Cardiometabolic and Cardiovascular Complications of Obesity in Children

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Abstract: The rise in obesity in both children and adults has made obesity one of the biggest public health problems of this century. Obesity along with other factors such as hypertension, insulin resistance, dyslipidemia and diabetes mellitus are risk factors for the development of cardiovascular diseases. Overweight and/or obesity during childhood and its maintenance until adult life has been associated with early stages of cardiovascular disease. For this reason, the aim of this study is to revise the state of the art of cardiometabolic and cardiovascular complications related with overweight and/or obesity in children and adolescents. The first consequence of weight gain is an increase in adipose tissue, with different distribution depending on the sex. The excess of fat mass entails dysfunction of adipose tissue with an altered secretion of adipokines and instauration of a proinflammatory environment, which may derive in metabolic syndrome condition. The increase of adipose tissue along with an increase in sympathetic nervous system, triggers an increased left ventricular mass and with a reduced diastolic function.

Therefore, obesity should be prevented from the early stages of life, in order to avoid obesity itself and the metabolic disturbances that could undermine quality of life further on.

Keywords: Obesity, Children, Adolescents, Cardiometabolic complications, Cardiovascular complications.

INTRODUCTION

Obesity is currently a worldwide pandemic that has extremely increased in the last decades, being nowadays one of the most serious public health concerns, both in developed and developing countries. Besides, obesity is an independent and strong risk factor for the development of cardiovascular diseases (CDVs) [1]. Due to the multifactorial nature of obesity, there are many factors to take into account for its approach. Socioeconomic factors such as having a low income or immigrant origin (black, Hispanic) have been found to influence the development of overweight or obesity. However, this set of factors seem to act as a whole and have shown a clearer relationship with the development or not of obesity, which can be observed as soon as the child is gestating [2]. Obesity development implies extra medical costs that range between 0.7% and 2.8% of total health spending in a country. In addition, when BMI is higher than 25 kg/m^2 medical costs increase up to 9.1% of total healthcare expenditures [3]. In the USA, the estimated cost relative to obesity is $149.4 billion [4].

The increase in obesity prevalence has also been observed in children and adolescents. Indeed, in 2016, 124 million children and adolescents had obesity [5]. Finkelstein *et al*., observed that those children with overweight or obesity had an increase in medical cost of US$180 and US$220, respectively, compared to children with normal weight [6]. Children and adolescents with obesity very likely will have this condition in adulthood, also having a high risk for premature death [7]. Moreover, having overweight or obesity during childhood is associated with metabolic changes, an altered adipokine profile and a low-grade inflammatory state, which is more expressed during adolescence [8]. Physical exercise can improve the BMI of those children with obesity or overweight by two different ways: physical education lessons in school and sports participation in their leisure-time [9]. Although there is still no agreement on how many hours are necessary to exert a protective effect on the development of obesity [9], a reduction of overweight or obesity has been observed in children who attended 90 min of physical education per week [10]. However, other intervention programs have increased until 270 min/week without significative differences. For this

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E-ISSN: 2311-8687/20

reason, those children who do not perform physical activity in their school hours are recommended to exercise in their leisure-time. Opposite to this, in last 20 years, children have become more sedentary than before with an increase in their screen time. That increase has been associated with greater consumption of unhealthy foods. And this has translated into a positive relationship between screen time and obesity [11, 12].

Recently, the term metabolically healthy obesity (MHO) has been proposed to describe those individuals with obesity but no cardiometabolic complications [13]. However, individuals with MHO may eventually develop CVDs later in life [14].

The propensity to develop obesity and the responses to metabolic challenges are different between the sexes [15, 16]. It is not only the differences as to weight gain and adipose tissue accumulation and distribution, but also, the secondary complications associated to having overweight or obesity that also differ between the sexes, even before puberty [17]. The mechanisms underlying these differences still need further research to be completely understood, but sex steroids, sex chromosomes and fetal/neonatal programming as well as epigenetic changes seem to be responsible factors [18, 19].

Hence, it is important to consider the lifelong perspective starting from childhood, trying to prevent an early initiation of atherosclerotic disorders and the development of future CVDs and hearth failure [20, 21]. In this sense, parental role is crucial to influence in the propensity to become or not obese in the future. It is well described that the likelihood to become obese begins as soon as in utero and even before conception [22]. Therefore, maternal health, nutrition during gestation or fetal exposure to stress can be key in the future development of obesity or metabolic diseases. Besides, nutrition during infancy, childhood and adolescence are key periods for the future development or not of obesity. One of the best methods to prevent obesity from the early ages is the role that parents have in their children everyday routine. Adopting a healthy lifestyle from childhood is crucial to decrease the probabilities of developing metabolic diseases in adulthood [23], therefore parents must clearly understand this message that might avoid future obesity development and its associated comorbidities. They must actively promote healthy eating habits, setting good examples in their everyday routines and establish physical activity as a priority from the very early ages, which will positively affect both, parents and children.

Based on the available literature regarding the complications of obesity in children, the aim of this

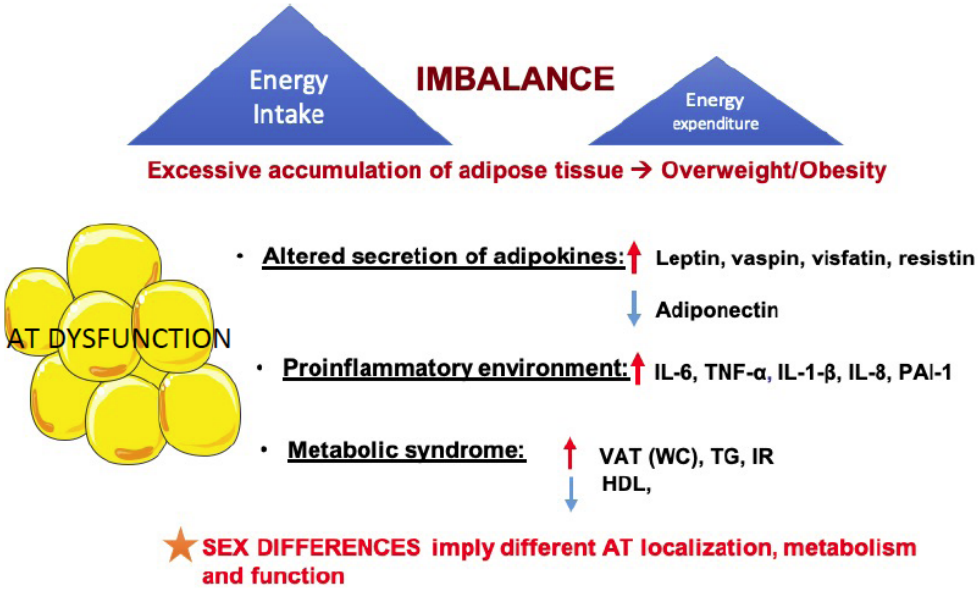

Figure 1: Metabolic complications in children and adolescents with obesity. The increase in the amount of adipose tissue as a consequence of an imbalance between energy intake and energy expenditure leads to overweight or obesity and diverse metabolic disturbances: adipose tissue dysfunction, altered adipokine profile, metabolic syndrome and instauration of a proinflammatory environment. Of note, there are metabolic differences between the sexes residing on different adipose tissue localization, metabolism and function.

Figure legend: AT: Adipose tissue, IL-6: Interleukin 6, TNF-α: Tumor necrosis factor alpha, IL-1-β: Interleukin 1 beta, IL-8: Interleukin 8, PAI-1: Plasminogen activator inhibitor-1, VAT: Visceral adipose tissue, WC: Waist circumference, TG: Triglycerides, HDL: High density lipoproteins, IR: Insulin Resistance.

review is to gather the evidence regarding the cardiometabolic and cardiovascular complications related with overweight and/or obesity in children and adolescents (Figure **1**). As general knowledge, we will first describe how we should assess the excess of adiposity, with an especial focus in the abdominal region.

BODY COMPOSITION ASSESSMENT IN CHILDREN AND ADOLESCENTS WITH OBESITY

Obesity is defined as an excess of adiposity. The most widely used tool for assessing obesity is the body mass index (BMI) [5]. In children, it is used taking into account sex and age specific percentiles [24]. BMI has important limitations as it also takes into account lean mass, which may arise mistaken conclusions. Fat mass may be assessed measuring skinfold thickness, using dual energy X-ray absorptiometry (DXA) or air displacement pletismography (BodPod), amongst other methods [25]. In children, adiposity should be described as the fat mass index (FMI = fat mass in kg / height^2).

The most metabolically active adipose tissue is located in the abdominal region; therefore, some authors suggest to assess in clinical practice, not only BMI, but also waist circumference (WC) or waist to height ratio (WHR) [1]. In this regard, abdominal [visceral) body fat has shown a greater association with the development of CVDs and mortality [26]. Indeed, WC measurement has shown a good correlation with visceral fat mass [27].

However, the mechanisms through which abdominal fat contributes to the risk of these diseases are not completely understood [28-30]. Thus, BMI, WC and WHR can be used as predictors for cardiometabolic risk in children and adolescents [31, 32].

In this sense, the anthropometric parameters have been associated with some of the abnormalities included within the metabolic syndrome (MetS), positively correlating with HOMA-IR and with an altered adipokine profile as it will be described in the sections below.

It is important to note the sex differences observed regarding adipose tissue accumulation and distribution. Puberty begins with a characteristic subcutaneous body fat mass that is independent of the age of onset and it is sex specific [33]. During puberty, fat mass increases in females in order to ensure reproduction while fat free mass increases in males [33]. This sexual dimorphism is mostly due to the influence of sexual hormones and sex chromosomes, with females often showing a more beneficial metabolic profile.

As to adipose tissue accumulation, it is worth noting that its expansion can occur by hyperplasia (recruitment of new adipocytes) [34] or hypertrophy of the existing adipocytes, which is associated with visceral adipose tissue and higher metabolic risk [35, 36]. Estrogens are suggested to favor hyperplasia, increasing adipocyte progenitor cells and facilitating vascular supply to adipose tissue [37].

Moreover, females have a continuous increase in fat mass throughout development, while males reach their maximum levels of fat accumulation at puberty [38]. Thus, women exhibit higher levels of adiposity through lifespan and accumulate more subcutaneous adipose tissue (SCAT) in contrast to males that accumulate visceral fat (VAT) [39]. It is well known that accumulation of fat mass in the upper zone of the body is associated with cardiometabolic complications associated with obesity, whereas fat mass accumulation in the gluteal-femoral region is not and could even be protective [40].

CARDIOMETABOLIC COMPLICATIONS

Obesity and Metabolic Syndrome in Children

Obesity and overweight in children are significant risk factors for developing the MetS early in life or during adulthood [21, 41]. MetS can be defined as the coexistence of several clinical manifestations: obesity, mostly as central (abdominal) fat accumulation, insulin resistance, glucose intolerance, high arterial blood pressure and dyslipidemia (high triglycerides and/or low high-density lipoprotein cholesterol (HDL-C) concentrations). All of them are the strongest risk factors for developing CVDs and type 2 diabetes (T2DM). Along with obesity, the prevalence of MetS in prepubertal children and adolescents is alarmingly increasing [20, 42] and young children and adolescents can be manifested with the same biochemical alterations as adults undergoing the MetS [43, 44]. However, adult criteria should not be simply used in children to define this condition. Indeed, to this date it is controversial and there is no unified definition of MetS in children and adolescents [45], although the international diabetes federation consensus of the MetS in children and adolescents is the most commonly used definition [46]. According to the definition [46], WC measurement is the main

component as it is an independent predictor of insulin resistance, lipid levels and blood pressure [47]. Besides, in children and adolescents with obesity and similar BMI, those with higher amount of visceral adipose tissue have lower insulin sensitivity [48]. Some authors suggest including other components related to insulin resistance as HOMA-IR or QUICKI to give a more adjusted definition for MetS in children [49].

Moreover, the presence of abdominal fat negatively affects the lipid profile, and this has been also observed in adolescents [50]. The atherogenic index of plasma [AIP), triglycerides (TG)/HDL-C ratio is a novel index used in young patients to predict cardiometabolic complications in children with obesity [51]. High TG plasma levels themselves are markers for cardiometabolic risk and one of the most common lipid disorders observed in children and adolescents with obesity [52]. Similarly, apolipoproteins AI and B (ApoAI and ApoB), lipoprotein-associated phospholipase A_2 (Lp-PLA_2) and ApoB/ApoAI ratio have also been reported as useful tools to predict insulin resistance and cardiovascular disorders [53]. Increased ApoB/ApoA1 ratio and its association with elevated body weight, excess adiposity and an altered lipid profile has been reported in children [54].

As previously mentioned, men and women accumulate adipose tissue in a different manner and these dissimilarities may as well imply differences in the cardiometabolic complications associated with obesity and MetS. Different fat mass localization implies different adipose tissue metabolism and function, including variations in adipokine production, insulin sensitivity, mitochondrial function, fatty acid release and lipolysis, as well as the inflammatory profile [16]. Furthermore, it is known that energy balance, glucose and lipid metabolism are differently regulated during growth and in men and women, with epidemiological evidence supporting that men are more prone to develop obesity and diabetes. The protective action of estrogens in women which express estrogen receptors in different tissues including the brain, adipose tissue and pancreatic beta cells seems to be critical to explain the sex differences [55, 56].

Adolescents with obesity already show cardiometabolic disorders around the onset of puberty [31, 57]. Indeed, accumulation of adipose tissue leading to overweight and obesity around 7 years of age that persists until puberty is a risk factor for T2DM in midlife [58, 59]. The duration of obesity increases the risk of T2DM development [60]. Nonetheless, if body weight is reduced towards normal BMI values before the onset of puberty, the risk for cardiovascular and metabolic diseases later in life, can be significantly reduced [58, 61]. Even so, if obesity is started in the very early ages and maintained during childhood and adolescence, the risk for developing coronary heart disease is greatly increased [62]. The normalization of BMI before the onset of puberty is key, as it seems to reduce to a great extent the risk for MetS and their associated complications [58].

Thus, puberty is a key period to normalize body weight, as insulin sensitivity decreases and there are major metabolic and hormonal changes [63]. In healthy young patients, this nadir in insulin sensitivity is resolved when puberty is completed. However, if obesity persists, insulin resistance can become chronic, increasing the cardiometabolic risk in these patients [63].

Altered Secretion of Adipokines

There is a wide variety of adipokines secreted by adipose tissue that inform the brain about energy stores, regulating food intake and satiety. Adiponectin and leptin are the most widely studied, although resistin, vaspin and visfatin have also been considered. Their secretion and function may be affected in individuals with overweight or obesity, disrupting the overall metabolic control.

In individuals with obesity, adipokines are mediators of the observed cardiometabolic risks and other obesity associated disorders such as hypertriglyceridemia and insulin resistance. This has been observed even in prepubertal children, although studies in adolescents are more numerous [43, 64-66].

Adiponectin is a protective adipokine, as its high concentrations are associated with beneficial effects such as an anti-inflammatory activity in the adipose tissue [67]. Besides, it has been reported to increase insulin sensitivity and, thus, help regulate lipid and glucose metabolism [68, 69]. On the other hand, low concentrations of adiponectin have been associated with oxidative stress in adipose tissue [70]. An inverse association between adiponectin concentrations and MetS and cardiometabolic parameters was shown in adolescents, indicating a potential role of adiponectin in the early development of MetS and other cardiometabolic complications [71, 72]. In addition to being a biomarker for MetS, adiponectin may also be indicative of inflammatory processes, as adiponectin concentrations have been inversely related to C-reactive protein concentrations (CRP) [73].

Plasma leptin concentrations are directly associated with fat stores, as this proteohormone is secreted from the adipose tissue to the bloodstream in proportion to the amount of adipose tissue. Leptin acts as a potent satiety signal, increasing with overfeeding and decreasing in starvation states [74, 75]. However, in addition to food intake and BMI, leptin concentrations also vary according to sex, age and circadian rhythms [76-78]. Individuals with obesity usually have high leptin concentrations, implying leptin resistance [79, 80]. In addition, obesity has been associated with a reduced leptin transport across the blood brain barrier, which could also contribute to the leptin resistance [81]. Leptin resistance is frequently associated with insulin resistance and adiposity, especially with visceral fat mass, being a risk factor for the MetS and other cardiovascular complications in children and adolescents [65, 66, 82]. In fact, leptin has been used as an efficient treatment in obese leptin deficient patients to reduce the amount of adipose tissue [83, 84].

Regarding the relationship between leptin and adiponectin, in spite of the many studies which have shown decreased levels of adiponectin and increased levels of leptin in children with obesity, their co-dependency is not well understood [85]. High leptin to adiponectin ratio is also a predictive value for obesity and an adverse metabolic profile in children that seems to be sex-specific [86]. Both adipokines, leptin and adiponectin, have been shown to be good biomarkers of future cardiometabolic risk, and have been found to be associated with adiposity biomarkers such as BMI and WHR, both in children and adolescents with obesity [85, 86]. High leptin levels along with elevated circulating triglycerides in children with obesity are associated with BMI, WC and WHR [87].

Other adipokines such as visfatin, vaspin and resistin have also been considered. In children with obesity, visfatin shows a positive association with insulin resistance and MetS and vaspin plasma concentrations are also increased in children with obesity; moreover, both adipokines are strong predictors of the inflammatory biomarkers tumour necrosis factor alpha (TNF-α) and interleukin 6 (IL-6) [88, 89]. Along with high leptin and low adiponectin plasma levels, higher serum resistin levels have been observed in metabolically unhealthy prepubertal children [90] and associated with MetS and early atherosclerosis in children with obesity [91].

Adipose Tissue Dysfunction

As already mentioned, adipose tissue is an active endocrine organ that releases a variety of cytokines (adipocytokines) which secretion can be altered due to different factors such as overweight or obesity. Dysfunction of adipose tissue in obesity includes impairment of TG storage and release of fatty acids to the bloodstream, perpetuating the obesity state and mediating obesity associated complications. Besides, the expansion of adipose tissue fat mass implies changes in the cytokine secretion profile from AT as well as increased turnover of free fatty acids which facilitate insulin resistance. Furthermore, it is not only the amount of AT, but also, the distribution of fat mass and its ectopic accumulation in organs or tissues which are key for insulin sensitivity [92].

Visceral adipose tissue (VAT), rather than subcutaneous adipose tissue (SCAT) is the responsible of the cardiovascular metabolic diseases [28]. Also visceral fat accumulation in adults and adolescents has been associated with a greater degree of insulin resistance [93]. Two types of VAT have shown associations with CVDs in children: the epicardial adipose tissue (EAT), localized between pericardium and myocardium [94] and the pericardial adipose tissue (PAT), between the kidney capsule and the renal fascia [95]. Both EAT and PAT are risk factors for CVDs development.

Metabolic alterations in AT also include an increased insulin secretion. Indeed, visceral adipose tissue is the one involved in the secretion of pro-inflammatory cytokines, that act local and systemically and it is associated with the metabolic complications of obesity such as T2DM. As is has been showed, obesity has also been associated with an inflammatory status in children and adolescents [96-100]. Low-grade inflammation linked to obesity is due in part to the abnormal accumulation of lipids in adipose tissue that leads to the production of pro-inflammatory cytokines including TNF-α, IL-6, IL-1β, IL-8, IL-1receptor antagonist. The relationship between inflammation and weight status in children has also been reported through CRP [101], as children with high levels of CRP present higher indices of central adiposity.

In addition to TNF-α, IL-6 and CRP, increased levels of the biomarker plasminogen activator inhibitor type 1 (PAI-1) have been observed in children with obesity and are proposed as risk factors for the development of CVDs [102].

Myeloperoxidase is also a biomarker of inflammation and cardiovascular risk in prepubertal children with obesity [102] and it is positively associated with CRP, HOMA-IR and resistin. Moreover, S100 Calcium binding protein A4 (S100A4) is also a novel marker for insulin resistance and dysfunction of adipose tissue in prepubertal and pubertal children with obesity [103].

As obesity is characterised by increasing levels of leptin and, at the same time, a drop-in adiponectin levels, the previously described leptin/adiponectin ratio is used a as a marker of dysfunction of adipose tissue, which leads to inflammation and oxidative stress. Therefore adiponectin/leptin ratio may be also used as an indicator of cardiometabolic risk associated to AT dysfunction [104, 105]

It should be mentioned that ectopic fat accumulation (especially hepatic fat accumulation, hepatic steatosis as a component of MetS) may also play a role determining the cardiometabolic risk via insulin resistance and adipose tissue inflammation [99].

Novel Markers: Circulating miRNAs as Prognostic Biomarkers for Cardiometabolic Complications

MicroRNAs (miRNAs) are short non-coding RNAs, representing a significant proportion of the human genome. They are involved in the fine control of gene expression. Thousands of different miRNAs have been described in humans so far and nowadays it is known that miRNAs play important roles in maintaining cellular homeostasis and functions [106].

In the past recent years, these set of nucleotides have contributed to identify epigenetic mechanisms related to obesity and its comorbidities. In this line, miRNAs related with preadipocyte proliferation, insulin secretion by pancreatic β-cell, and glucose uptake by skeletal muscle cells have been identified in children with obesity [107]. Thus, non-coding RNAs in children with obesity are potential biomarkers for T2DM [108] development in the future, support clinicians to identify patients at higher cardiometabolic risk and thus, establish preventive measures.

CARDIOVASCULAR COMPLICATIONS

Haemodynamics

As previously mentioned, obesity is an anabolic state characterized by an increase in adipose tissue fat mass and its derived metabolic alterations. The whole body adapts to the excess adiposity to maintain homeostasis [109], and the circulatory system is one of the most affected by this adaptation. The increase in fat mass predisposes children with overweight/obesity to a high preload and afterload state [110]. In individuals with obesity, there is an increase in blood volume, stroke volume, arterial pressure and cardiac output [111]. Moreover, young people may already have an increase in heart mass depending of their degree of obesity [112] (Figure **2**).

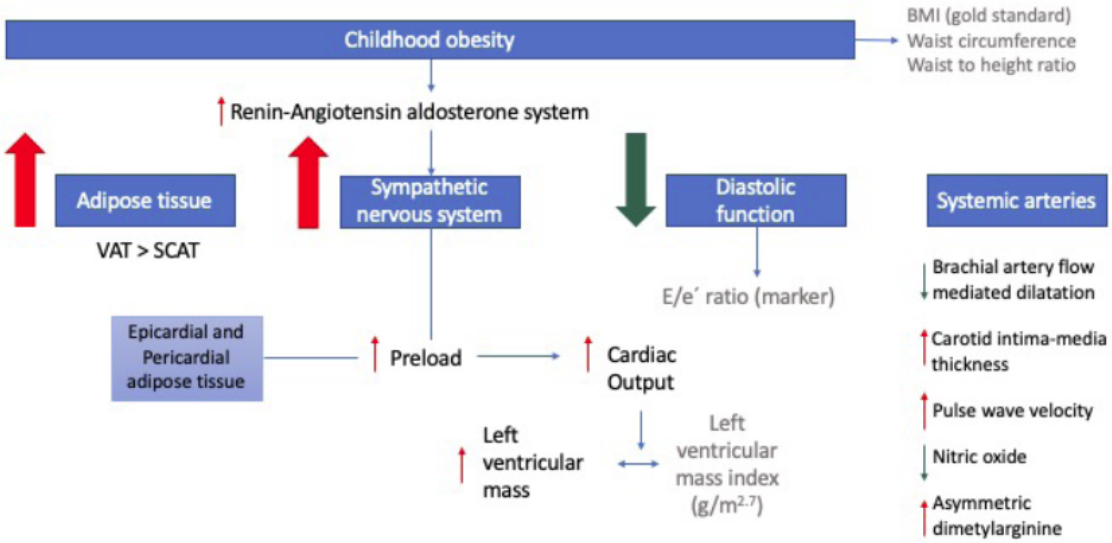

Figure 2: Cardiovascular complications in children and adolescents with obesity. Childhood obesity implies an increase in adipose tissue and sympathetic nervous system, this triggers an increase in the left ventricle mass. In addition, childhood obesity decreases diastolic function and generates alteration in the Systemic arteries.

Figure legend: BMI: Body mass index, SCAT: Subcutaneous adipose tissue, VAT: visceral adipose tissue.

Cardiac or Vascular Structure

Left Ventricle

Left ventricular mass (LVM) increases with age and the most commonly used clinical index is the left ventricular mass index (LVMI) [113], which is calculated from LVM divided by height raised to 2.7 ($g/m^{2.7}$) [114]. In adults, BMI has been observed to be associated with LVM and this association seems to start in early adolescence [115]. Indeed, along with the increase of obesity in the last decades, an increase in LVM has also been found [116]. This is also true for children with obesity, who show a LVM around 4 times higher than the normal cut-off point for their age, weight and sex reference [117]. Other characteristics such as uric acid and birth weight were found to be good predictors for LVMI [118]. Moreover, adults with an excess of LVM have a reduced LV systolic function and myocardial performance [117].

Another useful parameter to obtain information about cardiac structure is relative wall thickness, which gives information about LV geometry [119]. Children with overweight/obesity go through left ventricular remodeling and an increase in LV wall stress [111]. LV remodeling leads to different types of geometry: eccentric hypertrophy with high LVMI and normal relative wall thickness; concentric hypertrophy with elevated LVMI and relative wall thickness; and concentric remodeling with normal LVMI and increased relative wall thickness [119]. This changes occur independently of the existence or not of hypertension and may influence the development of CVDs [120]. However, it should be taken into account that eccentric hypertrophy appears in 30 % of children in the US with obesity showing normal levels of blood pressure [116]. On the contrary, another study with a high percentage of African and American youth found a higher incidence of LV concentric hypertrophy in children with obesity and hypertension than in children with obesity alone. Whereas these difference did not appear in concentric remodeling [121], although concentric hypertrophy is the type of remodeling most related with mortality in adults [122]. The best predictor of both concentric remodeling and concentric hypertrophy is obesity. Additionally, it should be noted that systolic and diastolic blood pressure should also be taken into account as concentric hypertrophy mediators [121]. Other study showed that the increase in LV mass leads to eccentric hypertrophy in children with obesity but without hypertension, concluding that relative wall thickness could be a late parameter in the cardiac changes in children with obesity [123].

Left ventricular hypertrophy (LVH) is a marker of organ damage and its presence can only be observed by echocardiography [124]. As hypertension, its presence does not always coincide with any symptoms and it is usually underdiagnosed. Both hypertension and obesity are independently associated to LVH. Anatomic changes in the left ventricle have been shown in children and adolescents before the development of hypertension [123]. One study found a 35% of primary hypertension in participants with obesity and 41% of the participants with essential hypertension showed LVH, concluding that echocardiography should be a common practice in children with newly-diagnosed hypertension [125]. Early detection of LVH could prevent from future cardiovascular problems [123].

Finally, it should be mentioned that three-dimensional (3D) speckle tracking echocardiography is a new tool with a significant role in the prevention of myocardial alterations. Left ventricular ejection function (LVEF) had been used as a parameter for the assessment of systolic function. However, is not useful for an early dysfunction assessment [126]. Indeed, children with overweight/obesity have shown a preserved function of LVEF, whereas a decreased LV strain have been observed [120]. This suggests that 3D strain variables could be useful for the assessment of early alterations in cardiac function and the prevention of future mortality.

Right Ventricle

Although most studies have focused on the structural changes of the LV, a few authors have studied the association between obesity and the right ventricle (RV) [127, 128]. A study in children showed a positive correlation between LV strain and RV strain, indicating an association between the abnormalities in both left and right ventricles [128]. Another study done in children with obesity and without other comorbidity showed that children with obesity had a significant reduction of systolic myocardial deformation, both in LV and RV [127]. However, other studies did not find changes in RV function. Cardiac magnetic resonance (CMR) is the gold standard for the assessment of RV function but, until now, it has only been used in research studies [128].

Cardiac Function

The echocardiography is a noninvasive method widely used in the assessment of cardiovascular function. This technique allows for the identification of

two possible types of cardiac dysfunction: systolic dysfunction and diastolic dysfunction. Systolic dysfunction is easily determined from the ejection fraction. However, diastolic dysfunction is more difficult to diagnose. For this reason, several characteristics are measured to evaluate the diastolic function. The first characteristics are weak E and A, which are the two phases of left ventricle filling in early and late diastole, respectively. The other parameter is used to measure the distance from the mitral annulus to the base during early diastole (e`). Moreover, the E/A fraction is obtained to assess the relaxation of the ventricle and the E/e´ ratio is used to estimate the left ventricular filling pressure [129].

Other techniques have been proposed for the assessment of cardiac function. Cardiac magnetic resonance (CMR) is used for the evaluation of systolic function, but with increasing interest in its use to assess diastolic function. CMR has advantages over echocardiography due to its high spatial resolution, which can measure left atrial size and trans-mitral flow [130]. However, its costs outweigh the benefits. Another technique is echocardiographic strain rate imaging, which is based on the deformity of the cardiac muscle during the contraction and relaxation processes [131]. This technique is not yet used in the classification of diastolic dysfunction because it is believed that restoring forces and early diastolic load also influence in ventricular relaxation [132].

In children and adolescents, a positive association has been found between obesity and diastolic dysfunction. Being the group of patients with obesity those with the reduced diastolic function. [133]. In addition, Porcar-Almela *et al.* proposed the E/e´ ratio as the most valid marker of diastolic dysfunction in children with obesity [134].

Systemic Arteries

Endothelial Function

An adequate vascular endothelial function is determinant to avoid the development of atherosclerosis [135]. However, although clinical manifestations of CVDs take many years to appear [136], an accelerated atherosclerosis has been observed in youth with obesity [137].

The most widely used parameter to determine endothelial dysfunction is the brachial artery flow mediated dilation (FMD) [138, 139]. Several studies have shown a lower FMD in children with obesity compared with children with normal weight [140-143]. Whereas other have not observed any differences [144, 145]. Lo *et al*., found a reduced FMD with the increase of age in adolescents with obesity from 14 years [146]. One meta-analysis found that FMD is an indicator of special importance in children at low risk of CVD. Because children with advanced cardiovascular risk factors have dysfunction of NO metabolism and stiffness of the vessels [147].

Arterial Stiffness

Another risk factor associated with CVDs in adults is vascular stiffness [148]. A study in adults with and without vascular disease showed that an elastic vascular system was associated with a decrease in atherosclerotic progression [149]. It also reduces the cardiac demand of the hearth and increases coronary artery perfusion [150]. The most widely used variable to assess arterial stiffness is central pulse wave velocity (PWV) [151]. PWV measures the velocity of the pulse wave, created in systole, while it is propagated across the arterial tree. There are different methods for PWV, being carotid-femoral PWV (cfPWV) the gold standard [152]. Children with obesity have shown an increase in arterial stiffness at the carotid artery [153, 154] and in central measures of PWV. In contrast, Lo *et al*. did not find an association between PWV and adiposity *per se*, but a higher arterial stiffness in hypertensive children with increased adiposity [146]. A systematic review which aim was to describe the normal progression of cfPWV and its association with other cardiometabolic risk factors showed that arterial stiffness increased 0,12 m/second per year in children, with no differences between sex [155] . Moreover, a positive association was found between BP and impaired glucose metabolism and PWV. However, they mentioned the need of more longitudinal studies to confirm their affirmations [155]. In addition, a positive correlation between hypertension and PWV was also observed in another study in children [152].

Endothelial Vasodilatory Response

NO (nitric oxide) is a molecule with a vasodilatation effect, and it is produced in the endothelium by the NO synthase during the transformation of L-arginine into citrulline [156, 157]. In addition to the previously mentioned parameters, the bioavailability or not of NO, the increase of asymmetric dimethylarginine (ADMA) and the L-arginine/ADMA ratio [AAR) have been studied as predictors of endothelial function [158]. Children with high BMI showed a reduction in NO serum levels and an increase in ADMA compared with children with normal weight [159]. Lo *et al.* observed higher levels of ADMA and AAR in hypertensive

children with obesity, although without statistical significance [146].

Arterial Thickness

Carotid intima-media thickness (cIMT) is a non-invasive technique that allows clinicians to diagnose subclinical atherosclerosis [160]. However, although there are discrepancies among the different expert committees on the adequacy of the use of this technique, the Association for European Paediatric Cardiology (AEPC) recommends the measurement of cIMT [152]. Indeed, cIMT has been associated with CV risk factors and could predict the possibility of future cardio-cerebrovascular disease (35). Based on different children cohorts followed up until adulthood, they observed that cardiovascular risk factors in children above 9 years of age are associated with IMT and its consequent impact on adulthood. While the cardiovascular risks observed in children below 9 years did not show such association [161]. A systematic review done in showed an increase in cIMT in children and adolescents with overweight or obesity compared with their normal weight peers [162]. One study in children showed a positive correlation between EAT and cIMT [28]. Another cross-sectional study in adolescents found a positive association between cIMT and truncal fat. The cIMT of a subgroup of these adolescents also showed a positive association with soluble intercellular adhesion molecule 1 [163]. Other authors have observed that in prepuberal children EAT and PAT are better predictors of cIMT than BMI [164]. Similarly, another study found that HOMA-IR and QUICKI, markers of insulin resistance, are independent predictors of cIMT in boys with overweight and obesity, but not in girls. This differences also occur in adulthood, in which cardiovascular events in men occur years before than in women [165].

High blood pressure, one of the previously mentioned cardiovascular risk factors, has also been observed as a good parameter to identify children with impaired cIMT [161]. Hypertension has shown a linear relationship with cIMT in children and adolescents independently of other confounders [166]. One study in healthy adolescents showed a positive correlation between the levels of blood pressure (BP) and IMT [167], while others have observed a stronger relationship according to the degree of hypertension [168]. Independently of obesity, Lande *et al.* also found a strong positive correlation between systolic blood pressure levels during daytime, measured with ambulatory BP monitoring, and cIMT in children [169]. Also, another study using 24-hour ambulatory BP monitoring in youth with type 1 diabetes mellitus observed higher IMT in patients with a reduced nocturnal dipping [170] .

Finally, cIMT has also been associated with other parameters such as LVH, taking into account age, sex or BMI as confounders [171]. Páll *et al.*, showed a higher cIMT in adolescents with white-coat hypertension and sustained hypertension. However, only the group of sustained hypertension showed a significant increase in LVMI [172].

Autonomic Nervous System

The autonomic nervous system (ANS) modulates cardiovascular function through the sympathetic nervous system (SNS) and the parasympathetic nervous system (PSNS). And there is a dynamic balance between SNS and PSNS called “sympathovagal balance” [173]. The sum of ANS, SNS and PSNS is the cardiac autonomic modulation (CAM) [174]. Heart Rate Variability (HRV) is a non-invasive method for the assessment of CAM, and there are two ways to obtain information [175]. One is a time domain, with two indexes: SDNN, the standard deviation of all RR intervals, which is a marker of sympathetic activity and RMSSD, the square root of the mean of the sum of the squares of the differences between adjacent RR intervals, which indicates parasympathetic activity [176]. The second is a frequency domain, from which 3 parameters are used: Power low frequency (LF) affected by PSNS and SNS [177], power high frequency (HF), which is a marker of parasympathetic activity [178] and LF/HF ratio, that is the parameter to measure the sympathovagal balance [179]. In addition, the baroreflex has also been used as an indicator of CAM [174].

The impairment in fat storage present in children and adults with obesity implies a high blood flow demand [180]. Moreover, the increase in adipose tissue is associated with an extra activation of renin-angiotensin aldosterone system, which leads to an increased activation of the SNS with a consequent enhancement of systemic vascular resistance that is traduced in a higher intravascular volume. This cascade of events produces an increase in ventricular preload [181] which, as mentioned before, implies an increase in LVM with an impairment of cardiac functions [180].

Due to the changes in the cardiac structure of patients with obesity, an impairment of CAM has also been observed [174]. In adults, CAM impairment has

been associated with an increase in mortality and its early detection is suggested by clinicians as a good tool for the prevention of CVDs [180]. Recently, in children with obesity a reduction in parasympathetic activity and an increase in sympathetic activity have been observed [182-187]. Also, a rise in LF/HF ratio was found in children with obesity [182-185]. A case-control study in children showed that those with obesity had a lower HF, SDNN, RMSSD and higher LF and LF/HF ratio than children with normal weight [183]. Similarly, another case-control study that compared children with obesity and with normal weight showed an increase in LF and LF/HF ratio and a decrease in HF in children with obesity [186]. Regarding the baroreflex, an inverse association between baroreflex and childhood obesity was also found [188-190]. In adolescents with obesity, the same results have been obtained [191]. Finally, other cardiovascular risk factors, such as blood pressure have been shown to be associated with CAM [174]. The highest blood pressure levels were associated with a reduction in HF and a positive balance in the "sympathovagal balance" (LF/HF) both in children and adults between 18 and 21 [192, 193].

CONCLUSIONS

Obesity in children and adolescents is associated with several metabolic, physiologic and anatomic complications. However, there are more contributing factors for CVDs risk, such as sex, hypertension and insulin resistance, which support that obesity should not be considered independently. Anthropometric, clinical, biochemical and cardiovascular parameters, as well as atherogenic indices, are key for the early diagnosis of potential cardiovascular and cardiometabolic risk in children and adolescents with obesity.

Research focusing on finding biological markers for early detection of children with increased cardiovascular and cardiometabolic risk is key for preventing obesity related complications and the tracking of obesity into adulthood. In addition, more longitudinal studies should be carried out starting in childhood and continuing into adult life in order to understand the relevant developmental changes and their consequences along the complete lifespan.

Preventing the development and maintenance of overweight and obesity is the best strategy to face the appearance of CVDs. Policies to promote healthy lifestyle habits as early as possible in life through physical activity and a balanced diet will be critical to minimize the future effects on cardiovascular risk factors. Moreover, more research focused on sex specific differences in energy balance and glucose metabolism is a priority to manage individual approaches in obesity and T2DM prevention and treatment.

Finally, there is nowadays a need to mention the influence of the health crisis we are facing due to Coronavirus disease (COVID-19), which will undoubtedly bring associated health consequences related to overweight and obesity in children and adolescents. Social isolation and outside activities reduction lead to increase fat accumulation, along with psychological disorders that may impair the overall situation. Moreover, according to the available data, it has been observed that patients with obesity are at higher risk for developing COVID-19 [194], due in part to impaired metabolic health or inflammatory states undergoing in patients with obesity.

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Received on 6-10-2020 Accepted on 11-11-2020 Published on 09-12-2020

DOI: https://doi.org/10.12974/2311-8687.2020.08.8