromic obesity: appetite suppressants (noradrenergic), thermogenesis stimulants (adrenergic), and nutrient absorption inhibitors. This first pharmacological stage has been overcome, which does not mean that the present one offers more effective results, although it does have fewer side effects.

The indications for pharmacotherapy for obesity in adolescents have been reviewed by a group led by the *Boston Medical Center* [114], and this publication includes an extensive table with the drugs that have been used and those that may be used at present, which will be discussed below. But perhaps it is worth reflecting on the poor response to pediatric obesity, and in the face of which and the failure to change lifestyle, how swiftly bariatric surgery occurs, ignoring drugs that could be useful. Let us analyze initially the drugs in disuse, but not withdrawn in their totality and the reason for their contraindication.

Amphetamines and other adrenergics have been discouraged even for adults. The reduction of fat absorption by means of pancreatic lipase-colipase-dependent lipase binding drugs (orlistat) reducing the hydrolysis of fatty acids in the sn-1 (–3) position of triglyceride never had a firm indication in the treatment of pediatric obesity due to its malabsorptive component, and its later version (cetilistat) continues to have the same problems; therefore its use is not recommended. The combination of phentermine-topiramate (sympathomimetic amine and anticonvulsant) was not approved in EU due to side effects but has a renewed interest due to its modest weight-reducing action in adults, as well as in adolescents. With respect to noradrenergic drugs,

norepinephrine and serotonin reuptake inhibitors, by increasing their content in the synaptic space, produce a decrease in appetite and improve weight control. Sibutramine, which was the most widely used drug even in pediatric patients, has also been withdrawn from the European market due to significant cardiovascular damage. Within the group of drugs and/or products to avoid, dietary supplements and herbal preparations should be included, due to the lack of reliable studies and the risks of their use due to co-existing products such as alkaloids, ephedrine, etc. [115]. This sample of withdrawn drugs has been deliberately singled out because of their short life after the expectation generated by their launch and first data.

The drugs that can be used are varied and many are at an experimental stage. This is because, if we review the homeostatic circuits of food intake (see Chap. 4), the existence of potential agents investigated experimentally and in humans is enormous and theoretically ranges from neuropeptides modifying food intake (e.g., leptin analogues, neuropeptide Y antagonists, etc.) to agents that increase peripheral satiety (cholecystokinin receptor agonists, ghrelin inhibitors, etc.), to activators of thermogenesis ($\beta 3$ receptor agonists), or to the recent possibilities of acting on beige fat tissue. Basic research, for example, on human adipocyte cultures, despite the interesting effort that has been made, is not close to clinical use. The same can be said of new mechanisms to increase weight loss, such as methionine aminopeptidase 2 inhibitors, which would increase fat mobilization and oxidation [116], which require further studies on their efficacy and lack of risk. Dinitrophenol (DNP), despite being unfit for human use, continues to be sold through atypical channels with lures such as “burning dangerous belly fat”, and continues to cause deaths [117].

The nutritional evolution of Prader-Willi syndrome to hyperphagia is a good model for assessing the therapeutic action of various hormonal compounds such as tesofensine/metoprolol, but this requires careful and accurate evaluation. FDA [118], as well as the Australian government, have approved for adults: the already mentioned association of phentermine-topiramate, the agonist for the 5HT_{2C} receptor 2C (lorcaserin), naltrexone-bupropion, and GLP-1 receptor agonists (liraglutide). From this group of four, and for pediatric patients and with reservations, the following remains: lorcaserin, because its binding to the 2C receptor of the anorexigenic neurons (POMC) of the hypothalamus located in the brain increases satiety but also acts on the neurophysiological mechanisms that influence food intake, and which could operate even below the level of consciousness of the individual specifically on the rewarding sensation and impulsivity that food arouses [119], and which leads to its excessive consumption. At the present time, there are no data on its use in pediatrics, and therefore in children under 18 years of age, its use would be off-label. However, it could have a certain therapeutic value given that the cardiovascular complications of previous serotonergic drugs do not occur with lorcaserin, a fact verified in the CAMELIA-TIMI study [120] on 12,000 adults, with an average follow-up of 3.3 years and who presented an associated weight loss compared to the control group (OR 3.01). However, the European Medicines Agency [121] withdrew it from the market pending further research due to certain side effects, and the FDA recommended the manufacturer to withdraw the product voluntarily due to its added association with colorectal and pancreatic cancer. Pharmacological studies with lorcaserin have been initiated in patients aged 6–11 years and may still be ongoing (ClinicalTrials.gov identifier: NCT 02398669). This is consistent with the

robust review of available drugs and their side effects by *Apovian* and *The Endocrine Society* [122]. A thorough meta-analysis (certainty of evidence) has clarified the pharmacotherapeutic panorama [123] in favor of the use of phentermine-topiramate and receptor agonists (GLP-1) for the obese adult, but with an application in pediatrics. The pharmacotherapy for children and adolescents present developments show clearly which of them are in the safe and efficient side [112, 113, 124] where the glucagon-like peptide-1 (GLP-1) and the glucose-dependent insulinotropic peptide (GIP) have the greatest relevance. But also information on the adverse effects of these drugs [125] is equally valuable. Pharmacogenomics has reached a new step for obesity and T2D preventive issues [126]: the genomic wide pharmacogenomic study of GLP-1 receptor has found genetic variants at determined loci that alter the the glycemic response, therefore individuals with these variants might benefit from early GLP-1 receptor agonists administration.

Metformin It is one of the drugs that can be used in the treatment of childhood obesity given that in addition to being a first-line drug for type 2 diabetes, it has a moderate weight-reducing action due to hypothalamic modulation of appetite [127] but without forgetting the vitamin B12 deficiency that appears after prolonged use or by described contamination with nitrosamines. Metformin has been and is widely used for its weight-reducing action and protection against further development of type 2 diabetes. However, its administration to children without high insulin levels and no familial risk of type 2 diabetes does not seem justified, although if adipocyte targeted [128], it has been effective in obese mice. The initial and primary indication is T2D given its ability to decrease postprandial and basal hyperglycemia by slowing hepatic production and stimulating peripheral glucose utilization. In pediatric patients, a dose of 500 mg twice daily is usually the starting guideline (it can be increased up to 2500 mg) and gives good results. The liquid form is not available in all countries. The same could not be said regarding its BMI-reducing effect when was evaluated in a systematic review [129]. A logical consequence is great caution regarding its use, as seen at the beginning of this chapter in favor of lifestyle change [3]. Until there is stronger evidence, the use of metformin should be restricted to pediatric patients with T2DM while exploring the possible mechanisms by which weight reduction is mediated [130, 131]. This is what the present scientific basis suggests, but clinical reality sometimes follows other paths: in a study of medications used in 150 obese children seen in different medical centers in the UK, 59% received orlistat, 47% metformin, and 5% both [132].

Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs) They constitute a group of drugs obtained by recombinant DNA technology from the human peptide in *Saccharomyces cerevisiae* cells and have a proven response in the treatment of comorbidities and adult obesity itself. Their mechanism of action is based on (1) increased insulin secretion by pancreatic beta cells; (2) inhibition of glucagon release by alpha cells; (3) delayed gastric emptying and consequent decrease in food intake; and (4) activation of satiation circuits in the central nervous system (see Chap. 4, *Pathogenesis*). The first FDA-approved drug was liraglutide in 2014 for adults and in 2019 for children with T2D. Subcutaneous liraglutide combined with exercise programs continues to provide good results in adult weight reduction and also contrib-

utes to less weight gain in patients after bariatric surgery. Within this growing group, liraglutide (Victoza) was followed almost immediately by semaglutide in its parenteral form, pre-filled syringe for subcutaneous use with 1 mg (Ozempic) or 2.4 mg (Wegovy), and above all by the oral route (Rybelsus tablets of 7 and 14 mg). In some European countries, only the parenteral form is currently registered for weekly administration, but pediatric prescribing is off-label. The therapeutic results of semaglutide (sometimes added of tirzepatide, glucose-dependent insulinotropic polypeptide GIP) in reducing BMI were soon reported in adults. After the approval of semaglutide for the management of T2D in adults, the Food and Drug Administration similarly approved on 4 June 2021 its use for chronic weight management through 2.4 mg subcutaneously weekly. The efficacy and safety emerged from the double-blind, randomized, placebo-controlled, and recent four STEP studies [133, 134] on almost 5000 adults with BMI > 30 kg/m² and subject to strict dietary and physical activity guidelines. After 68 weeks of treatment, the weight reduction was 15–16% (depending on the dose administered) compared to 2% in the placebo group. There were no significant side effects. The use of this type of agonists, especially the oral form (semaglutide), could open a field of application even in pediatrics. In this way, data in adolescents with liraglutide (3 mg/day) showed a BMI reduction of 26% vs 8% placebo with respect to the initial data [135], but these results still do not have the strength they have shown in obese adults. New trials combining liraglutide and exercise increased weight loss in adults. The weekly administration and BMI-reducing effect of GLP-1 receptor agonists, despite their discrete digestive side effects, have led to renewed consideration of semaglutide for obese pediatric patients with type 2 diabetes, according to initial data from the *Ellipse Trial Investigators*. A recent meta-analysis of six studies on glucagon-like peptide-1 receptor agonists showed their safety and efficacy in obese children and adolescents [136]. In adults, semaglutide 2.0 mg (vs 1 mg) once weekly has exerted better control of Hb A1c, greater weight loss, and consequently reduced visceral adipose tissue, with a similar safety profile. As RCT progresses even in different ethnicities [137], in STEP 8 [138] in adults under regular therapy, the use of subcutaneous semaglutide resulted in significantly greater weight loss after more than 1 year of treatment. Presently a large amount of adult 2 studies favor the use of semaglutide. Fortunately the STEP TEEN rigorous study [139] on adolescents receiving subcutaneously up to 2.4 mg of semaglutide has shown a higher weight reduction than the placebo group. At the end of 2022 FDA approved semaglutide for obese adolescents.

Glucagon-like peptide-1 receptor agonists are a new group of drugs presently allowing a more efficient treatment for adult (and pediatric) obesity with lesser collateral damages [140], reducing the appearance of long-term cardiovascular disease, stroke, and mortality linked to obesity (beyond pediatrics) and are also effective in maintaining weight loss in adolescents after treatment (i.e., bariatric surgery). New associations or combinations such as tirzepatide are justified. In the case of GLP-1 with GIP, glucose -dependent insulinotropic polypeptide is an incretin hormone component favoring the physiological insulin stimulation in response to higher glucose levels. It also has a coherent glucagon action [141]. Tirzepatide is a novel engineered injectable peptide from the native GIP sequence with agonist activity at both the GIP and GLP-1 receptors, its use in obese adults provided important weight

reductions in body weight [142], for the moment there is no experience in adolescents. The combination with SGLT2 inhibitors also known as gliflozins is reasonable not only for obesity cardiometabolic risk reduction but also for decreasing the level of adiposity. A new therapeutical possibility is the effect of intranasal insulin for modifying appetite [143]. Drug treatment of comorbid conditions is discussed in Chap. 6. Among this vast panorama of offers we cannot overlook the efficacy the melanocortin-4 receptor agonists (setmelanotide) in the treatment of Bardett-Biedl syndrome and other monogenic obesities [144].

Other therapeutic aspects in pediatric patients that should not be overlooked because of the emotional impact they can have are stretch marks due to distension of the dermis. The prevention of *striae rubrae* does not have a specific topical application; only creams with collagen and elastin hydrolysates and others containing allantoin and hyaluronic acid, common components of anti-stretch mark creams used profusely in pregnant women, have shown level 2 evidence. On the other hand, the treatment of submental fat by injecting cytolytics, such as deoxycholic acid, would not be justified. On the other hand, vitamin D supplementation or intranasal oxytocin, oral butyrate or changes in the microbiota and intestinal barrier function and their relationship with pancreatic beta-cell apoptosis require further study before they can be considered as effective treatments for obesity [145]. A different advance in the treatment of non-alcoholic steatohepatitis is the use of obeticholic acid, accepted by the FDA for the treatment of accompanying fibrosis also in addition to gliflozins, and the same could be said of the treatment of larval hypothyreosis coexisting with steatohepatitis, either by the usual route or by the use of resmetirom (agonist of the hepatic receptor for T4) with effective results in adults. In the same situation is leptin deficiency with or without lipodystrophy by means of the human leptin analogue (metreleptin). New drugs with new therapeutic aims such as the direct action on the hypothalamus by tesofensine [146] or the long-acting amylin analogue [147], with data in obese adults, may offer good options for the future.

Finally, there are other drugs that are recommended in the treatment of obesity, many of them with a theoretical approach and in the experimental phase, as might be the case of the administration of conjugated linoleic acid (CLA). Hypothetically based on its anti-adipocytic character that does not reduce weight, results in humans have not justified its use. The same could be said of long-chain n-3 polyunsaturated fatty acids [148] or in similar way the replacement of a food with almonds for their satiating effect [149]. Apart from these futuristic lines, we can consider the use of mineralocorticoid antagonists as stimulants of brown adipose tissue or the pediatric use of the aforementioned sodium glucose cotransporter 2 (SGLT 2) inhibitors, fundamentally indicated for T2D and more widespread due to the coexistence of T2D or taurocholate use in mice for its postprandial bile acid elevating action [150]. Something similar occurs with low levels of 25-hydroxycholecalciferol. Obviously they are not desirable especially if they are related to restrictive diets, and it is questionable whether their plasma normalization results in weight loss [145]. The use of carbohydrate digestive enzyme inhibitors such as alpha-glucosidase inhibitors (acarbose sometimes added to orlistat) has the limitation of side effects on the intestine. Some food medications, such as drinks with esters of ketone bodies, or supplements with inulin-type fructans, or β -glucans or so-called active phytochemicals of natural origin (*chamomilla* or *coffea* species), or avocado-derived avocatin that

would improve insulin resistance, all require more testing before being used in pediatrics. One more step in the pseudoscientific path consists of the miracle drugs (slimming plants, algae, elixirs, etc.) that with carefully researched marketing take advantage of the difficulty of treating obesity. The study carried out by the Institute of Preventive Medicine in Lausanne, Switzerland, concludes that with terms such as “natural”, “scientific” or similar [151] they offer false and unattainable promises of weight loss.

Bariatric Surgery (BS)

Compared to the 2003 guidelines for pediatric bariatric surgery from the *European Chapter ACN* meeting in Göttingen, one can safely say that these have been considerably refined, not only by the laparoscopic procedures but also by their positive results, all due to the extensive experience gained with adult surgery. This refinement is based on the increasing number of interventions performed, which is estimated to have more than tripled globally so far this century; the standardization of procedures—vertical sleeve gastrectomy, Roux-en-Y gastric *bypass* (RYGB), and adjustable gastric banding—with precise indications according to the patient and his associated pathology; the great safety of the procedure, 0.3% mortality rate in the following 30 days; the efficacy of the results, especially in T2D, weight loss, depressive behavior, etc.; and, as far as we are concerned, the lowering of the age of intervention, which now includes adolescence, with an increasing number of interventions and a mortality rate of 0%, which is to be expected in adolescents [152]. It is appropriate to return to the efficacy in adults, as surgery has been more effective than intensive medical treatment [153] and as 12 years after the intervention (RYGB) weight loss is maintained with practical normalization of T2D, hypertension, and dyslipidemia [154]. A large cohort (7000) analyzed two years ago showed that all-cause mortality and especially adverse outcomes of diabetes and cardiovascular and renal complications after 4.5 years of follow-up are lower than in obese people treated by purely medical means. A larger cohort (21,837) matched (1:1) with conventional treatment with a follow-up of 13.2 years (median) the mortality was significantly lower (16%) in the bariatric group and mortality after surgery decreased significantly in the cases of patients with CVD, cancer and diabetes, although the rate of suicide was slight higher in the bariatric group. These values support the surgical treatment [155]. As regards the risk of suicide the same can be said in a similar study carried out in Sweden [156]. Other minor advantages, but advantages nonetheless, are that alcohol consumption, as measured by phosphatidylethanol levels, decreases after the intervention or the disappearance of joint pain and improvement in motor function when the load is reduced, and this also occurs in adolescents. Its use has been increasing due to new indications such as idiopathic intracranial hypertension [157]. There is no doubt that there are complications, and perhaps those of the depressive type are less well known [158]. Monitoring of hemoglobin levels after RYGB is desirable because of the increased frequency of anemia. After the recent, positive results (life expectancy versus usual management) in a systematic review of 175,000 bariatrically treated adults [159] together with other similar

results, the term “metabolic surgery” has appeared because in addition to weight reduction, the procedure is capable of modifying positively the hormonal profile of the patient.

Surgery continues to advance in the field of adult obesity. Thus, aspiration therapy through a gastrostomy performed endoscopically allows the removal of 30% of what is ingested with acceptable results after 4 years. The success and safety of bariatric surgery (RYGB or SG) have led to its consideration as one of the primary treatments of non-alcoholic fatty liver disease and fibrosis [160]. Endoscopic bariatric surgery for intragastric volume reduction is also a reality and has its indications. In another field and in a highly experimental phase, the freezing of the posterior vagal trunk that conducts hunger signals to the diencephalon could be another therapeutic approach.

Bariatric Surgery in Adolescents

Specifically in the adolescent, the indication for BS is based on the fact that typical medical interventions (nutritional, physical activity, and perhaps pharmacological) have limited success and a high emotional cost, hence the increasing number of surgical interventions. But, as the adolescent is by no means a young adult, the eligibility criteria are stricter than in the adult. There is a multiplicity of criteria, but after analysis of those proposed by Pratt [161] and the *Canadian Institute for Health Information*, they can be systematized as follows:

- Severe obesity assessed by any of the methods: BMI-Zs > 3.5 SD, BMIr >140%, BMI > 40 kg/m².
- Existence of comorbid conditions.
- Full physical maturation (bone age).
- Lack of response to conventional treatment.
- Assessment of adherence to the therapeutic program by both the adolescent and the family; this point is difficult to assess, but is decisive.
- Pre- and post-surgical experience of the care team.

These criteria have been updated by the American Society for Metabolic and Bariatric Surgery [162]. The age limit has been reduced (now 12 years) and also the BMI value (now 35–40 kg/m²) not only for normal weight but also to avoid organ alteration and because of the difficulty of reducing high- and long-term BMI. In favor of this idea is the recent finding [163] that BS implies a decreased risk of incident cancer and cancer mortality in adults with long-standing obesity.

BS for adolescents began in 1970 and has always enjoyed a favorable attitude among surgeons, which has led to an increase in its use, estimated at 2.4 adolescents/100,000 [164], although it is difficult to know the exact number of operations.

At this point, it is necessary to discuss the results, following a manual, non-systematic review of 15 studies, of which only 9 contained information that could be assessed (Table 9.2 [165–167, 169–174]). The review can be summarized as follows: the sample size was 1336 adolescents undergoing surgery with criteria similar to those mentioned above, all above the age of 16, initial BMI between 46

Table 9.2 Outcomes after bariatric surgery in adolescents

Author [ref.] Year, country	Type of study No. of cases	Criterion CB	Intervention type	Evolution (time) results
Sachdev [165] 2014, UK	Prospective	BMI 62 kg/m ² Medical treatment failure Comorbidities	BGRY Gastr band	2 years BMI -16%
Inge [166] 2015, US	Prospective 242	BMI 53 kg/m ² Medical treatment failure Comorbidities	BGRY Gastr band	3 years BMI -26% Comorbidity better
Goldschmidt [167] 2017, US	Prospective 234	BMI > 50 kg/m ² Medical treatment failure Craving for food	BGRY Gastr band	4 years Eating craving: 6 months null 4 years = initial
Dewberry [168] 2017, US	Prospective	BMI 58 kg/m ² Medical treatment failure Comorbidities	BGRY	5 years BMI -29% Comorbidity better Anemia, hyper PTH
White [169] 2017, UK	Prospective 50	53.1 kg/m ² (53.1 kg/ m ²) Medical treatment failure	Gastr band BGRY	1 year BMI -26% C lost 27% C lost 27
Herget [170] 2014, Germany	Systematic rev. 400	46–64 kg/m ² (46–64 kg/m ²) Mental health	BGRY, LAGB Gastr band	6 months–2 years Depression better
Ryder [171] 2017, US	Comparative group 50, 30	59 kg/m ²	BGRY	5 years IMC -40% (+10% GC)
Ryder [172] 2016, US	Prospective 242	51.2 kg/m ² Physical resistance Cardiovascular func.	BGRY Gastr band	6–12 months Significant improvement
Jaramillo [173] 2017, US	Prospective	46.7 kg/m ² (46.7 kg/ m ²) Medical treatment failure Comorbidities	LAGB LGB	1 year BMI -47% HGNA 100% resolution

BGRY Roux-en-Y gastric bypass, *LAGB* laparoscopic adjustable gastric banding, *LGB* laparoscopic gastric banding, *UK* United Kingdom, *US* United States, *NAFLD* non-alcoholic fatty liver disease, *Gastr band* banded gastrectomy, *NAFLD* non-alcoholic fatty liver disease, *LAGB* laparoscopic adjustable gastric banding

and 64 kg/m², with a presence of comorbidities and failure of medical treatment, and only one study involved drug treatment. Roux-en-Y gastric bypass (RYGB) was performed in 54% of the cases, and the remaining cases were included in smaller groups of sleeve gastrectomy, laparoscopic adjustable gastric banding, and other unnamed techniques. The follow-up of the patients has been between 6 months and more than 5 years and showed a reduction of the BMI between 14 and 16%. It should be noted that in the study with a comparative group (# control) after 5 years of follow-up, the BMI in this group increased by 10%. Within the comorbidities and in the studies in which these were evaluated, improvement or even remission occurred in cases of non-alcoholic fatty liver disease and in cases of T2D, although less effective in cases of dyslipidemia and hypertension. From the mental health point of view, it was only evaluated in two studies and was highly favorable in depressive disorders, but not in the case of anxiety disorders. The loss of control over food intake, either in large quantities or continuously, improved at first, but from year 2 to year 5 of follow-up, it decreased, which was associated with a worse evolution of BMI. Mental problems in obese adolescents are more difficult to solve with BS than metabolic problems.

Systematic reviews are difficult, for example, the analysis carried out by the pediatric surgical services of the *Massachusetts General Hospital* [175] on 14,178 bariatric interventions performed over 9 years only deals with the variation in surgical techniques over that period. The Sweden study carried out in three hospitals on 450 severe obese adolescents, after two years of follow-up, points out how the bariatric group achieved a greater BMI reduction of -12.4^{kg/m²} than that of the non-surgical control group, plus negligible adverse events [176]. And finally, in a systematic review and meta-analysis on adolescents and young adults at *Imperial College London*, out of 16,372 studies identified, only 83 could be selected [177], which makes it clear that more and better designed studies are required for the investigation of this therapeutic procedure in childhood and adolescence [178]. The fact that a greater number of adolescents have undergone surgery has made it possible to assess the results, many of which are positive, such as the reduction in BMI or regression of cardiovascular risk factors [179], but also the need to be vigilant and support weight loss after the intervention, as this predicts better results after 2 years [180, 181]. Finally, we should bear in mind that the metabolic adaptation of adolescents after the intervention predisposes them to regain weight [182] and that other negative effects have also appeared when this intervention is carried out in adolescents. Thus despite the improvement in BMI, gastrointestinal complications such as gastroesophageal reflux [168] or alterations in bone metabolism sometimes develop [183].

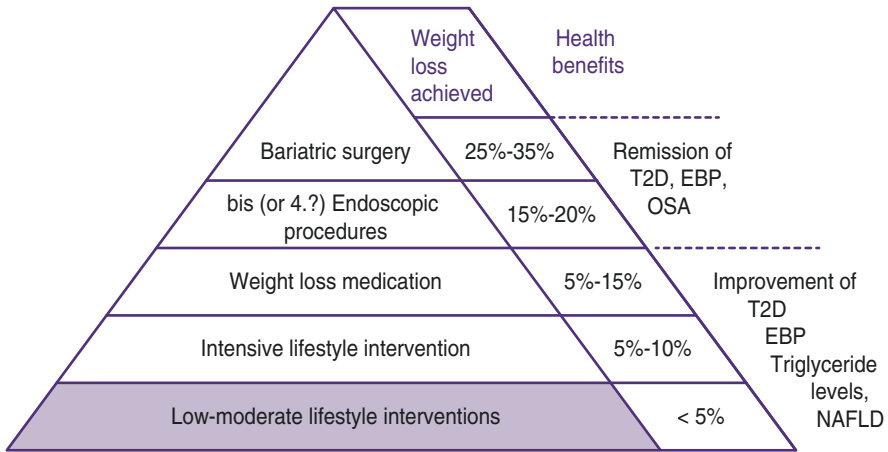
Despite the presented efficacy of BS, we must not overlook the fact that the studies are short; only two of them went beyond 5 years, and complications (decreased ferritin and discrete hyperparathyroidism) already appeared and were labelled as minor. More recently and in the regular follow-up up to 5 years after the intervention at Cincinnati Children's Hospital, it was concluded that nutritional deficiencies only led to a decrease in ferritin (71% of those operated on) and to a lesser degree a reduction in vitamin B12 levels [184], which provides greater safety for this procedure. Therefore, considering the young age of our patients, a greater number of

controlled studies with longer duration are required before establishing a more liberal recommendation. In this sense, the recent update by the *American Academy of Pediatrics* [185] refines the indications and results and analyzes new factors such as eligibility in light of the social context of the child and the existing barriers due to insurance coverage and, above all, the large increase in the number of interventions implying inhomogeneous eligibility.

Final Considerations

As a final reflection of this chapter, it can be said that the treatment of obesity is a consequence of a failure or absence of prevention programs and involves entering a long and complex path. Some time ago [186], we already pointed out the need for a multidisciplinary team to have a minimum of success, but progressively our criteria [187, 188] have become more flexible and individualized in light of the significant increase in pediatric obesity prevalence, and it is now worth reflecting on how this more simplified team can and should facilitate medical treatment effectively with only the physician and preferably an expert nurse and perhaps a health visitor, a figure that is now beginning to become generalized. The enhancement of the same with dietitians, psychiatrists, etc. is desirable, but in no way should it be a justification for not attending to these patients. Training in this sense of primary care medical actors would provide better care coverage in the case of obesity [189]. Also and for severe obese adolescents it is advisable to consider bariatric surgery not only for the positive results just analyzed, but for the newer aspects such as the reduction of choline compounds in the brain that have a neuroinflammatory activity, or the higher self-worth gained after surgery [190].

One of the most laborious tasks is to try to maintain the achieved reduction in BMI, and for this it is necessary to maintain direct and accessible contact [191], which requires a good primary structure as once again demonstrated by the care of the obese adult [192] and in more detail is also collected in the USPSTF 2018 [193]. In the latter, therapeutic aspects appear that primary care frequently cannot provide, such as behavioral reinforcement [194, 195]. Although its clinical application is not immediate, there is a highly promising study carried out [196] on the epigenetic changes that occur after BS, which would expand the age indications for the problem of pediatric obesity. In this regard, and as a summary of the treatment of obesity, the *Mayo Clinic* Editorial [197] on weight loss in adults according to the therapeutic procedure used could not be more illustrative, as shown in Fig. 9.2. The valuable review [198] of 20,925 articles published between 1991 and 2018 on the clinical consequences of overweight and obesity in the general population shows extremely varied results, but two consequences are evident: the first is the progressive increase of family-based interventions, and the second, already mentioned in the chapter on Prevention, refers to the poor coverage that the problem of overweight and obesity has in low- or middle-income countries. This will lead to worse outcomes once comorbidities make their appearance, because the study of *omics* (genomics,



T2D: T2D type 2 diabetes; EBP: Elevated blood pressure; OSA: Obstructive sleep apnea; NAFLD: Nonalcoholic fatty liver disease.

Fig. 9.2 Weight loss interventions, weight reduction achieved, and health benefits. Intensive lifestyle interventions are defined as more than 14 visits in a 6-month period with trained staff. Weight loss medications are FDA-approved preparations (phentermine, topiramate, naltrexone-bupropion, lorcaserin, liraglutide). Endoscopic procedures include banded gastroplasty. Bariatric surgery includes Roux-en-Y gastric bypass and banded gastrectomy. (Adapted from ref. 197)

proteomics, metabolomics, and microbiomics) will be present in these countries in a much diminished form, leading to worse outcomes [199]. This negative environment as well as food insecurity [200] also appears in high-income countries when looking at the 30.3 million children in underserved communities [201, 202]. In this final consideration, it is necessary to look at the small positive aspects that have already appeared such as the efficacy of the new derivatives of GLP-1 receptor agonists that approximate the efficacy of bariatric surgery [203]; and perhaps in the not so long term, the CRISPR will be capable of increasing the browning of the human adipocyte [204]. Despite all these circumstances, the obese child should be given all possible support, in the full knowledge that his or her limited resources will produce a reduced positive association, but that their attitude [205, 206] will always bear some clinical relevance, besides the beneficial cost-effectiveness of preventive interventions in children [207].

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Chapter 10

Pediatric Obesity: Where Do We Stand Now?



The situation is complex and far from favorable: the number of obese children and adolescents continues to increase globally, except in certain communities in high-income countries; there is an ineffective preventive effect of current programs and to a lesser extent of therapeutic ones; and there is a social reaction to obesity in general that leads to the stigmatization of those who suffer from it. It should not be forgotten how in our present society the idea still persists that obesity has negative personal connotations (gluttony, laziness) and that weight loss can be achieved quickly by eating less and moving more, which is neither easy nor quick, and possibly, this is the basis of the stigma. In addition, there is a counteraction of a fraction of obese individuals, those known by the unpronounceable term of irredeemably obese, whose motto is that life does not begin only when you lose weight and that in the case of obese parents of children with high weight, it is a preventive and therapeutic brake often not taken into account.

On the positive side, there has been an increase in knowledge about the disease of obesity and the progressive awareness of obesity as a non-communicable disease and undoubtedly a more effective therapy with fewer side effects. The other positive aspect is the accessibility of information from different parts of the world and being able to analyze how local factors and characteristics can lead to different results.

Socioeconomic Aspects in Relation to the Development of Pediatric Obesity

Indiscriminate economic growth [1] reasonably driven by governments over the past century has provided undoubted benefits, but also to a lesser degree some negative consequences such as, among others, a global increase in overweight and obesity even in low- and middle-income countries where they coexist with undernutrition. The emergence of more negative clinical and social aspects has rested on an almost

absent, if not confused response of health systems [2] to the acquisitive and lifestyle change that has taken place at the individual level. Thus, in adolescents, we can see how the 12 primary indicators of health and well-being analyzed in 195 countries clearly demonstrate this fact [3], and among them inequality is manifest, as a paradigm, the low levels of education and its relationship with high weight [4]. Another negative factor that should be reversed is the lack of reliable information about the long-term effects of nutritional deviations, in this case due to excess, which are real after the just mentioned study in 195 countries around the world on the increase in mortality and years of life with disability [5]. For these negative issues, perhaps some facts have not received the merited attention: the multimorbidity of 21 diseases grouped as cardiometabolic, digestive, respiratory, musculoskeletal, and infectious is associated with obesity with a hazard ratio ≥ 1.50 when compared to adults of normal weight [6, 7]. This high cut-off (1.50) has excluded well-known associated conditions such as colorectal cancer from the list. This burden of non-communicable diseases to which obesity is so closely related occurs also in adolescents [7–140] when years lived with disability (YLD) and disability-adjusted life-years (DALYs) are evaluated. Not to mention the changes in life expectancy [7, 9–141] considered in Chap. 7. The possible charitable spirit or little time with the patient should disappear in the face of the forcefulness of this data, as the Illinois Ethics Center for the past decade has been claiming. It should not be forgotten that in a general health system, if poverty decreases, so will obesity.

The ten most obese countries according to the WHO are led by American Samoa followed by Nauru, Cook Islands, Tokelau, Tonga, Samoa, Palau, Kiribati, Marshall Islands, and Kuwait. All of them, except Kuwait, are located in the South Pacific. However, if we consider the ten most obese countries in the world according to the OECD, which includes 35 countries with highly developed economies and better anthropometric assessment, the list is somewhat different (% of obese adults): United States (38.2%), Mexico (32.4%), New Zealand (30.7%), Hungary (30.0%), Australia (27.9%), United Kingdom (26.9%), Canada (25.8%), Chile (25.1%), Finland (24.8%), and Germany (23.6%). This recent assessment (<https://www.valnewalk.com/2019/01/top-10-most-obese-countries-oecd-who>) is sufficiently explicit on the globalization of the problem, and, in the case of Spain, it is close to forming part of this undesirable list. Unfortunately and with recent data, it seems that prevalence in some countries of obesity is growing at the expense of the upshifting of overweight [6].

Some situations illustrate the impact of these nonmedical aspects: the lack of parental training brings with it the family anchoring of factors in addition of food insecurity favoring weight gain [8]. Social discrimination, children under 9 years of age discriminate negatively against their overweight peers. This fact together with the socioeconomic and environmental poor circumstances determine a trend to violent crime [9] without there being a mechanism to prevent it. Surprisingly, this discrimination has also been detected in some pediatric medical services [10] although this is generally not publicized unless it borders on ethical limits [11, 12] such as the situation of a barrier to renal transplants for obese adults with advanced renal disease. Almost quaint, but discriminative after all, is the case of the Irish

adoption organization (Tusla) which rejects obese adopters. Even by law, members of the UK parliament have called for an end to the use of BMI as a marker of health due to the stigma risk [13]; this (vain) attempt would cover more the dimension of obesity.

The role of the media must be taken into account because of its potential (mis)informative capacity, when it can also influence a vulnerable population such as children. For example, in a TV program in the United States, it is stated that food is toxic and that it is necessary to detoxify every 3 days, that genetically modified food is the present antichrist, or that an egg is as harmful as smoking five cigarettes. The promotion in these programs of quality food and in adequate quantity is less attractive and, therefore, not often considered. To this we must add that not only *influencers* [14] but also *snack* advertisers themselves create ads (e.g., for a 50–70 kcal chocolate bar) which, if ingested daily, can lead to overweight (or how watching TV and eating the aforementioned *snacks* increase the risk of metabolic syndrome in adolescents) [15] which are produced without the slightest hindrance. For example, the broadcasting situation and the ethics of the advertisement itself in this country are evaluated as a whole, and the greatest advertising burden is placed on foods of poorer nutritional quality [16], but no action has followed this information. This is especially important in the current context of the ease with which food is purchased even by the child himself/herself. The increasing possession and use of mobile phones have an entertainment character, especially for young people, and lead to a certain decrease in physical activity. Thus, in a study published by the *American College of Cardiology* [17], it is pointed out that its use for more than 5 hours a day implies an increase in the risk of obesity of more than 40%. It is not the case here to analyze the effectiveness of the *social-influencers* but to learn from the use that the food industry makes of them, as recently pointed out by the *Catalyst* section of the *New England Journal of Medicine*. The situation is exacerbated by lectures or presentations by industry-sponsored speakers [18], and especially harmful is the advertising of infant supplements or ultra-processed food to the public [19].

A different matter is the so-called false or fraudulent science (with respect to obesity the latest published finding has been that of Healing Meditation) and the damage it does to the real thing, especially when it has a semblance of plausibility; hence it is important to identify and confine it. So-called predatory journals pose a global threat in terms of articles accepted for publication, and it is difficult to solve this problem as we shall see below. The initiative of the Russian Academy of Sciences through its Dissernet network to withdraw 800 articles published in 1500 Russian journals is good news, and although it is an established practice in our media, it should be more widespread. Spin is defined as a specific way of reporting, whether intentional or not, to highlight some beneficial effect of rapid weight loss. This is a recent practice in some abstracts and systematic reviews dealing with obesity [20]. The second life of retracted papers can be a problem for research [142]. At the present time, the role of the institutions where research is carried out is crucial to protect its integrity, as the National Center for Professional and Research Ethics (University of Illinois) for the past decade has been claiming [22].

Medical Aspects

Among them, the following positive facts can be considered.

Increasing Awareness of Obesity

The amount of general scientific literature, and therefore of obesity, would be dissuasive here from any analysis, however brief, especially if we take into account the studies on the growth of science initiated last century by Derek de Solla Price [23] (Price's Law), where it was proven that from the seventeenth century to the present, it has followed not only an exponential pattern but also another crucial fact which is that of a limited survival due to the proven half-life of the published articles. Therefore, we will mention only some of the studies with a reasonable future.

Genetics Mendelian randomization (Gray and Wheatley, 1986) deserves a brief comment. It is a method that, based on natural genetic variation, allows testing or estimating the amount of causal effect on a disease, which brings with it the elimination of confounding variables that would act on proximate subjects exposed to them. It is a powerful method provided it is used appropriately. This is possible after the analysis of a series of data obtained in observational studies and among which there are confounding factors, constituting a necessary step to obtain the correct randomized studies. It is a complex technique [24] due to its design (identification of key assumptions); its application to two large masses, although smaller than those used in genome-wide association studies (> 50,000); and the use of genetic variants that may be unique for a single risk factor (e.g., PCSK9 gene variant and elevated LDL cholesterol), but the study of a single variant explains a small proportion of the variation in the phenotype (coronary heart disease). For this reason, the use of multiple genetic variants has become widespread, since collectively they better explain the variation (disease or trait) in the phenotype, as is the case with the use of single nucleotide polymorphisms (SNPs), which are the most common form of DNA variation in humans. The study of Mendelian randomization requires extensive and sophisticated statistical techniques. For example, if from the various SNPs associated with the development of obesity a selection is made of the 8–10 with the greatest predictive or associative strength, it is possible to evaluate those that may or may not be confounding factors, such as microbiota, higher weight during gestation, and a whole series of circumstances that are sometimes strongly defended in certain publications. Mendelian randomization has begun to yield results, as in the case of heritable genetic variations related to ATP citrate lyase and reduced LDL cholesterol synthesis [24]. This new approach does not reduce the value of others that are also genetically based and have provided clinical benefits, such as extended exome sequencing (WES) studies for prenatal diagnosis [25]. Congenital heart diseases will require further studies before relating them to maternal BMI, smoking or alcohol habits [143].

Within this transference of basic studies, we must consider the advances already mentioned (Chap. 3) that have provided epigenetic studies, where the presence of certain events in early stages of life and through DNA methylation can be associated with the subsequent development of pediatric obesity, being of special interest the presentation of the associative picture of high or low methylation with high or low BMI, which present and should continue to be researched [27–29]. The experience from the estimations of genetic risk for obesity in a general adult population (polygenic scores) could be applied to a pediatric population [144], allowing tighter prevention attitudes in face of the early environmental causalities. Finally, the possibility of DNA repair using the CRISPR technique [30] is a reality for certain monogenic diseases [31] and can even be applied to the DNA of germ cells [32] and achieve an embryo free of the defect, although this has sparked a movement against it that has led the WHO to create a working group on the subject [33]. Although studies on the human genome have been reduced in cost from 3,000 million dollars for the first genome to less than 1,000 dollars for the current sequencing, it is still a complex technique that requires extensive genetic, bioinformatics, and organizational resources of the clinical units, as well as adequate information to the patients themselves and their families. Although these techniques have been commercialized in some countries, the exclusive circuit between laboratory and patient is not recommended [34, 35]. Thus, to get a good comparative basis requires the sequencing of the genome of one million people (in the United States) or 5 million according to the British project to be developed in 5 years [36]. The diagnostic possibilities for the increasing identification of Mendelian inherited disorders benefit almost directly from this type of study, although globally these patients account for 5% of the general population in high-income countries. More complex is the procedure for common diseases, where there are currently more than 70,000 associations between single nucleotide polymorphisms (SNPs) with different diseases (or risk for them) and which have a small effect on the development of the disease. However, it is already possible to estimate the polygenic risk (PRS) for certain cancers (and their response to chemotherapy) for non-communicable diseases including obesity. Progress in monogenic obesities is also occurring bridging pathogenic gaps (i.e., MC4R) [37].

In the non-genomic field, the increase in knowledge has also been outstanding. The initiative of *The Lancet* [38] such as *The Global Syndemic* opens new conceptual perspectives, which together with the contents related to obesity and undernutrition includes those of climate change in order to identify and expand the determinants and which require more effective actions as a whole than the present ones to reduce these pandemics. The analyses of the evolution of the process [39, 40] are enriching and also concordant in many aspects with another important publication on this pandemic [41]. Epidemiological studies have been enriched by analyses of discrepancies within and between high-income countries [42], while inducing caution when evaluating results from low- and middle-income countries [43]. In particular, in the field of pediatric obesity epidemiology and because of the real increase in obesity despite specific actions that have been adequately supported,

studies in children aged 2–4 [44], and even earlier, together with the extension of the pediatric age at the expense of early adolescence (10–14 years), late adolescence (15–19 years), and young adults (20–24 years) again show health interest [45]. Some peculiar uses of obesity epidemiology have been carried out as the autoregressive regression that linked obesity to the vote of a presidential candidate [46].

In the clinical field, the points of interest can be so many that it is impossible to even list them. However, at the risk of bias, the concentration of adipokines or even insulin in breast milk [47], leptin levels in saliva [48], the determinants of non-alcoholic fatty liver disease [49–51], Notch proteins [52], bisphenols A, F, and S [53], post-oral sensing of fat [54], or measurements of the thickness of the cerebral cortex or digital anthropometry for young children [55] all of them and many more may be, for the time being, targets for study. However, even the content of the Franklin H. Epstein lecture [56], where the impulses to maintain homeostasis are analyzed, would no longer be as paradigmatic as before due to the great flow of real science. A problem in this context for obesity is new analytical parameters are the definition of normality [145], especially when they are measured in a pediatric population.

There is a certain publicity opportunism and an unprecedented speed at which information has emerged in the heat of the generalized COVID-19 situation. Therefore discrepancies have appeared for the moment: i.e., severe obesity in adults together with the raised higher prevalence implies higher mortality [57, 58]. This fact is not new and also the publications or reviews raised have rarely been complete or enlightening [59, 60]. WHO [61] signals the great risk for food insecurity not only in LMIC with the inherent dual malnutrition and nutritional critical care required [62]. Focusing now on the consequences of COVID-19, they have not been too positive for the epidemic of pediatric obesity [63, 64]. In westernized countries when comparing incidences of high BMIs during the same periods of 2019 (before the pandemic) with 2020 (pandemic), there were increases in overweight and obesity although the estimation was made through the less precise percentiles [65]. The attenuated efficacy of pediatric obesity treatment during the COVID-19 pandemic that was also manifest as regards other pediatric diseases normally attended [70] in emergency departments has contributed to this situation [66]. With regard to the COVID-19 pandemic, what is not opportunism are the UN figures where to the 650 million people suffering from food insecurity, we must add 118 million more due to the pandemic with its obesogenic capacity in addition to the human damage. Also interesting is the microsimulation study on childhood obesity [57, 137], among other negative issues of lockdown.

With respect to the increase in knowledge, the progress of biostatistics must inevitably be considered. The article that appeared in *Nature* [59], with the title “Scientists rise up against statistical significance” could not be more suggestive when stating the persistent problems of interpretation errors due to not being able to take into account the risk ratio, confidence intervals, confounding factors, or dichotomies [60, 67]. A scientific warning is advisable when performing meta-analysis studies, it is important to check the sample sizes of the selected studies [146]. From another point of view and with a broad mathematical basis, the weaknesses of the values of “ $p <$ ” are confirmed because it includes certain variables that were not

individualized in the statistical study, although the Bayes factor is included [60, 68]. This manifesto, signed by more than 800 researchers, gives reason to what we have been surreptitiously incorporating in recent years: it is necessary to take care in the selection of the statistical design to avoid undue conclusions [69] especially if it is a clinical trial [70]. Once again, the assessment of the quality of evidence should be recommended when making clinical decisions, which should not be confused with the strength of the recommendations [71].

Predictive Studies Perhaps the problem started with the establishment of cut-off points for pediatric overweight and obesity, which have always been established from cross-sectional studies, but to predict these situations in young adults, it is preferable to obtain them from longitudinal studies, assessing the trajectory of BMI between the starting point (childhood) and in that same cohort when it reaches the young adult stage. The initial idea is based on the i3C study, *International Childhood Cardiovascular Risk Cohort Consortium Outcomes Study* [69, 70, 72, 74], which analyzes a representative sample of the overall cardiovascular risk factors in children and their relationship with the disease already established in adults and where its greater specificity was confirmed. A later study analyzed these same data but focused on the evolution of BMI [73], with precise measurements and using the cut-off points for overweight and obesity offered by the i3C and those of the study by T.J. Cole, so highly considered in this publication (Chap. 1). By applying [70] the AUROC (*Area under the receiver operating characteristic curve*) model, which has various intervals ranging from 0.5 (null value) to 1.0 (excellent value), it turned out that the cut-off points of the i3C are lower than those of Cole, with a value, respectively, for obesity of 0.8 and 0.57, which means that the cut-off points of the i3C are lower than those of Cole, which in addition indicates that the i3C cut-off points better predict the risk of overweight and obesity for young adults than the standard cross-sectional graphs, allowing earlier preventive action, and suggests that switching to i3C may be a practical issue in the future. Among these predictive studies, it is worth mentioning the one that relates pediatric lifestyle and comorbidity [74] the study assessing non-LDL cholesterol levels [75, 76] carried out in adults, but easily applicable to the pediatric population including the fat profile intake. The predictive field always has new actions, such as the anticipation of non-alcoholic fatty liver disease by means of the so-called artificial intelligence, under development in a prestigious clinical center linked to Harvard University, although for these novel processes, it is time that weighs and endorses their usefulness. Alongside these projects, basic improvements must always be present; if the classic body mass index can be improved [77, 78], there is no doubt that it must be researched.

Energy Intake

This is probably the major component in the genesis of obesity and must be tackled from the earliest ages in order to create a habit as firm as that of daily study or work. This is due to the situation of economic growth that allows the widespread acquisition and consumption of caloric and highly palatable foods [78].

Regarding prevention, the modification of family habits is more effective; thus involving the parents in this task early on [79] and creating a compact family environment are better than entrusting this nutritional education to external institutions or organizations, for example, summer camps [80], with positive but more temporary results, which could also be applied to the line of community actions. We should all be especially informative about fast-food restaurants with increasing use and progressive energy content [81] and not forgetting the possible higher consumption of salt when eating out [78, 82]. Although there are some doubts about the cardiovascular disease preventive efficacy of Mediterranean-type diets [83], it would certainly be justified to maintain them in those areas where they are common, particularly if we keep in mind the chronic overweight association with late type 2 diabetes [84]. The best thing would be to achieve an adequate diet acceptable for the family environment [85]. The increased consumption of vegetables and fruit should be encouraged in all main meals because of their effectiveness in adult weight loss [86]; the intake of red meat should be restricted, especially if it is processed, but not eliminated, because of its association with increased mortality from any cause [87, 92], and be replaced by other dietary proteins such as those from legumes, nuts, and, failing that, poultry, fish, dairy products, and eggs. At the moment these two battles, quantity and quality, are far from being won. The increase in taxes on sugary drinks will always be welcome, but this action, although suggested and reasoned by the medical establishment, is beyond its remit, as the newspaper *USA Today* pointed out on 25 March 2019. Fortunately in 2 years' time, the situation started to change (see Chap. 9 Treatment).

Specific pediatric calorie reduction plans are rare in comparison with those for adults; however, some can be mentioned, including the 2020–2025 Dietary Guidelines for Americans [88–90], for their adequate content and assessment of dietary intake. General plans are necessary, and updates of these plans often assess previous results and identify errors that can be corrected, even in some large countries such as China [92]. Perhaps the method followed by the Ministries of Health and Agriculture of the United States for the development of the *Dietary Guidelines for Americans* (DGA) is worth taking into account, since they are reviewed and updated every 5 years according to the evidence collected. The Guidelines for 2020–2025 have already been published, and their five chapters cover pregnancy through to adulthood with precision, but adherence to the guidelines is at a minimum level in childhood and adolescence [89]. Any action that reinforces adherence to the guidelines should be supported and tested, such as the behavioral economic perspective. A long-term effect of higher energy intake should be considered: obese adolescents studied through restriction spectrum imaging (RSI), restricted normalized directional (RND) and RN isotropic (RNI) showed major white matter tracts that were segmented according to myelin oriented organization and glial and neuronal cell bodies changes [90].

The plans, general or otherwise, must be fully supported by the clinician and by the health administration. This is because there is a certain skepticism about them, a fact reflected in *The Irish Times* (12/03/2019) when referring to the three plans that the Irish government has launched since 2009 when they conclude that after the plans “nothing has happened.” Perhaps also because the best schemes are not

selected because they are more expensive [91, 92] but the shorter life expectancy and higher risk of dementia from the mid-life [97] are there.

The encouragement of physical activity should not be undermined by these dietary considerations. In this context, this would be motivated by the study of nearly 500,000 participants evaluated for their physical fitness, where those with higher physical fitness had longer life expectancy [91, 94]: in addition, the recent findings show that regular exercise is capable of increasing levels of irisin, a peptide with actions on the adipocyte and which also fundamentally improves bone mineralization. In the recently mentioned Cochrane review [92], the meta-analysis of randomized studies involving diet and physical activity in children under 5 years of age shows that when both actions coexist, they can be effective.

As regards the energy intake factor, two basic actors should be mentioned here: First is the new knowledge on brain circuits acting on the appetite component. The homeostatic circuit (hunger-satiety) was the first to be studied and perhaps misleadingly considered the main factor responsible for adiposity, while the newer non-homeostatic circuit (appetite in absence of hunger) had a minor role. There is growing literature pointing out that the importance of the non-homeostatic circuit is probably greater than thought, due to the coordinated action of both through orexigenic and anorexigenic connections [147]. The second is related to the model of energy balance for obesity development. Besides the widely accepted energy balance model, a new carbohydrate-insulin model (CIM) has been presented [148], due to the importance of insulin in the genesis of obesity comorbidities.

Treatment

After the comments on preventive plans, another type of more modest actions becomes important, but theoretically with better possibilities of access to obese children and adolescents, which are the added interventions based in the community that would provide support for lifestyle modification and facilitate better integration of therapeutic resources. There are numerous examples, almost always from high-income countries, and in this regard, it is perhaps worthwhile to focus on two of them with good designs [95, 96] because they offer results, albeit in the short term (< 6 months). In this phase they show that the reduction in BMI does not differ from that obtained in the control groups with usual multidisciplinary treatment. However, a systematic review would be appropriate that would obviate the shortness and sample size. In relation to the optimization of therapeutic actions according to the degree of obesity, the study [97] that establishes four stages of pediatric obesity considering other parameters in addition to the usual BMI and that allows the formation of more uniform groups for a more differentiated treatment has proved to be a better predictor of health risk than definers of the level of obesity [96–98], but a firm infrastructure and economic support are required. A solution more in line with the European state health systems could be that of the University of Bristol (UK): the Care of Childhood Obesity (CoCO) clinic at the Bristol Royal Hospital for Children was developed at the beginning of this century and integrating the regional hospitals

for treating obesity and pediatric comorbidities. Again, these obstacles should not be a deterrent to delve into this more complex therapeutic activity. From the professional side of pediatrics, things are probably improving, and a practice as elementary as BMI assessment at each health visit has risen in certain high-income countries to 97% in the last decade [99] which is an important milestone in the difficult task of prevention and treatment.

Considering more direct and quantifiable aspects, we cannot ignore the NHANES 2011–2016 study [100] conducted on children and young people, which includes the intake of sugar-sweetened beverages versus that of water. Taking the total figures (without age stratification), those who do not drink water (20% of the population studied) and whose entire liquid intake is based on other beverages ingest 100 kcal/day during the entire time of the study; this should definitely lead to a specific action to encourage people to drink water. Results from WHO European Region indicate a large disparity among the types of adopted policies by Member States, but more cohesive strategies have been initiated [101]. In general, progress in crucial areas of pediatric obesity is evident in prevention [102], nutrition [103], and evaluation [104], together with other questionable [105] or even picturesque approaches [106].

With respect to drugs, there is little to add to what was expressed in Chap. 9, only to highlight the possible future of the use of cellulose hydrogel particles and citric acid which, ingested before meals, absorbs water from the stomach, increasing the volume of gastric contents and creating the sensation of satiety early; a study conducted in adults versus controls [107] has led to significant weight loss (OR 2.0), but more recently these results could not confirm these result [108]. In relation to drug treatment, the initial finding that the administration of metformin (PedMet study 2019) in the treatment of type 2 diabetes had a BMI-reducing effect opened a new path, although with effects on the BMI of offspring when used during pregnancy [109]. We may be at a key therapeutic moment with the emergence of the glucagon-like peptide-1 (GLP-1) receptor agonists discussed in the treatment chapter. The use of semaglutide [110, 111] may constitute a turning point in the treatment of overweight or obese adults, but also in children. This therapeutic saga has only just begun, as demonstrated by the efficacy of tirzepatide due to its greater dual action [112]. An unresolved problem, which is a daily occurrence at least in pediatric care, is the irregularity of treatment in primary care. The NEJM editorial that recognizes this situation also for adults [113] is a positive point for the medium- to long-term management of obesity. In the case of hypothalamic obesity, severe and progressive, usually post-traumatic, the use of Tesomet [149] could be of interest. When drugs are used it is a possibility that the effects of placebo and nocebo (experienced side effects, despite being on placebo) can be seen [150].

Lastly, and within the current status of treatment, it should be added that bariatric surgery in adolescents is a fact with its pros and cons, and its indications have been well outlined by Sperling's group [114]. The *Integrated Care* model as it is conceived today reflects the aspiration for quality in modern healthcare, and, although it is still in a more academic than healthcare phase, it will probably be incorporated gradually, as has occurred with adolescent bariatric surgery. The existence of confident indicators for type 2 diabetes remission [115] even in younger ages confirms the present therapeutic efficacy.

Final Reflection

The milestones of the *Millennium Development Goals* set for 2015, and subsequently those of the *Sustainable Development Goals* for 2030, have undoubtedly achieved an uneven and certainly growing success in relation to mortality in children under five (perinatal and infectious diseases); however, the expected progress in the area of pediatric and adolescent nutrition has been much slower, if not nonexistent, due to the lukewarm incorporation into health programs. In fact, the progress is varied specially in LMIC where the planned reduction of mortality from non-communicable diseases for 2030 would require further investments [151].

In other fields, the complementary actions of the WHO [116] now advocate self-care in a vast document and where self-assessment (*by proxy* in our case) is essential. If this were decided in the case of obesity and with the same support as for infectious diseases, it would be effective in the case of children with a high BMI. As Dr. W H. Dietz rightly expresses in this regard (*The Hill*, 30 Nov 2019), “if obesity is an epidemic, why haven’t we responded adequately,” and he draws comparisons with other epidemics in numerical terms, but something that is especially significant is the number of deaths caused to this day by different epidemics. This is pertinent because, from a frequency point of view, this will be increasing to 250 million kids worldwide by 2030, according to the health section of *The Guardian* (2 Oct 2019). In addition, we should consider the life expectancy that was progressively increasing in the second half of the last century, an increase that was followed by a certain plateau until 2014 that began to decrease. This decrease happened due to specific causes (systemic or organ diseases, suicides, overdoses, etc.) and obesity, as seen in Western countries [117]. The real integration of public health, healthcare systems, and clinical medicine with prevention will be more efficient against non-communicable diseases [118]. An unexplored contributory resource is the undergraduate medical education in the field of obesity [119, 152].

From the point of view of lifestyle and specifically physical activity, there is a global trend of insufficient PA. In 298 population-based studies conducted in adolescents [120], those corresponding to hot areas, in Spain, indicate an insufficiency of PA that affected 84% of adolescents in 2001 and 85.7% in 2016. All this is consistent with the almost global trend of lower implementation of policies against non-communicable diseases, and thus, in another study on the percentage of implemented actions carried out in 151 countries, Spain and Italy rank, respectively, 19th and 20th out of 20 high-income countries [121]. These implementations are at least at the state level [122], and consequently it is worth reflecting on how appropriate food production has been effective following FAO’s actions to combat undernourishment in many parts of the world; however, efforts regarding obesity have not had the same fortune so far. The positive results are already known, the White House releases the Strategy to Address Hunger, Nutrition, and Health in the US [153] with a budget of \$ 8 billion, probably this, besides the the rational targets, can be a firm starting point. Also the USDA passed in Congress the Healthy Hunger-Free Kids Act [154]; school meals markedly improved not only for the existence of poor

nutritional quality but for the motion towards balanced meals with a sharp decrease of sugars and with an increase of slow carbohydrates, two (or three) for the price of one. Other good initiatives targeting global food safety or obesity prevention would be more effective when less frugalness economy infrastructure happens. Other steps eg World Day of Obesity and similar local deeds will require more time to evaluate their efficacy.

As is the norm, excellent guidelines continue to be produced, such as that of the *National Academies of Sciences, Engineering and Medicine* [123], but the question arises as to whom this document will reach and whether it will ultimately reach the patient. Recognition of the lack of efficacy in rigorously designed and carried out plans [124] is a confirmation of poor patient access. Keeping it simple, in this case by maintaining waist size to less than half of that of height, as a mass educational tool could be clear and effective [155, 156]. Less ambitious would be information on the relationship between BMI and mortality that should make it less dramatic and is more understandable [125] and more easily disseminated at all levels. The increasing global prevalence of obesity is not usually a cause of death in the pediatric age, but if the criterion of health-adjusted life expectancy (HALE), which refers to the number of years of full health that an individual can live, estimated at a certain age (e.g., HALE 0 refers to newborns) [126] is assessed, then the greater preventive effort at early ages of non-communicable diseases, including obesity, makes more sense due to the aforementioned general and specific trajectories. This leads to the consideration that obesity must be treated in a much broader context, with measures that are not always achievable. Recall the large study on HIV [57, 127] which shows how democratic improvement (choices) also improves health and survival conditions, in addition to micro-elimination actions. However, major advances and positive standards are also reaching or will reach the patient, such as the study of the associations of certain gene variants carried out in children under 1 year of age with overweight and obesity, which will allow early prevention [128], and in another field and aimed at improving clinical studies, there is the initiative to improve the definition of cohorts to use hospital databases [129] to gain uniformity in the study groups.

From the clinical point of view, we must always be alert, because the real novelties appear in the form of more effective treatments [130], in diagnostic terms such as the polygenic prediction of weight and obesity trajectories [131, 144] or the selection of in vitro fertilized embryos to reduce the risk of comorbidities [132] and now specifically for the Hurler syndrome [133] or in a more general way such as artificial intelligence and its relationship with global health [134, 135] with its vast field of action, and this is not chimerical. Faced with this advent of information, it is certainly advisable not to fish in polluted waters: should one publish in an open access journal (predatory journals) on a pay-per-article basis [136–138]? Effective and optimal health from the periconception to adulthood is basic for overweight/obesity prevention. In order to achieve this ideal, preclusive medical action [157] and state spatial angles should converge at the center of the holistic sphere of obesity management.

I would like to conclude by saying that the biggest challenge we face is to enable our knowledge about the main causes of the increased prevalence and of obesity itself to be turned into effective action, because a health crisis becomes a social crisis, however small they may seem.

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