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Treatment of Metabolic Syndrome in Children

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Keywords
Metabolic syndrome · Insulin resistance · Hypertension · Fatty liver disease · Children

Abstract
Although metabolic syndrome (MetS) in children and adolescents is a frequently discussed topic in the literature, uniform guidelines on its definition and treatment are still lacking. Insulin resistance, central obesity, dyslipidaemia, and hypertension are commonly considered the main components of MetS. The first recommended approach to all these pathological conditions in children and adolescents is lifestyle intervention (diet and physical exercise); however, in some selected cases, a pharmacological or surgical treatment might prove useful for the prevention of metabolic and cardiovascular complications. The aim of this review is to present the more recent evidence about the treatment of the major components of MetS in children and adolescents, focussing on the current recommendations concerning lifestyle changes, available drugs, and bariatric surgery.

Introduction

Although >40 definitions of metabolic syndrome (MetS) in children and adolescents have been suggested in the literature, its diagnostic criteria have not been standardized yet [1]. The American Heart Association (AHA) did not provide a definition of MetS for children, underlying the limitations of adapting the adult definition to paediatric population [2]. The International Diabetes Federation (IDF) proposed a consensus definition which was appliable only to children aged 10–16 years, defining abdominal obesity as a value of waist circumference >90th percentile, while for children older than 16 years adult criteria were adopted [3]. The more recent definition of paediatric MetS has been provided by the Identification and prevention of Dietary- and lifestyle-induced health EFfects In Children and infantS (IDEFICS) consortium, suggesting the use of percentiles for each diagnostic criterion and differentiating cutoffs for close monitoring or intervention [4]. Table 1 summarizes some of the most common definitions of MetS proposed by different authors in recent literature [3–6].

Regardless of the definition used, the prevalence of MetS is increased in the last decade, in accordance with the trend of obesity, in children and adolescents. However, Reinehr et al. [7] conducted a study on a population of 1,205 Caucasian overweight children and adolescents aged 4–16 years using 8 proposed definitions of MetS and revealed that the prevalence of MetS was widely variable (between 6 and 39%) depending on the different definitions.

In summary, most authors consider insulin resistance (IR), central obesity, hypertension, and dyslipidaemia as major components of MetS. However, non-alcoholic fat-

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Table 1. Diagnostic criteria of MetS in children and adolescents according to different definitions

Cook et al. [5]	Viner et al. [6]	IDF [3]	IDEFICS [4]
≥3 of the 5 criteria below: – WC ≥90th percentile – BP ≥90th percentile – Triglycerides ≥110 mg/dL – HDL-chol ≤40 mg/dL – Impaired fasting glucose	≥3 of the 4 criteria below: – BMI ≥95th percentile – Systolic BP ≥95th percentile – 1 of the 3 criteria below: Triglycerides ≥150 mg/dL HDL-chol <35 mg/dL Total chol ≥95th percentile – 1 of the 3 criteria below: Impaired fasting glucose Impaired glucose tolerance Fasting insulin ≥15 mU/L pre-pubertal ≥30 mU/L pubertal ≥20 mU/L late/post-pubertal	Central obesity + ≥2 of the 4 criteria below: – WC ≥90th percentile in children 10–16 yr or >94 cm (male) or >80 cm (female) in children >16 yr – BP ≥130/85 mm Hg – Triglycerides ≥150 mg/dL or HDL-chol <40 mg/dL – Impaired fasting glucose	≥3 of the 4 criteria below: – WC ≥90th percentile (monitoring level) or ≥95th percentile (action level) – Systolic and/or diastolic BP ≥90th percentile (monitoring level) or ≥95th percentile (action level) – Triglycerides ≥90th percentile (monitoring level) or ≥95th percentile (action level) or HDL chol ≤10th percentile – HOMA-IR or fasting plasma glucose ≥90th percentile (monitoring level) or ≥95th percentile (action level)

MetS, metabolic syndrome; IDF, International Diabetes Federation; IDEFICS, Identification and prevention of Dietary- and lifestyle-induced health EFfects In Children and infantS; BP, blood pressure; chol, cholesterol; WC, waist circumference; HDL, high-density lipoprotein; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance.

ty liver disease (NAFLD), hyperuricaemia, and sleep disturbances are being recently considered as additional elements of MetS [8].

Although MetS is a well-known risk factor for the development of cardiovascular diseases (CVD) and type 2 diabetes mellitus (T2D) in adults, its diagnostic criteria seem not to have the same predictive value in childhood [9]. Furthermore, it has been observed that many individuals that meet the diagnostic criteria of MetS in children do not fall within its definition 3–6 years later [10, 11]. This might be due to many factors among which IR, which is one of its diagnostic criteria, is physiologically increased during puberty and resolves when puberty ends [12, 13]. Another limitation lies in the definition of IR itself. In fact, a valid test for its diagnosis in clinical practice is not available yet. In 2009, HbA1c was recommended as the parameter to be taken into consideration, defining pre-diabetes in asymptomatic individuals with HbA1c ≥6.0% (≥42 mmol/mol) and <6.5% (39 to <48 mmol/mol), not only for adults but also for adolescents [14]. Nevertheless, several studies showed that HbA1c had a very low predictive value, underestimating the prevalence of pre-diabetes in paediatric population. Furthermore, racial/ethnic disparities in the correlation between HbA1c and ambient blood glucose represent another limitation [15]. Thus, the fasting or random glucose or oral glucose tolerance test has been recently recommended as the complementary test for the detection of IR, accompanied by medical history, familial risk, race/ethnicity, and/or the presence of additional risk factors for diabetes. Even if some definitions of MetS suggest the use of the Homeostatic Model Assessment for IR (HOMA-IR) [4] for the detection of impaired insulin sensitivity (IS), this technique is not recommended by the Endocrine Society for Paediatric Diagnostic and Therapeutic Procedures [16]. The main limitations to the use of HOMA-IR are changes in β-cell function over time, lack of a standardized universal insulin assay, and lack of data demonstrating the efficacy of markers of IR to predict response to treatment [13].

Moreover, since most children and adolescents with MetS are obese, some authors have questioned the utility of the definition of MetS in children [9]. Nevertheless, it may represent an additional tool for the follow-up and treatment of obese patients if used with awareness of its limitations. Therefore, as recommended by the American Academy of Paediatrics (AAP), each component of MetS should be recognized as a cardiovascular risk factor and treated individually [9].

Currently, the only adopted treatment approaches, which are dietary modifications, increased physical activ-

ity, and behavioural changes, lead to positive outcomes only in cases of high adherence to intervention. Unfortunately, these recommendations are often difficult to achieve, especially for adolescents [17]. The aim of this review is to present the more recent evidence on treatment of IR, obesity, dyslipidaemia, hypertension, and NAFLD in children and adolescents, focussing on the current recommendations concerning lifestyle changes, available drugs, and bariatric surgery.

Lifestyle Intervention

Lifestyle intervention is the first step in the treatment of children with MetS. The amount of overweight reduction to achieve improvements has not been established yet. A prospective observational study conducted on 1,388 overweight children, with a mean age of 11.4 ± 0.1 years, showed that a BMI-SDS reduction of 0.25 or greater significantly improved hypertension, hypertriglyceridaemia, and low HDL cholesterol, whereas a BMI-SDS of >0.5 doubled the effect [18]. The Endocrine Society Clinical Practice Guidelines recommend a minimum of 20 min of moderate-to-vigorous physical activity (PA) daily, with a goal of 60 min and a maximum of 1-2 h per day of non-academic screen time in order to discourage sedentary behaviours [16].

PA is associated not only with weight loss but also with higher IS itself, independently from adiposity [19–23]. Although the preferable type of exercise for children and adolescents with MetS is unknown, a combination of low aerobic and resistance exercise has been suggested because this training programme seems to improve IS in overweight and obese children regardless of changes in body weight and percent body fat [24, 25]. Moreover, positive feedback from the visible strength gain could improve patients' self-esteem and compliance [26]. Any type of exercise, whether it is aerobic, resistance, or combined training, appears to be beneficial in lowering blood pressure (BP) too [27].

In addition to PA, sleeping habits can also affect weight and IS [28]. In fact, short sleep duration and obstructive sleep apnoea syndrome (OSAS) have been demonstrated to be associated with IR in obese children [29, 30].

The optimal nutritional management of MetS is still debated. Benefits from high-fibre intake due to their bulking effect of adding low-energy food to the diet, the slowing of gastric emptying and absorption of dietary carbohydrate and fat contents, increased satiety, effects on inflammatory markers, and gut hormones, have been highlighted by several studies. It has been associated with increased IS [31–34], lower odds of MetS in children and adolescents [33], improved body composition in children [35, 36], lower systolic BP, and fasting glycaemia [37]. On the other hand, high-fat intake has been shown to impair IS [38, 39] independently of body fat in adolescents [40]. Also, increased fat/carbohydrate ratio seems to be negatively correlated with IS and insulin clearance in pre-pubertal children [41]. Few studies conducted on adults suggest this association is independent from dietary fat quality [42].

High-glycaemic index food may increase risk for obesity, T2D, and CVD [43]. Data from studies about the effects of low-glycaemic-load diet (LGLD) on insulin-resistant patients are variable among children and adults. Some randomized controlled trials in overweight and obese adults showed significant advantage of LGLD in reducing IR, while others did not [44]. The AAP recommends adopting Dietary Approaches to Stop Hypertension (DASH), including a diet that is rich in fruits, vegetables, low-fat milk products, whole grains, fish, poultry, nuts, and lean red meats and poor in sugar, sweets, and sodium, for hypertensive children and adolescents [45].

Pharmacological Treatment

Obesity

In addition to the well-known lifestyle advices for obese children and adolescents, weight loss drugs may be helpful in selected situations. To date, orlistat, an intestinal lipase inhibitor able to reduce a weight of about 3% in a month, and phentermine, a sympathomimetic amine, are the only weight loss drugs approved by the FDA for adolescents aged ≥12 and ≥16 years, respectively. On the contrary, no drugs have been approved by the European Medicines Agency (EMA) for the treatment of obesity in children. The Endocrine Society Clinical Practice Guidelines recommend using FDA-approved medications for obesity only with a concomitant lifestyle modification program of the highest intensity and only if clinicians are experienced in the use of anti-obesity agents and aware of the potential for adverse reactions and discontinuing them if the patient does not achieve a >4% BMI/BMI *z*-score reduction after a 12-week lasting treatment at the medication full dosage [16]. The common adverse drug reactions of orlistat are steatorrhoea and flatulence, which are poorly tolerated [9, 46], while dizziness, headache, heart palpitations, diarrhoea, or constipation are the most common side effects of phentermine in adults [47].

Topiramate and zonisamide are 2 anti-convulsant medications. Topiramate is approved for the treatment of epilepsy in patients as young as 2 years old [48], while zonisamide is not currently FDA approved in the United States for use in children, but clinical trials have shown its efficacy and safety [48].

It has been widely demonstrated that adults treated with topiramate or zonisamide commonly experience weight loss [49–51]. However, few and variable data are available about their effects on weight in paediatric population. Shapiro et al. [48] conducted a preliminary investigation into the effectiveness of these 2 drugs in reducing weight in a paediatric sample seeking treatment at a psychiatric clinic and reported statistically significant weight reduction with both topiramate and zonisamide, with no significant difference between the two. Minimal side effects are reported in the literature for these 2 drugs: for zonisamide (the least tolerated of the two), the most common adverse reactions, which are dose and titration dependent in most patients and less common in children, include sleepiness, cognitive impairment, and dizziness. More specific to children and adolescents is oligohydrosis [48].

In addition to the previously listed medications, fluoxetine and other selective serotonin reuptake inhibitors (SSRIs) have shown efficacy in inducing loss of weight in obese adults over the short term, but these effects are lost over the longer term and the degree of initial weight loss seems to inversely correlate with the degree of subsequent weight regain [52]. This is probably due to physiological compensatory changes in hormones involved in the gut-brain axis; a similar effect has also been observed in adolescents [53].

Insulin Resistance and Obesity

A pharmacological intervention in obese children may be necessary in some cases, with the aim to improve the effects of lifestyle interventions on IR, although the use of drugs would be off-label since no medications have been approved for the treatment of IR in children yet (Table 2). Metformin may represent the first-line pharmacological approach. It is an oral glucose-lowering agent, being part of biguanides. It inhibits gluconeogenesis in the liver by blocking a mitochondrial redox shuttle [54, 55]. Furthermore, some studies have shown that it increases intestinal glucose uptake and the concentration in the gut lumen of glucagon-like peptide-1 (GLP-1), a hormone able to reduce the release of inflammatory cytokines and inhibit the infiltration of macrophages into the adipose tissue and the liver [56, 57]. At high concentrations, it also improves peripheral IS, although the mechanism of action is not entirely clear [58].

In adults with IR, metformin has been shown to reduce the risk of developing diabetes (7.2% absolute risk reduction; $p < 0.001$) and to induce modest weight loss [59]. It is approved by the US FDA for T2D in children aged ≥10 years, and it is the only treatment evaluated in clinical trials in children and adolescents with pre-diabetes, even if long-term and consistent data of its role in paediatrics are still missing [60]. Data on its effect on IS in children are scarce and controversial. Wiegand et al. [61] did not find statistically significant differences in HOMA-IR between obese adolescents treated with metformin (500 mg twice a day for 6 months) and obese adolescents receiving placebo, both in addition to lifestyle intervention. In contrast, in a randomized double-blind placebo-controlled trial conducted on 100 severely obese children with IR aged 6–12 years, metformin was demonstrated to modestly reduce body weight and adiposity, but to improve measures of glucose homeostasis. In fact, although a scarce weight loss was obtained, metformin resulted a promising method to prevent or delay the manifestation of impaired glucose homeostasis in children at high risk for the development of T2D [62]. There is also evidence that metformin improves IS in adolescents with T2D and polycystic ovary syndrome (PCOS) [17]. Common side effects, such as abdominal pain, nausea, metallic taste, bloating, and diarrhoea, can be prevented or substantially reduced by beginning with a dose of 500 mg/day, titrating up slowly, and using extended-release formulations [63]. The dose could be increased, as tolerated, to a total of 2,000 mg/day (or even more in some patients) in divided doses [64]. Although its safety and efficacy have been reported, further studies on its long-term benefits are needed and the 2017 Paediatric Obesity Clinical Guidelines from the Endocrine Society still suggest its use only in selected cases.

Among the potential pharmacological options for the treatment of IR and obesity, GLP-1 analogues, such as liraglutide, deserve consideration. In fact, thanks to their capability of interfering with inflammatory processes in the adipose and hepatic tissues, they could reduce IR, at the basis of whose pathogenesis lays inflammation [58]. Moreover, liraglutide increases the postprandial insulin level, reduces glucagon secretion, delays gastric emptying, and induces weight loss through reductions in appetite and energy intake [65, 66]. Since now, it has been approved by the FDA in addition to lifestyle intervention for the treatment of obese or overweight adults with at least one weight-related coexisting condition [67]. In a study

Table 2. Mechanism of action and common side effects of the main drugs potentially useful for the treatment of insulin resistance in children and adolescents

Drug	Mechanism of action	Common side effects (in adults)
Biguanide (e.g., metformin)	In the liver, it inhibits gluconeogenesis by blocking a mitochondrial redox shuttle At high concentrations, it improves peripheral insulin sensitivity (the mechanism is unknown)	Abdominal pain, nausea, metallic taste, bloating, and diarrhoea
Glucagon-like peptide-1 receptor agonist (e.g., liraglutide)	It interferes with the inflammatory processes by reducing the release of inflammatory cytokines and inhibiting the infiltration of macrophages into the adipose tissue, the liver, and the blood vessel wall It increases the post-prandial insulin level in a glucose-dependent manner, reduces glucagon secretion, delays gastric emptying, and induces weight loss through reductions in appetite and energy intake	Nausea, vomiting, diarrhoea, painful urination, headache, fever, sore throat, and cough
SGLT-2 inhibitor (e.g., sotagliflozin)	It inhibits the SGLT-2, which is in the kidney and is responsible for the reabsorption of 90% filtered glucose	Diarrhoea and genital mycotic infections
DPP4 inhibitor (e.g., sitagliptin and linagliptin)	It decreases the inhibition of endogenous incretins to induce the secretion of insulin in relation to glucose blood levels	Diarrhoea, stomach pain, upper respiratory infections, sore throat, and headache

Note that none of the medications listed has been approved for the treatment of insulin resistance in children yet. SGLT-2, sodium-glucose cotransporter type 2; DPP4, dipeptidyl-peptidase-4.

conducted on 21 obese adolescents from 12 to 17 years old, improvement of BMI z-score, body weight, fasting plasma glucose, HbA1c, and fasting serum insulin occurred, but none in a statistically significant manner, probably because of the short duration of the trial and small number of participants [68]. Kelly et al. [69], in a randomized, double-blind trial on 125 adolescents with obesity and a poor response to lifestyle therapy alone, demonstrated that liraglutide, administered with a dose of 3.0 mg daily in addition to lifestyle therapy, led to a significantly greater reduction in the BMI standard deviation score than placebo plus lifestyle therapy. In this study, no substantial difference between case and control groups was observed in terms of glycaemic and cardiometabolic variables. Both trials reported mild-to-moderate, mainly gastrointestinal, adverse effects [68, 69]. Clinical trials on wider populations are needed to confirm its efficacy in weight loss and to determine its role in the treatment of IR in children.

Sodium-glucose cotransporter type 2 (SGLT2) induces the reabsorption of 90% filtered glucose in the kidney [69]. Sotagliflozin, an oral SGLT2 inhibitor, has been demonstrated to improve glycaemic control with lower HbA1c in adults with type 1 and type 2 diabetes. However, data about the treatment of insulin-resistant adults and children are still insufficient [70]. Since these medications also lead to weight loss without causing hypoglycaemia, they have a similar effect to metformin. However, their efficacy has been demonstrated as an add-on therapy to metformin in patients with known CVD, while their role in drug-naïve or with low cardiovascular risk patients is still unknown and no studies about its effects on insulin-resistant children are available [71].

Dipeptidyl peptidase-4 (DPP4) inhibitors are involved in impairing the inhibition of endogenous incretins to induce the secretion of insulin in response to glycaemia, leading to improved fasting plasma glucose, postprandial glucose, and HbA1c level. This class of drugs, added to insulin, have been shown to decrease HbA1c levels with a minor weight gain and incidence of hypoglycaemia in adults with T2D. There is no evidence about its effect in children yet, but it may represent a valid alternative for the treatment of impaired IS in children [56].

Dyslipidaemia

In 2008, the AAP published its updated clinical report with prevention and treatment strategies for children and adolescents. They suggested adding pharmacological treatment to lifestyle modifications in patients aged 8 years or older with LDL cholesterol (LDL-C) ≥190 mg/dL, or with LDL-C ≥160 mg/dL in addition to a positive family history of premature CVD or presence of risk factors, or with LDL-C ≥130 mg/dL in addition to presence of diabetes mellitus. For children younger than 8 years, they suggested using medications just in case of LDL-C values ≥500 mg/dL [72]. In 2011, the National Heart Lung and Blood Institute (NHLBI) published its Guidelines for Cardiovascular Health and Risk Reduction in Children

Table 3. HMG-CoA reductase inhibitors: paediatric approvals and indications, recommended dosing ranges, and supporting clinical trials

Medication	Paediatric approvals and indications	Dosing	Comments	Supporting clinical trials
Atorvastatin	Age 10–17 yr Heterozygous familial hypercholesterolaemia	10–20 mg/d	May be titrated at ≥4-week intervals	McCrindle et al. [75]
Fluvastatin	Age 10–16 yr Heterozygous familial hypercholesterolaemia	20–80 mg/d	May be titrated at ≥6-week intervals	van der Graaf et al. [76]
Lovastatin	Age 10–17 yr Heterozygous familial hypercholesterolaemia	10–40 mg/d	Initiated at 20 mg/d for ≥20% LDL reduction, may be titrated at ≥4-week intervals	Clauss et al. [77] Lambert et al. [78] Stein et al. [79]
Pravastatin	Age 8–18 yr Heterozygous familial hypercholesterolaemia	20–40 mg/d	Age 8–13: 20 mg/d Age 14–18: 40 mg/d	Knipscheer et al. [80] Rodenburg et al. [81] Wiegman et al. [82]
Rosuvastatin	Age 10–17 yr Heterozygous familial hypercholesterolaemia	5–20 mg/d	May be titrated at ≥4-week intervals	Avis et al. [83]
Simvastatin	Age 10–17 yr Heterozygous familial hypercholesterolaemia	10–40 mg/d	May be titrated at ≥4-week intervals	de Jongh et al. [84] de Jongh et al. [85]

LDL, low-density lipoprotein.

and Adolescents, in which lifestyle intervention remained an integral part of treatment for paediatric lipid disorders; however, they recommend not to treat pharmacologically children younger than 10 years unless they have a severe primary hyperlipidaemia or a high-risk condition associated with severe medical morbidity (homozygous hypercholesterolaemia, LDL cholesterol level ≥400 mg/dL, primary hypertriglyceridaemia with a triglyceride level of ≥500 mg/dL, and evident CVD in the first 2 decades of life post-cardiac transplantation). Instead, the NHLBI suggests considering medications in a 10-year-old or older child in case of LDL cholesterol levels constantly higher than 190 mg/dL after a 6-month trial of lifestyle intervention [73]. Statins, HMG-CoA reductase inhibitors, are recommended as the first-line treatment of paediatric patients [74]. Table 3 summarizes recommended dosing ranges and supporting clinical trials for statins, which are FDA approved for children with heterozygous familial hypercholesterolaemia [75–78]. Statins presented variable efficacy in clinical trials in paediatrics. With the longest terminal half-life, rosuvastatin revealed to have the higher potency, followed by atorvastatin. Adverse effects are likely uncommon and mild, including headache, dizziness, myalgia, and gastrointestinal symptoms. It should also be reminded that as statins being a major substrate of CYP3A4, multiple drug interactions may occur [74, 75].

Hypertension

It has been widely demonstrated that currently recommended therapeutic schemes can even reverse target organ damage in youth with hypertension [86–88]. The AAP Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents, published in 2017, recommends starting with a single medication to treat children who remain hypertensive despite a trial of lifestyle modifications of at least 6 months, or who have symptomatic hypertension, or any stage of hypertension associated with type 1 diabetes mellitus or chronic kidney disease (CKD) [45].

Table 4 summarizes the age and dosing recommendations by the AAP guidelines, their contraindications, and adverse reactions. The AAP recommends starting a single pharmacological treatment with an angiotensin-converting enzyme (ACE) inhibitor, an angiotensin II receptor blocker (ARB), a long-acting calcium channel blocker, or

Table 4. Anti-hypertensive drugs: age and dosing recommendations, contraindications, and adverse drug reactions

Drug	Age	Initial dose	Maximal dose	Dosing interval	Contraindications and adverse drug reactions
ACE inhibitors					
Benazepril	≥6 yr	0.2 mg/kg per d (up to 10 mg/d)	0.6 mg/kg per d (up to 40 mg/d)	1/day	**Contraindications:** pregnancy and angio-oedema **Common ADR:** cough, headache, dizziness, and asthenia **Severe ADR:** hyperkalemia, acute kidney injury, angio-oedema, and foetal toxicity
Captopril	Infants	0.05 mg/kg per dose	6 mg/kg per dose	1–4/day	
	Children	0.5 mg/kg per dose	6 mg/kg per dose	3/day	
Enalapril	≥1 month	0.08 mg/kg per d (up to 10 mg/d)	0.6 mg/kg per d (up to 40 mg/d)	1-2/day	
Fosinopril	≥6 yr				
	<50 kg	0.1 mg/kg per d (up to 5 mg per d)	40 mg per d	1/day	
	≥50 kg	5 mg per d	40 mg per d		
Lisinopril	≥6 yr	0.07 mg/kg per d (up to 10 mg/d)	0.6 mg/kg per d (up to 40 mg/d)	1/day	
Ramipril	–	1.6 mg/m^2 per d	6 mg/m^2 per d	1/day	
Quinapril	–	5 m per d	80 mg per d	1/day	
ARBs					
Candesartan	1–5 yr	0.02 mg/kg per d (up to 4 mg/d)	0.4 mg/kg per d (up to 16 mg/d)	1-2/day	**Contraindications:** pregnancy **Common ADR:** headache and dizziness **Severe ADR:** hyperkalemia, acute kidney injury, and foetal toxicity
	≥6 yr				
	<50 kg	4 mg per d	16 mg per d		
	≥50 kg	8 mg per d	32 mg per d		
Irbesartan	6–12 yr	75 mg per d	150 mg per d	1/day	
	≥13 yr	150 mg per d	300 mg per d		
Losartan	≥6 yr	0.7 mg/kg (up to 50 mg)	1.4 mg/kg (up to 100 mg)	1/day	
Olmesartan	≥6 yr			1/day	
	<35 kg	10 mg	20 mg		
	≥35 kg	20 mg	40 mg		
Valsartan	≥6 yr	1.3 mg/kg (up to 40 mg)	2.7 mg/kg (up to 160 mg)	1/day	
Thiazide diuretics					
Chlorthalidone	Child	0.3 mg/kg	2 mg/kg per d (50 mg)	1/day	**Contraindications:** anuria **Common ADR:** hypokalemia and dizziness **Severe ADR:** dysrhythmias, cholestatic jaundice, new onset diabetes mellitus, and pancreatitis
Chlorothiazide	Child	10 mg/kg per d	20 mg/kg per d (up to 375 mg/d)	1-2/day	
Hydrochlorothiazide	Child	1 mg/kg per d	2 mg/kg per d (up to 37.5 mg/d)	1-2/day	
CCBs					
Amlodipine	1–5 yr	0.1 mg/kg	0.6 mg/kg (up to 5 mg per d)	1/day	**Contraindications:** hypersensitivity to CCBs **Common ADR:** flushing, peripheral oedema, and dizziness **Severe ADR:** angio-oedema
	≥6 yr	2.5 mg	10 mg		
Felodipine	≥6 yr	2.5 mg	10 mg	1/day	
Isradipine	Child	0.05–0.1 mg/kg	0.6 mg/kg (up to 10 mg per d)	Capsule: 2-3/d Extended-release tablet: 1/day	

ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; CCBs, calcium channel blockers.

a thiazide diuretic. Since Afro-Americans usually present a weaker response to ACE inhibitors, a higher initial dose for the ACE inhibitor or beginning with a thiazide diuretic or a long-acting calcium channel blocker may be considered [45]. The dose of the first-line drug should be titrated every 2–4 weeks, with a close monitoring, until BP <90th percentile is achieved, the maximal dose is reached, or the patient experiences side effects. A combination agent can be considered in case of poor control of BP with the initial drug at its maximum dosage or once BP control has been achieved with the first product, in order to improve adherence and reduce costs. Because of the salt and water retention that many anti-hypertensive medications induce, a thiazide diuretic usually is the most appropriate add-on drug. In children with hypertension and CKD, proteinuria, or diabetes mellitus, an ACE inhibitor or ARB is recommended as the first-line antihypertensive medication unless there is an absolute contraindication [45].

Non-Alcoholic Fatty Liver Disease

Even though NAFLD is not yet included in the current definition of MetS, it is well known to be its frequent hepatic manifestation [89]. No pharmacological treatment is recommended in addition to lifestyle intervention for the treatment of paediatric NAFLD; however, several studies are currently focussed on the research of appropriate medications and integrators. Metformin has proven to be very useful in reducing serum alanine aminotransferase (ALT) levels and inducing improvements in the histological pattern and in IS in some studies [90–93], but no statistically significant results have been shown in others [92–94].

Outcomes of studies conducted on the effects of antioxidant vitamins (vitamin E and vitamin C) on NAFLD in adults are disappointing. In a meta-analysis evaluating their efficacy in children [95], only 2 trials assessing vitamin E efficiency in reducing hepatocyte ballooning were identified and their results were contradictory [94, 96].

Regarding N-3 polyunsaturated fatty acids, a randomized controlled trial revealed statistically significant reduction in liver fat content at ultrasonography (US) and IR in children treated with docosahexaenoic acid (DHA) in combination to lifestyle intervention [97]. Moreover, Alisi et al. [98] demonstrated significant improvement of NAFLD Activity Score, ALT, and HOMA-IR and reduced activation of hepatic stellate cells in obese children with biopsy-proven NAFLD and vitamin D deficiency treated with DHA and vitamin D. The effects of some probiotics (*Lactobacillus* GG and VSL-3) on paediatric NAFLD were examined in small-population and short-term studies with promising results in US observation and improvement of serum ALT [99]; however, available data are still insufficient.

Surgical Treatment

The American Society for Metabolic and Bariatric Surgery (ASMBS) Paediatric Committee guidelines have recently suggested the new indications and controindications for bariatric surgery in paediatric age. They advise to consider surgical intervention in adolescents, defined as any person between 10 and 19 years old, with a BMI of ≥35 kg/m^2 only in presence of severe comorbidity, such as T2D, OSAS, benign intracranial hypertension, or non-alcoholic steatohepatitis. They also indicate adolescents with a BMI of ≥40 kg/m^2 and less severe comorbidities as potential candidates. An evaluation by a multidisciplinary team is also recommended to establish whether the patient and his/her family have the ability and motivation to adhere to recommended treatments pre- and post-operatively, including consistent use of micronutrient supplements [100].

Currently, vertical sleeve gastrectomy is the first-choice technique in both adults and adolescents because of its relatively technical simplicity, low complication profile, and high efficacy in losing weight and reducing MetS comorbidities. More recent techniques, based on the use of intragastric balloon device or endoscopic-assisted placement of a percutaneous gastrostomy device termed AspireAssist, have been approved by FDA in adults, but data in adolescents are not available yet [100].

Conclusion

Unique definition and therapeutic scheme for MetS and its components in children and adolescents are not currently available. However, this topic has aroused a lot of interest in recent times, stimulating the continuous research of new ideal alternatives for the paediatric population, with the main objective of preventing CVD in adulthood. Although some mechanisms of action are promising and very interesting data have been reported in the literature, further studies, in order to evaluate the efficacy and safety of new drugs and bariatric surgery techniques, are actually needed.

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