An Overview about Metabolic Syndrome and associated risk factors among obese school-aged Children

Ghada Mohammed Abdellatef [1], Hend Mohammed Ahmed Ibrahim [1],Weaam Ibrahim Ismail [2], Nahed Mahmoud Helmy Khater [1]

1 Pediatrics Department, Faculty of Medicine, Zagazig university, Zagazig, Egypt.
2 Clinical Pathology Department, Faculty of Medicine, Zagazig university, Zagazig, Egypt.

Email: hends209@gmail.com, hend.m21@medicine.zu.edu.eg

Abstract

Background

The International Diabetes Federation (IDF), National Heart, Lung, and Blood Institute (NHBLI), American Heart Association (AHA), World Heart Federation and the International Association for the Study of Obesity published a joint statement in 2009 that provided a "harmonized" definition of metabolic syndrome (MetS). According to this joint statement, a diagnosis of the MetS is made when any 3 of the 5 following risk factors are present: enlarged waist circumference with population specific and country-specific criteria; elevated triglycerides, defined as ≥ 150 mg/dL, decreased HDL-c, defined as < 40 mg/dL in male and < 50 mg/dL in female, elevated blood pressure, defined as systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg and elevated fasting glucose, defined as blood glucose > 100 mg/dL, with the inclusion of patients taking medication to manage hypertriglyceridemia, low HDL-c, hypertension and hyperglycemia. This definition is frequently referred to as the current Harmonization definition. Pediatric metabolic syndrome (PMS) in childhood can lead to early onset of diabetes mellitus and cardiovascular diseases in adulthood. PMS among school-age children is considered to be present when at least 3 or more of the following clinical and metabolic abnormalities are present together: insulin resistance, abdominal obesity, low level of high-density lipoprotein (HDL), high triglycerides (TGs), high fasting blood glucose (FBG), and elevated blood pressure (BP). The numbers of childhood MetS are high in the US, in the Middle East and in South American countries, with the highest proportion of MetS diagnoses occurring among overweight and obese individuals. As MetS is on the rise in children and adolescents, and given the disagreement on the diagnosis of MetS in children and youth, cardio-metabolic risk evaluation should rather be based on established risk factors such as nutritional status, hypertension, dyslipidemia, IR, clinical status, and familial predisposition.

Keywords: Metabolic Syndrome, Children

INTRODUCTION

The International Diabetes Federation (IDF), National Heart, Lung, and Blood Institute (NHBLI), American Heart Association (AHA), World Heart Federation and the International Association for the Study of Obesity published a joint statement in 2009 that provided a "harmonized" definition of metabolic syndrome (MetS). According to this joint statement, a diagnosis of the MetS is made when any 3 of the 5 following risk factors are present: enlarged waist circumference with population specific and country-specific criteria; elevated triglycerides, defined as ≥ 150 mg/dl, decreased HDL-

c, defined as < 40 mg/dl in male and < 50 mg/dl in female, elevated blood pressure, defined as systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg and elevated fasting glucose, defined as blood glucose > 100 mg/dl, with the inclusion of patients taking medication to manage hypertriglyceridemia, low HDL-c, hypertension and hyperglycemia. This definition is frequently referred to as the current Harmonization definition **(1)**

Table (1): Criteria for Diagnosis of the Metabolic Syndrome in children **(2).**

Criteria / components	Age		
	5 to < 10 years old	10 to 16 years old	> 16 years old
Adiposity definition	WC ≥ 90 th percentile	WC ≥ 90 th percentile	WC ≥ 90 cm (boys) or 80cm (girls)
Glucose metabolism	Fasting blood glucose ≥ 110mg/dl	Fasting blood glucose ≥ 100mg/dl	Fasting blood glucose ≥ 100mg/dl
Dyslipidemia	TG ≥ 110mg/dl or HDL-ch ≤ 40mg/dl	TG ≥ 150mg/dl or HDL-ch ≤ 40mg/dl or taking LLD	TG ≥ 150mg/dl or HDL-ch ≤ 40 (boys) or ≤ 50mg/dl (girls) or taking LLD
Arterial hypertension	Blood pressure ≥ 90 th percentile **(Cook et al. 2003)**	DBP ≥ 85 or SBP ≥ 130 mmHg or taking AHD	DBP ≥ 85 or SBP ≥ 130 mmHg or taking AHD

Table (2): Suggested diagnostic workup in overweight/obese children and adolescents if metabolic syndrome is suspected **(3).**

Step 1: Patient's history: Chronic disease, medication, SGA or LGA **Family history**: Gestational diabetes (mother), first or second degree relatives with obesity, type 2 diabetes or other features of the MetS
Step 2: Anthropometric data: Body weight, body lengths (calibrated scales), WC: Calculation of BMI and WHtR to define the degree of general and visceral obesity.
Step 3: Clinical examination: Signs for syndromal obesity; acanthosis nigricans, signs for virilization, striae distensae 3 blood pressure measurements at rest in the lying position → if elevated, perform a 24-hour blood pressure measurement
Step 4: Fasting blood sample: glucose, insulin, HbA1c, cholesterol, HDL-C, LDL-C, triglycerides, ASAT, ALAT; GGT, uric acid, Additional parameters, if clinically relevant: Cortisol, TSH, fT4, gonadotropines, steroid hormones
Step 5: Oral glucose tolerance test (according to ADA criteria)
Step 6: Additional diagnostic procedures if appropriate: - Abdominal ultrasound (stetatosis hepatis; degree of NAFLD?) - Ultrasound of the genital organs (polycystic ovaries?) - Intima media thickness - BIA measurement
Abbreviations: ASAT: aspartate aminotransferase; ALAT: alanine aminotransferase; BIA measurement: bioelectrical impedance analysis; BMI: body mass index; fT4: free tetraiodothyronine; GGT: gamma glutamyl transferase; HDL-C: high-density lipoprotein cholesterol; LGA: large for gestational age; NAFLD: nonalcoholic fatty liver disease; SGA: small for gestational age; TSH: thyroid stimulating hormone; WC: waist circumference; WHtR: waist to height ratio

Prevalence

The prevalence of metabolic syndrome (MetS) depends on the definitions used as well as the population being studied. Prevalence rates vary greatly depending on criteria used to define MetS, the age,

gender, ethnicity and environment of the population being studied and obesity prevalence of the background population. Regardless of which criteria are used, however, the prevalence of MetS is high and is on the rise in many western societies **(4)**.

The National Health and Nutrition Examination Survey (NHANES) reported the age-adjusted prevalence of MetS between 2009 and 2010 at 22.9%, a decrease from 25.5% between 1999 and 2000, in the United States population ≥ 20 years **(4).**

Worldwide, more than 340 million children and adolescents aged 5–19 were overweight or obese which estimated to be 70 million by 2025. The vast majority of overweight or obese children live in developing countries, where the rate of increase has been more than 30% higher than that of developed countries **(5).**

Hamed et al**. (6)** reported that worldwide 39% of children and adolescents less than 18 years were overweight in 2018 and 13% were obese. More than 41 million children under the age of 5 years were overweight or obese in 2018.

In Egypt, Soliman et al. **(7)** found that 13.12% of children and adolescents were estimated to have MS. Prevalence of MetS increased with age (a finding that has been seen in other studies worldwide) **(8).**

Hamed et al. **(6)** reported that one out of seven of 6-12 year-old-children in Qena city were obese. Locality of residence, gender, guardian education, obese guardian, feeding formula in early life, bad dietary habit (fast food consumption and missed breakfast) and lack of physical activity were likely to be the predictors of this alarming issue. In Port Said city the overall prevalence of overweight and obesity in governmental pupils (6–12 years old) was 17.7 % and 13.5% respectively. In Cairo, the overweight and obesity prevalence was 11% and 3.8 % respectively. In Alexandria the overall prevalence of overweight and obesity in governmental pupils (6–12 years old) is 16.8 and 9% respectively (5). In El-Sharkia, overall prevalence of overweight and obesity showed 20% for overweight and 10.7% for obesity. In Assuit city, the overall prevalence of overweight and obesity among primary school children aged from 6 to 11 years was11.24% and 12.28% respectively **(9).**

Urban populations have higher rates of MetS than rural populations. Similar to trends in western societies, recent studies demonstrate rising rates of MetS in many developing countries **(10).**

The westernization of these countries, bringing along a higher calorie diet and decreased physical activity, is thought to be largely response for the increased rate of MetS that is being observed **(11).**

Criteria for assessing pediatric metabolic syndrome

The school-age children were identified to be suffering from PMS based on different classifications:

- International Diabetes Federation (IDF) classification: A child was identified to be suffering with PMS when he/she along with abdominal obesity had any of the 2 following parameters were present: (i) TG ≥150 mg/dl, (ii) HDL <40 mg/dl, (iii) FBG ≥100 mg/dl, and (iv) BP ≥SBP 130/DBP 85 mmHg).
- Modified adult treatment panel-III (modified-ATP-III) classification: A child was identified as suffering with PMS when any of the following three parameters were present concomitantly (i) WC ≥ 90th percentile, (ii) TG ≥ 150 mg/dl, (iii) HDL < 40 mg/dl, (iv) FBG≥100mg/dl, and (v) hypertension (>95th percentile for SBP or DBP).**(12).**
- de Ferranti classification of MetS in pediatrics: A child was identified to suffer from PMS when three or more of the following criteria were present concomitantly (i) WC > 75th percentile, (ii) TGs ≥ 100 mg/dl, (iii) HDL-C < 50 mg/dl (< 45 in boys 15-19 years), (iv) FBG ≥ 110 mg/dl, and (v) HTN > 90th percentile (age, sex and height specific). **(13)**.
- Cook et al definition of MetS in pediatrics: A child was identified to suffer from PMS when three or

more criteria were present concomitantly (i) WC ≥ 90th percentile, (ii) TGs ≥ 110 mg/dl, (iii) HDL ≤ 40 mg/dl, (iv) FBG ≥110 mg/dl, and (v) hypertension ≥ 90th percentile (age, sex and height specific). **(14)**.

Pathogenesis

There are many different factors that contribute to the development of MetS. Genetics, lifestyle (such as diet and physical activity), obesity and insulin resistance can all play a role. These are all important elements in the pathogenesis of MetS. However, as initially proposed by Reaven, insulin resistance is thought to play a paramount role in connecting the different components of MetS and adding to the syndrome's development **(15).**

Elevated free fatty acids (FFAs) and abnormal adipokine profiles can result in the setting of insulin resistance and can contribute to the pathogenesis of MetS **(16).**

Insulin Resistance (IR)

Insulin resistance is defined as a decreased ability of insulin to stimulate glucose uptake from peripheral tissues. There are several factors thought to mediate insulin resistance and its adverse effects in MetS. These include but are not limited to elevated levels of FFAs and abnormal adipokine profiles **(17).**

Effects of insulin resistance:

- Hyperglycemia and T2DM

In insulin resistant individuals, there is an abnormal response of the β cells to glucose resulting in an initial loss of the first-phase insulin response, followed by an augmented second-phase response leading to hyperinsulinemia. With continued nutrient overload, the β-cells eventually fail. Thus, chronic hyperglycemia results in increased basal levels of insulin, but decreased β cell response to glucose stimulation. Furthermore, FFAs also increase basal insulin levels; however at high concentrations inhibit the release of insulin from the β cell in response to glucose. Thus, these phenomena respectively known as glucotoxicity and lipotoxicity mediate β-cell dysfunction in insulin resistance. The increased demand for insulin results in endoplasmic reticulum stress and cell death **(18).**

- Hypertension (HTN)

Insulin resistance and/or hyperinsulinemia are present in the majority of hypertensive patients. Via PI3K signaling and phosphorylation of endothelial nitric oxide synthase (eNOS), insulin stimulates nitric oxide (NO), a potent vasodilator. In an insulin sensitive individual, nutrient intake results in insulin release and glucose disposal, which then leads to vasodilatation of the skeletal muscle vasculature. Endothelin-1 (ET-1) is a vasoconstrictor, which is stimulated by insulin activity through the MAPK pathway. ET-1 is inhibited by NO. In insulin-sensitive individuals, the effects of insulin stimulated ET-1 (via the MAPK pathway) are offset by the insulin stimulated production of NO (via PI3K), resulting in hemodynamic hemostasis. However, in the setting of insulin resistance, insulin signaling through the PI3K signaling pathway is impaired, leading to decreased NO production and increased ET-1 secretion and subsequent hypertension **(19).**

Activation of the renin-angiotensin system (RAS) may also play a role in the association between HTN and MetS. The RAS is a hormonal system that regulates blood pressure. Renin is secreted in response to low blood volume and carries out the conversion of angiotensinogen to angiotensin I. Angiotensin I is then converted to angiotensin II, a potent vasoactive peptide that causes vasoconstriction, resulting in increased blood pressure. The elevated circulating levels of angiotensinogen in obese individuals may be secondary to increased fat mass as increased angiotensinogen can lead to more vasoconstriction and elevated blood pressure **(20).**

- Dyslipidemia

In MetS, the lipid profile often involves a low HDL-c and elevated TG. Insulin resistance leads to abnormal lipid profiles. In insulin resistance, there is increased FFAs production from adipocytes through loss of inhibition of hormone sensitive lipase. In addition, endothelial lipoprotein lipase function is impaired, leading to a further increase in circulating FFAs **(21).**

- Polycystic Ovarian- Syndrome (PCOS)

PCOS is present in approximately 20% of premenopausal female and a large proportion of these female are obese. Female with PCOS tend to display an abdominal and/or visceral pattern of fat distribution, associated with increased insulin resistance and adverse metabolic sequelae **(22).**

However, studies in lean female with PCOS demonstrate that they are equally insulin resistant as obese female with PCOS, suggesting that insulin resistance, and not obesity, may be a primary feature of PCOS. In fact, female with PCOS have significant insulin resistance that is independent of obesity and body composition. Female with PCOS also demonstrate abnormal adipogenesis, thought to be due to the elevated androgen level. PCOS is associated with insulin resistance and is frequently observed in female with MetS **(23).**

According to the criteria proposed by the World Health Organization, the nutritional state is classified based on the BMI z-score (z-BMI). Individuals are categorized as overweight ($+1 \leq$ z-BMI $< +2$) or obese (z-BMI $\geq +2$). The body fat percentage (BFP) is calculated using the sum of four skinfolds as the criterion as in the equations of Slaughter et al. **(24),** who measured triceps and subscapular skinfold thicknesses. WC is measured while the individual was in a standing position, midway between the lowest rib and the top of the iliac crest, at the end of a normal expiration, with a non-extensible tape measure with millimeter graduations. WC is considered high when the value is within or above the 90th percentile according to sex and age. Physical examinations also included a detailed evaluation of the skin with respect to clinical signs of insulin resistance, manifested by the presence of acanthosis nigricans, which is assessed visually in the neck, armpits and groin **(25).**

Systolic and diastolic blood pressures (SBP and DBP, respectively) are measured in the right arm, and the obtained values are classified according to sex, age and height following the criteria of the I Guideline for Preventing Atherosclerosis in Childhood and Adolescence of the Brazilian Society of Cardiology. The pubertal stage is evaluated by a single researcher and classified into pre-pubertal and pubertal, according to the criteria of Marshall and Tanner **(26).**

Laboratory and Adipokine markers

To assess the levels of:

- Fasting blood glucose.
- Insulin.
- Total cholesterol, high- and low-density lipoprotein cholesterol (HDL-C and LDL-C, respectively), triglycerides (TGs).
- Leptin and adiponectin **(25).**

The homeostasis model assessment of insulin resistance (HOMA-IR) index is calculated by multiplying fasting plasma insulin (μU/mL) by fasting glucose (mmol/L), divided by 22.5. The cutoff point was $\geq$2.5 for pre-pubertal and $\geq$3.43 for pubertal individuals of both sexes **(27).**

Treatment

In patients with MetS, aggressive approaches toward lifestyle modification, such as dietary restriction, and increased physical activity play a paramount role in treatment, as these factors all play a role in the metabolic dysfunction comprising MetS **(28).**

Table (3): Treatment of metabolic syndrome **(29).**

Mets components	First-line approach	Treatment
Obesity	Lifestyle interventions: 1. Diet (caloric restriction, specific targets suggested by dietitians) 2. PA (60 min of moderate/vigorous PA every day, including vigorous activity 3 day per week)	1. PHARMACOLOGIC TREATMENT Orlistat, when indicated 2. SURGICALTREATMENT Bariatric surgery, when indicated
Hypertension	Lifestyle interventions: 1. Diet (reducing sodium, increasing olive oil polyphenols, increasing intake of fruits, and vegetables) 2. PA(30–60 min of moderate/vigorous PA at least 3–5 days per week)	PHARMACOLOGIC TREATMENT Start with a single medication at the low end of dosing range. Titrate every 2–4 weeks. ACE inhibitor, angiotensin receptor blocker, long acting calcium channel blocker or thiazide dieuretic are the first choices
Dyslipidemia	Lifestyle interventions: 1. Diet (reducing total fat between 25 and 30% of daily calories and cholesterol intake <300 mg/day, reducing simple carbohydrate intake, possible use of plant sterols or stanol esters) 2. PA	PHARMACOLOGIC TREATMENT Statins when indicated
Glucose impairments and T2DM	Lifestyle interventions: 1. Diet 2. PA	PHARMACOLOGIC TREATMENT 1. Glucose impairments: the use of metformin is uncommon 2. T2DM: metformin and/or insulin
NAFLD	1. Lifestyle interventions and weight loss. 2. Probiotics and omega3 fatty acids may ameliorate disease progression. 3. Vitamin E can improve hepatocellular ballooning	

PA, physical activity; BP, blood pressure; T2DM, type 2 diabetes mellitus; NAFLD, non-alcoholic fatty liver disease.

1- 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, hypertriglyceridemia, and low HDL cholesterol, whereas a BMI-SDS reduction of >0.5 doubled the effect. 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.PA is associated not only with weight loss but also with higher insulin sensitivity (IS) itself, independently from adiposity. 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 programe seems to improve IS in overweight and obese children regardless of changes in body weight and percent body fat **(30).**

Moreover, positive feedback from the visible strength gain could improve patients' self-esteem and compliance. Any type of exercise, whether it is aerobic, resistance, or combined training, appears to be beneficial in lowering blood pressure (BP) too. In addition to PA, sleeping habits can also affect weight and IS. In fact, short sleep duration and obstructive sleep apnea syndrome (OSAS) have been demonstrated to be associated with IR in obese children. The optimal nutritional management of MetS is still debated. Benefits from high-fiber 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, lower odds of MetS in children and adolescents, improved body composition in children, lower systolic BP, and fasting glycaemia **(31).**

On the other hand, high-fat intake has been shown to impair IS independently of body fat in adolescents. Also, increased fat/carbohydrate ratio seems to be negatively correlated with IS and insulin clearance in pre-pubertal children. Few studies conducted on adults suggest this association is independent from dietary fat quality. High-glycemic index food may increase risk for obesity, T2D, and CVD. Data from studies about the effects of low-glycemic 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. 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 **(32).**

2- 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. The common adverse drug reactions of orlistat are steatorrhea and flatulence, which are poorly tolerated. **(33).**

Topiramate and zonisamide are 2 anticonvulsant medications. Topiramate is approved for the treatment of epilepsy in patients as young as 2 years old, while zonisamide is not currently FDA approved in the United States for use in children, but clinical trials have shown its efficacy and safety. It has been widely demonstrated that adults treated with topiramate or zonisamide commonly experience weight loss. However, few and variable data are available about their effects on weight in pediatric population. 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 **(34).**

- 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. 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. 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. At high concentrations, it also improves peripheral IS, although the mechanism of action is not entirely clear **(35).**

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 pediatrics are still missing. There is evidence that metformin improves IS in adolescents with T2D and polycystic ovary syndrome (PCOS). Common side effects include abdominal pain, nausea, metallic taste, bloating, and diarrhea. Among the potential pharmacological options for the treatment of IR and obesity, GLP-1 analogues, such as liraglutide. In fact, thanks to their capability of interfering with inflammatory processes in the adipose and hepatic tissues, they could reduce IR. Moreover, liraglutide increases the postprandial insulin level, reduces glucagon secretion, delays gastric emptying, and induces weight loss through reductions in appetite and energy intake. Sodium-glucose cotransporter type 2 (SGLT2) induces the reabsorption of 90% filtered glucose in the kidney. Sotagliflozin, an oral SGLT2 inhibitor, has been demonstrated to improve glycemic 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 **(36).**

Since these medications also lead to weight loss without causing hypoglycemia, 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. 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 hypoglycemia 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 **(35).**

- Dyslipidemia

In 2011, the National Heart Lung and Blood Institute (NHLBI) published its Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, in which lifestyle intervention remained an integral part of treatment for pediatric lipid disorders; however, they recommend not to treat pharmacologically children younger than 10 years unless they have a severe primary hyperlipidemia or a high-risk condition associated with severe medical morbidity (homozygous hypercholesterolemia, LDL cholesterol level ≥400 mg/dl, primary hypertriglyceridemia 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 **(37).**

Statins, hydroxy methylglutaryl-CoA (HMG-CoA) reductase inhibitors, are recommended as the first-line treatment of pediatric patients. Summaries recommended dosing ranges and supporting clinical trials for statins, which are FDA approved for children with heterozygous familial hypercholesterolemia. Statins presented variable efficacy in clinical trials in pediatrics. 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 **(38).**

Table (4): HMG-CoA reductase inhibitors: pediatric approvals and indications, recommended dosing ranges, and supporting clinical trials **(38).**

Medication	Paediatric approvals and indications	Dosing	Comments
Atorvastatin	Age 10–17 yr Heterozygous familial hypercholesterolaemia	10–20 mg/d	May be titrated at ≥4-week intervals
Fluvastatin	Age 10–16 yr Heterozygous familial hypercholesterolaemia	20–80 mg/d	May be titrated at ≥6-week intervals
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
Pravastatin	Age 8–18 yr Heterozygous familial hypercholesterolaemia	20–40 mg/d	Age 8–13: 20 mg/d Age 14–18: 40 mg/d
Rosuvastatin	Age 10–17 yr Heterozygous familial hypercholesterolaemia	5–20 mg/d	May be titrated at ≥4-week intervals
Simvastatin	Age 10–17 yr Heterozygous familial hypercholesterolaemia	10–40 mg/d	May be titrated at ≥4-week intervals

LDL, low-density lipoprotein.

- Hypertension

It has been widely demonstrated that currently recommended therapeutic schemes can even reverse target organ damage in youth with hypertension. 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) **(39)**.

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 a thiazide diuretic. **(39).**

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. **(39).**

Table (5): Anti-hypertensive drugs: age and dosing recommendations, contraindications, and adverse drug reactions **(40).**

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.

Surgical Treatment

The American Society for Metabolic and Bariatric Surgery (ASMBS) Pediatric Committee guidelines have recently suggested the new indications and contraindications for bariatric surgery in pediatric 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/m2 only in presence of severe comorbidity, such as T2DM, OSAS, benign intracranial hypertension, or NASH. They also indicate adolescents with a BMI of ≥40 kg/m2 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 **(41).**

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 intra-gastric balloon device or endoscopic-assisted placement of a percutaneous gastrostomy device termed Aspire-Assist, have been approved by FDA in adults, but data in adolescents are not available yet **(41).**

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