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SPECIAL ARTICLE

A holistic perspective of the comorbidities in childhood obesity

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Abstract Childhood obesity is associated with comorbidities that affect almost all body systems, including, among others, the endocrine, gastrointestinal, pulmonary, cardiovascular and musculoskeletal systems, as well as medical and surgical procedures that may be required due to different clinical situations. The objective of this article is to describe the classic and emerging comorbidities associated with obesity and the complications of procedures that involve invasive manoeuvres. Although some of the problems associated with obesity during childhood are widely known, such as musculoskeletal and cutaneous disorders or apnoea–hypopnoea syndrome, others, such as changes in kidney function, non-alcoholic fatty liver and cardiometabolic risk, have received less attention due to their insidious development, as they may not manifest until adulthood. In contrast, there is another group of comorbidities that may have a greater impact due to their frequency and consequences, which are psychosocial problems. Finally, in the context of invasive medico-surgical interventions, obesity can complicate airway management. The recognition of these pathologies in association with childhood obesity is of vital importance not only in childhood but also due to their ramifications in adulthood.

PALABRAS CLAVE
Obesidad;
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Una visión holística de las comorbilidades en la obesidad infantil

Resumen La obesidad infantil está asociada con comorbilidades que afectan a casi todos los sistemas del organismo, incluidos, entre otros, los sistemas endocrino, gastrointestinal, pulmonar, cardiovascular y musculoesquelético, así como a los procedimientos médicos y quirúrgicos que puedan precisarse por situaciones clínicas varias. El objetivo del presente artículo

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es describir las enfermedades clásicas y emergentes asociadas a la obesidad, así como las complicaciones de procedimientos que requieren maniobras invasivas. Aunque algunos de los problemas asociados a la obesidad durante la infancia son ampliamente conocidos como los musculoesqueléticos y cutáneos, así como el síndrome de apneas hipopneas, otros como las alteraciones de la función renal, el hígado graso metabólico y el riesgo cardiometabólico han recibido menos atención debido a su desarrollo larvado que condiciona enfermedad en la edad adulta. Por el contrario, existe otro grupo quizá con mayor impacto por frecuencia y por sus consecuencias que son los problemas psicosociales. Por último, en presencia de acciones médico-quirurgicas invasivas la obesidad puede dificultar el acceso a la vía aérea. El reconocimiento de estas enfermedades asociadas a la obesidad infantil es de vital importancia no solo para el periodo infantil, sino también pro su proyección a la vida adulta.

Introduction

Childhood obesity is associated with comorbidities involving nearly every organ system, including, among others, the endocrine, gastrointestinal, respiratory, cardiovascular and musculoskeletal systems, with affects the medical and surgical procedures that may be required due to a variety of clinical conditions (Fig. 1). In the past, many of these complications were believed to occur in adults, but evidence has since emerged that demonstrates that they may start developing as early as childhood or adolescence, evincing the need to consider them in the comprehensive management of obesity in the paediatric population. It is clear that their severity tends to increase with the degree of obesity and the number of associated comorbidities.

In this review, we describe not only the comorbidities historically associated with obesity, but also those for which evidence is currently emerging. We also address the possible difficulties and complications in procedures that require invasive manoeuvres.

Frequent comorbidities

Respiratory

There is a bidirectional association between childhood obesity and decreases in sleep duration and/or quality. Sleep disturbances are a risk factor for the development and persistence of childhood obesity, and there is a high prevalence of sleep-related breathing disorders in obese children, including sleep apnoea−hypopnoea syndrome (SAHS).[1] The incidence of SAHS in school-aged children is estimated at 1%−5% and believed to be 4−5 times greater in adolescents with obesity compared to those with a normal weight. Although the main cause of SAHS in children is upper airway obstruction due to enlargement of the tonsils or adenoid glands, obesity is also a risk factor, especially among older children.[2] Frequent apnoeic episodes cause oxygen desaturation and sleep fragmentation. A persisting pattern of interrupted sleep is associated with cognitive and behavioural changes and emotional difficulties.[3] Children with severe obesity may also develop alveolar hypoventilation associated with oxygen desaturation. There is also evidence that childhood obesity is associated with bronchial hyperresponsiveness and asthma.[4]

The presence of sleep-related breathing disorders may go unnoticed by the parents. It is important to emphasise the likelihood of these disorders so that they can be assessed correctly. Snoring and daytime somnolence are potential red flags that facilitate their detection.

Musculoskeletal

Obesity increases the risk of several musculoskeletal problems, such as impaired mobility, fractures, joint pain in the lower extremities and malalignment of the extremities.[5,6] It is also a risk factor for unilateral or bilateral slipped capital femoral epiphysis and tibia vara.[7]

Many children with obesity exhibit the so-called paediatric inactivity triad, a concept proposed to assess inactivity in its 3 components: exercise deficit disorder (poor cardiorespiratory and muscle fitness), paediatric dynapenia (low muscle strength and power not secondary to neuromuscular disease and the associated functional limitations) and physical illiteracy (lack of competence, confidence, motivation and knowledge to move well).[8]

In addition, an increase in body weight can limit functioning and increase the risk of injury during daily physical activities, increasing the risk of falling due to decreased postural stability and control. Furthermore, recovery from injuries takes longer and the associated morbidity increases.

Renal

Renal involvement secondary to obesity has been found to de independent from the potential association with diabetes and the development of high blood pressure. A specific type of obesity-related glomerulopathy has been identified that manifests with progressive albuminuria with development of partial nephrotic syndrome over the years. Data are cur-

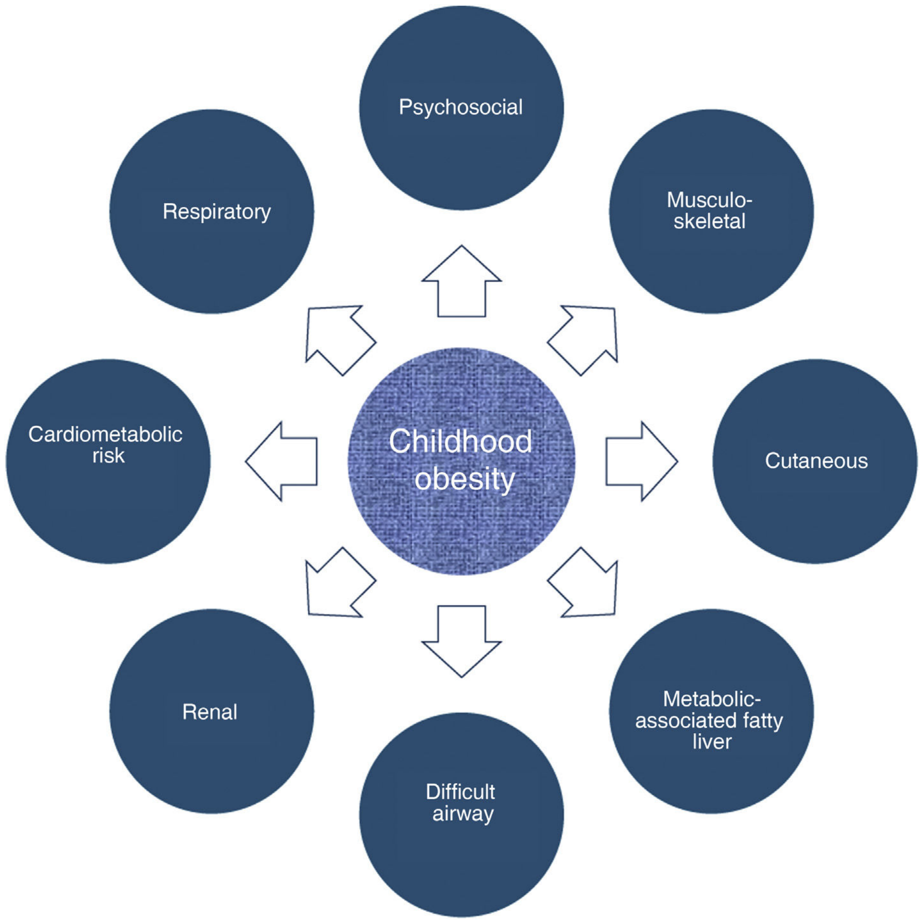

Figure 1 Comorbidities associated with childhood obesity.

rently emerging on the potential development of this form of glomerulopathy in obese children and adolescents, although they are still very scarce.

Although further research is needed on the potential mechanisms that underlie this association with the aim of implementing preventive strategies to halt the development of chronic kidney disease, as of now, detection of albuminuria in obese children should be interpreted as a warning of future risk and be followed by implementation of measures to reduce excess weight and control potential comorbidities like hypertension or type 2 diabetes.[9]

Cutaneous

Cutaneous manifestations may be classified into 3 groups: changes in skin physiology, cutaneous changes related to obesity and cutaneous disease associated with obesity. Cutaneous manifestations of obesity are directly related to the age of onset, chronicity and severity of obesity.

Multiple skin physiology changes are found in children with obesity, including excessive sweating and decreased tolerance to local and environmental increases in temperature, facial redness as a compensatory mechanism, xeroderma due to transepidermal water loss and chafing in friction areas. Among the skin changes associated with obesity, acanthosis nigricans (AN) is the most frequent cutaneous manifestation, developing in 49%–58% of adolescents with excess weight.[10] In addition, AN is the most frequent early cutaneous manifestation in children with obesity and/or insulin resistance. The development of stretch marks is directly associated with the degree of obesity, with an incidence of up to 40% in children with moderate to severe obesity. Lastly, there are cutaneous diseases that can be triggered and/or exacerbated by obesity, such as intertrigo, psoriasis, hidradenitis suppurativa and, to a lesser extent, atopic dermatitis.

Some of these manifestations, being visible, can exacerbate the psychosocial impact that paediatric patients with obesity inevitably experience. The assessment of cutaneous manifestations is essential to allow early diagnosis and the prevention of sequelae.[11]

Cardiometabolic risk

The growing prevalence of obesity in children and adolescents worldwide has raised concerns regarding a future increase in the prevalence of cardiovascular diseases. Obesity in children and adolescents can cause hypertension, dyslipidaemia, chronic inflammation and hyperinsulinaemia, which increases the risk of morbidity and mortality as children grow into adulthood and is a significant public health concern. Thus, the identification of cardiometabolic risk factors in obese youth can be used to define a high-risk group within the paediatric population with obesity. A cross-sectional study in adolescents aged 12–19 years in the NHANES 2017–2018 cohort showed that anthropometric measurements could predict cardiovascular risk in adolescents.[12] A study conducted in the Unit against Obesity and Cardiometabolic Risk of the Department of Paediatrics of the Hospital General de Valencia[13] assessed for the presence of cardiometabolic risk factors in 611 children and adolescents with moderate obesity and, in addition to obesity, identified one risk factor in 39%, 2 risk factors in 16.5% and 3 risk factors in 2.8%. Among the risk factors, the most prevalent was hyperinsulinism (30/8%), followed by dyslipidaemia (12.9%) and hypertension (10.5%). High blood pressure (BP) is frequently associated with one or more cardiometabolic risk factors. Although the clustering of cardiometabolic risk factors is interpreted as metabolic syndrome in adults, reaching a consensus in the definition of metabolic syndrome in the paediatric population has proven challenging. Understanding the relationships between excess weight, insulin resistance and BP in early life is important in order to develop intervention or prevention strategies. We found a significant correlation between insulin resistance and BP through the use of ambulatory BP monitoring over a 24-h period, a method that allows more accurate assessment of BP values.[14] This association was clearer at night, when BP is less affected by external factors. These findings support the role of insulin resistance in the elevation of BP.[15] Early elevation of nocturnal BP and heart rate associated with hyperinsulinaemia may be a forerunner of insulin resistance associated with hypertension and contribute to the increased cardiovascular risk associated with this condition.

There is evidence that children and adolescents with obesity, especially those with excess abdominal fat, may exhibit an atherogenic lipid profile, characterised by increased serum levels of total cholesterol (CT), triglycerides (TG) and low-density lipoprotein (LDL) and decreased serum levels of high-density lipoprotein (HDL); these abnormalities are found in up to 30% of obese children and adolescents. At present, it is widely accepted that abnormalities in the serum lipid profile in paediatric patients with obesity may be early indicators of cardiovascular risk or manifestations of metabolic syndrome.[16,17]

A metabolic factor that has barely been investigated in children and that has only recently garnered attention is uric acid. Several cross-sectional studies have analysed the association between serum uric acid levels and abdominal obesity.[18–20] In youth with overweight or obesity, uric acid levels were the main determinant and exhibited the strongest association with the waist circumference. There was a significant positive correlation between uric acid and the office BP, increased cholesterol values, TG levels and the HOMA index and an inverse correlation with HDL levels. In addition, the presence of low HDL values, elevated TG values and hyperinsulinaemia was associated with an increase in uric acid levels.[18] This is consistent with the findings of other studies and evinces the association between uric acid, visceral fat and cardiometabolic risk factors. Furthermore, the association between uric acid and waist circumference has also been observed in individuals with normal weight obesity, defined as excess body fat despite a healthy body weight.[20]

Emerging comorbidities

Psychosocial

Children and adolescents with obesity have a lower quality of life compared to their normal-weight peers. In addition to this impairment in their quality of life, they also exhibit psychosocial comorbidities, including low self-esteem[21] and an increased risk of depression, anxiety,[22] eating disorders and substance abuse.[23] Low self-esteem and greater body mass index values, whether actual or perceived, are associated with an increased probability of tobacco and alcohol use.[24]

In general, low self-esteem does not seem to become a problem until adolescence, as self-esteem is similar between preadolescents with obesity and their normal-weight peers. However, during adolescence, self-esteem is most strongly associated with body image and deteriorates rapidly; female adolescents with higher body mass index values and body dissatisfaction have lower self-esteem.[25]

The stigma attached to being overweight or obese does not stem solely from the clinical repercussions of the excess weight, but also from the socially-accepted rejection, exclusion and discrimination inflicted on individuals living with this condition. All of this has a deleterious impact on children and adolescents with obesity, who are more likely to be teased and bullied, socially isolated and have fewer friends than their non-obese peers, giving rise to a vicious circle depression/loss of self-esteem and social integration problem. A psychological evaluation should be conducted if any of the above conditions are detected to prevent their progression.[23]

Despite the substantial consideration devoted to the medical repercussions of obesity, the deleterious impact on children and adults with obesity that results from stigmatization, prejudice and discrimination is frequently ignored. Obese individuals are frequently stigmatized due to their weight in many spheres of everyday life. Research conducted over several decades has documented constant prejudice and stigmatization related to excess weight in work, health care and school settings, in the mass media and in interpersonal relationships. In youth with overweight or obesity, weight stigma leads to generalised intimidation, mockery and victimization. Exposure to weight stigma is associated with multiple adverse outcomes, such as depression, anxiety, low self-esteem, body dissatisfaction, suicidal ideation, poor academic performance, decreased physical activity, maladaptive eating behaviours and health care avoidance. This review summarises the nature and magnitude of weight stigma against individuals with overweight and obesity and the impact of these experiences on the social, psychological and physical health of the children and adults subjected to it.[26]

Metabolic fatty liver disease

Metabolic dysfunction-associated fatty liver disease (MAFLD),[27] is a metabolic disorder characterised by excessive accumulation of fat in the liver unrelated to infection, medication or an autoimmune disorder. It may range from simple fatty liver to steatohepatitis with manifest inflammation and cell damage. At present, it is the most frequent aetiology of chronic liver disease in the paediatric age group in developed countries and it is strongly associated with obesity, with an estimated prevalence of 36.1%.[28] Increasingly, MAFLD is being considered an aspect associated with cardiometabolic risk factors.[29]

The most noteworthy characteristic of MAFLD is that, while some affected individuals exhibit hepatocyte damage, most remain asymptomatic, and in obese children it manifests with transaminase elevation in routine blood panels. Sonography is frequently used to assess MAFLD. Magnetic resonance imaging is a less subjective technique for the measurement of hepatic steatosis, but there are barriers to its routine, including costs, lack of widespread availability and the potential lack of cooperation of the child. Liver elastography with FibroScan is the most widely used method for assessment, despite its limitations. Liver biopsy is the gold standard for diagnosis of MAFLD.[30]

Early detection of MAFLD is necessary, although the optimal timing, frequency and method for screening remain to be determined. Lifestyle changes and weight loss continue to be the cornerstone of treatment for MAFLD.

Interventions requiring anaesthesia

Obesity is usually associated with comorbidities involving multiple organs that may be relevant in patients who require anaesthesia for diagnostic and/or therapeutic procedures. The most important issues arise from difficulty in securing the airway and the pharmacokinetics of anaesthetic agents.

Pharmacokinetics of anaesthetic agents

The physiological changes associated with obesity alter the volume of distribution, protein binding and elimination of pharmaceuticals.[31–33]

Most drugs are dosed in terms of a dose mass per unit of body weight based on the principle that clearance is proportional to body weight and that the volume of distribution per unit of weight remains constant. In the case of obesity, there are changes in body composition, volume of distribution and renal and hepatic function. The volume of the central compartment (where a drug initially distributes upon administration) tends to be greater due to the blood volume and the size of the major organs, so that a higher initial dose is required to obtain the same pharmacological effect. The volumes of distribution at equilibrium also increase for lipid-soluble drugs (e.g., sodium thiopental, lidocaine, benzodiazepines) and water-soluble drugs (e.g., vecuronium, rocuronium) due to the increase in extracellular fluid in adipose and lean tissue. To this, we must add the increase in body fat, changes in protein binding and the increase in blood volume and cardiac output. All of it affects the distribution of water-soluble and lipid-soluble drugs, so there is a risk of overdosing (e.g., sufentanil) or underdosing (e.g., succinylcholine).

Plasma protein binding. It may decrease for some drugs, increasing the proportion of free drug due to the higher concentration of free fatty acids, TGs and cholesterol. The increase in α1-acid glycoprotein increases the binding of local anaesthetics and opioids.

Table 1 Dose adjustment strategies in paediatric patients with obesity.

Drug	Induction dose	Maintenance dose
Propofol	LBW	TBW
Etomidate	LBW	
Ketamine	IBW	
Benzodiazepines	LBW	IBW
Desflurane and sevoflurane	MAC[a]	MAC[a]
Fentanyl	LBW	LBW
Remifentanil	LBW	LBW
Morphine	IBW	IBW
Succinylcholine	TBW	
Non-depolarizing neuromuscular blockers	IBW	IBW
Neostigmine	TBW	
Sugammadex	TBW	

IBW, ideal body weight; LBW, lean body weight; MAC, minimum alveolar concentration; TBW total body weight.
[a] Adjusted based on minimum alveolar concentration.

Drug elimination. Renal clearance increases due to increases in renal flow, glomerular filtration and tubular secretion. The increase in glomerular filtration results in an increase in the clearance of drugs that do not undergo biotransformation prior to renal excretion and are filtrated by the glomeruli.

Despite the presence of steatosis, hepatic drug metabolism changes little in obese children. Oxidation, reduction and hydrolysis reactions are normal or increase slightly.

To prevent over- or underdosage,[34–36] clinicians can apply dosing equations based on the total body weight (TBW), ideal body weight (IBW) and the lean body weight (LBW), defined as follows: TBW as current total body weight of the patient, IBW as the BMI at the 50th percentile for the patient's age (ideal BMI) multiplied by the squared height in metres (IBW = ideal BMI $\times$ height^2) and the LBW as the difference between the total body weight and the body fat mass. The latter comprehends all lipids in the body (primary depots and other depots) and its calculation requires different equations for each sex. One of the simplest equations includes the height, waist circumference and head circumference. These are the strategies used to adapt the dosage of the main drugs used in paediatrics anaesthesia, as seen in Table 1.

In the case of propofol, the dose should be titrated using a depth of anaesthesia monitor (e.g., bispectral index [BIS]). When it comes to volatile anaesthetics, preferential use of desflurane and sevoflurane is recommended, as they are the 2 least lipophilic agents in this group, always adjusting the dose based on the minimum alveolar concentration (MAC), which is the minimum concentration in the alveoli of the inhaled agent that prevents 50% of subjects from moving in response to a painful stimulus.

Issues concerning the airway

The respiratory pathophysiology associated with obesity includes changes in ventilatory mechanics, respiratory muscles, ventilation regulation and the control of breathing during sleep. The fatty tissue that infiltrates the chest wall reduces the static and dynamic lung volumes, especially the residual volume (RV) and the functional residual capacity (FRC). There are ventilation/perfusion mismatches, with increases in oxygen consumption (11%), cardiac output (CO) (35%), cardiac index (35%) and peripheral vascular resistance (21%). Metabolic activity and work of breathing increase, leading to greater oxygen consumption and CO_2 production. Obese individuals with SAHS (5%) experience hypoxaemia with alveolar hypoventilation and hypercapnia possibly secondary to the submucosal fatty tissue infiltration in the upper airway. This can lead to airway narrowing and collapse.

Asthma

The underlying mechanisms are mechanical (airway narrowing), inflammatory and genetic. During general anaesthesia, obese patients have been found to be at increased risk of hypoxaemia and atelectasis, with hypoventilation and decreased tolerance to apnoea.[34,37]

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Conflicts of interest

The authors have no conflicts of interest to declare.

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