International Journal of Multiphysics
Volume 18, No. 3, 2024
ISSN: 1750-9548

An Overview on Metabolic syndrome

Ayman Elsayed Galal Ali[1], Hadeel Mohammed Abdulrahman[1], Doaa M. AbdElmonem[2], Diana Hanna[1]

1 Pediatrics Department, Faculty of Medicine, Zagazig University, Egypt

2 Clinical pathology Department, Faculty of Medicine, Zagazig University, Egypt

***Corresponding author:** Ayman Elsayed Galal Ali

Email: aymangalal1213@gmail.com,

Abstract:

Metabolic syndrome (MetS) in childhood and adolescence has emerged as a global health concern due to its strong association with obesity, insulin resistance, dyslipidemia, hypertension, and increased cardiometabolic risk in later life. Early identification of children with metabolically unhealthy phenotypes is crucial for prevention of type 2 diabetes and cardiovascular disease.

Keywords: Metabolic syndrome; Pediatrics; Obesity; Insulin resistance; Dyslipidemia.

Introduction:

Metabolic syndrome (MetS) is a complex disorder characterized by abdominal obesity, elevated blood pressure, hyperlipidemia and elevated fasting blood glucose levels **(1)**. Definitions of MetS in adults have been proposed by several organizations, leading to a consensus on the presence of 3 of the following 5 criteria for its diagnosis: (i) elevated waist circumference with cut-off based on the reference organization; (ii) blood pressure ≥130/85 mmHg or ongoing treatment for hypertension; (iii) fasting blood glucose ≥100 mg/dL or ongoing treatment for diabetes; (iv) triglycerides (TGs) ≥150 mg/dL; (v) high-density lipoprotein (HDL) cholesterol < 40 mg/dL in males and < 50 mg/dL in females or ongoing treatment for dyslipidemia. Currently, there is no consensus on the definition of MetS in children and adolescents and the diagnosis is based on a combination of clinical findings and laboratory tests **(2)**.

Epidemiology of MetS in childhood

MetS is becoming increasingly common in children and adolescents and the disparity in consensus makes it challenging for clinicians to compare studies that employ different diagnostic standards. Data obtained by de Ferranti et al., using an adapted children definition of Adult Treatment Panel from the Third National Health and Nutrition Examination Survey (NHANES III), identify a prevalence of 9.2% of children with MetS while nearly 64% of children present at least one metabolic alteration **(2)**. The ambiguity in using different definitions became evident in a recent comparative study of Reisinger C et al. where prevalence of pediatric MetS ranges between 2.1% using the IDF definition and 11.2% using Ferranti's definition **(3)**. There is however a consensus on the most frequent metabolic alterations, where central obesity and dyslipidemia are the major determinants.

Pathophysiology of MetS

Hypertrophic adipocytes, as consequence of visceral fat expansion during obesity, secrete inflammatory molecules which, coupled with the reduced insulin-mediated lipolysis suppression, results in increased release of circulating free fatty acids (FFAs). FFAs accumulate in ectopic sites leading to lipotoxicity in pancreatic β cells and inhibition of insulin signaling in liver and muscles **(4)**.

The mechanism undergoing IR in muscle is based on the competition of FFAs with glucose as energy substrate and the reduced expression of the glucose transporter 4 (GLUT4) **(2)**. IR in the liver is limited to glucose production, while insulin-induced lipolysis is preserved. This leads to an increased synthesis of triglycerides, which are secreted into the circulation as atherogenic VLDLs causing dyslipidemia and increased risk of

cardiovascular complications **(4)**. Increased glucose production from hepatocytes and concomitant decreased glucose uptake in skeletal muscle cells lead to hyperglycemia. Moreover, the concomitant presence of proinflammatory signals activated in obesity, vasoconstriction induced by FFAs and decreased insulin-mediated vasodilation may also explain hypertension **(4)**. The underlying mechanism has been proposed to be mediated by urotensin-II (U-II), a potent vasoconstrictor, whose serum levels are positively associated with hypertension, IR, inflammation and with the clinical outcome of T2D and cardiovascular disease **(5)**.

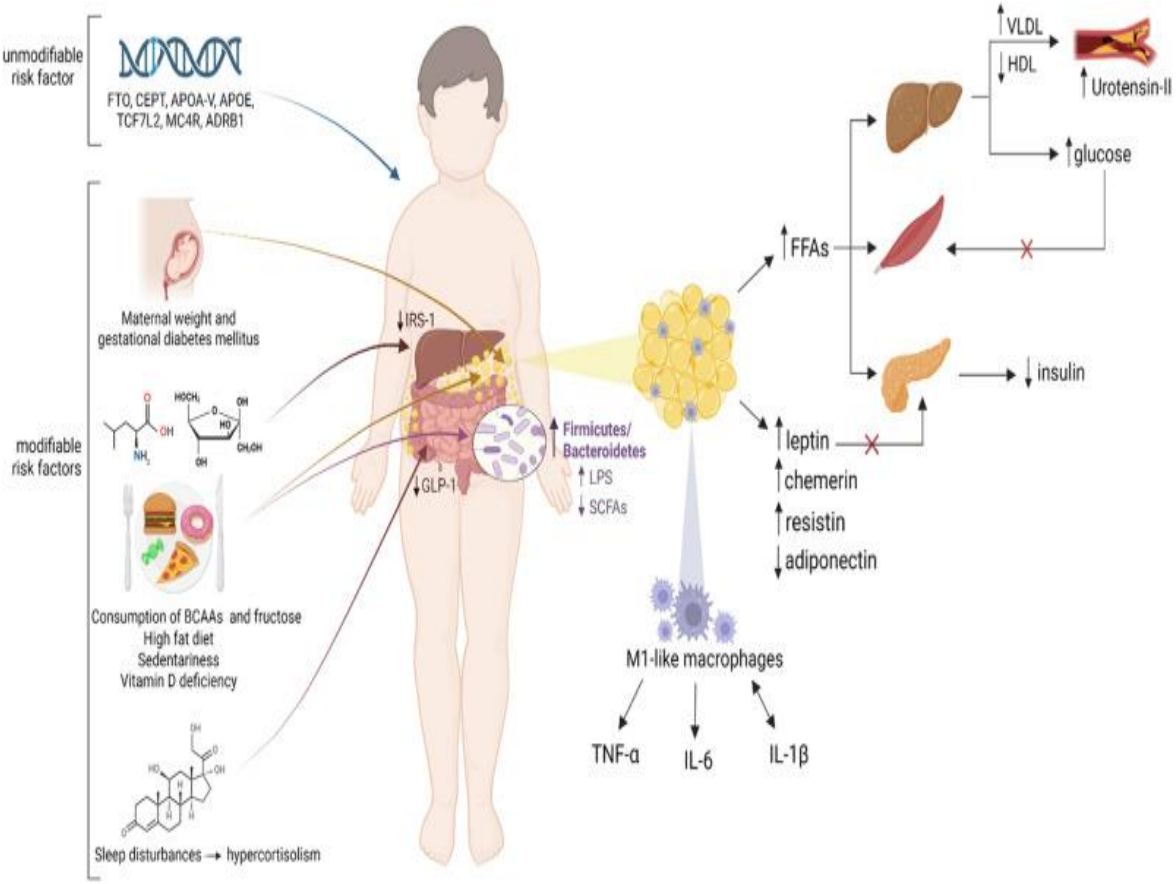

Figure 1. Pathogenesis of MetS in children and adolescents

Non-modifiable risk factor of MetS: genetic predisposition

MetS is the result of a complex interplay between genetic predisposition and environmental factors. Figure 1 depicts risk factors and mechanisms underlying the pathophysiology of MetS in pediatric individuals. In Europe, the herit ability estimates for MetS range from 10% to 30% depending on the diagnostic criteria used, meaning that genetic predisposition can explain only a small part of the pathogenesis of MetS.

A large number of single nucleotide polymorphisms (SNPs) have been described in risk of T2D and cardiovascular diseases. FTO fat mass and obesity associated gene, CETP cholesteryl ester transfer protein gene, APOAV apolipoprotein A-V gene, APOE Apolipoprotein E gene, TCF7L2 Transcription factor 7-like 2, MC4R melanocortin-4 receptor gene, ADRB1 beta-1 adrenergic receptor, BCAAs branched-chain amino acids, IRS-1 insulin receptor substrate 1, GLP-1 glucagon-like peptide 1, LPS lipopolysaccharides, SCFAs short-chain fatty acids, FFAs free fatty acids, VLDL very-low-density lipoprotein, HDL high-density lipoprotein, TNF-α: tumor necrosis factor alpha, IL-6 interleukin 6, IL 1β interleukin-1 beta relation to a single component of MetS; however, only few genes have been associated with MetS as a whole **(2)**.

The fat mass and obesity-associated gene (FTO) is located on chromosome 16 and plays a key role in weight control and energy balance. Although the A/A phenotype in the risk allele rs9939609 (T/A) has been strongly

associated with the occurrence of obesity, even in children **(6)**, several lines of evidence suggest it plays a central role in the development of MetS **(7)**.

The cholesteryl ester transfer protein (CETP) gene, also located on chromosome 16, may be equally involved in the pathogenesis of MetS. CETP encodes for a protein involved in reverse cholesterol transfer; in fact, high levels of CETP result in lower circulation of HDL and consequentincreases of low-density lipoproteins (LDL) and very low density lipoproteins (VLDL). Adult MetS is inversely associated with the presence of the Taq-1B (rs708272) allele which, by reducing CETP expression, protects from dyslipidemia **(7)**.

Apolipoproteins are responsible for lipid transport and some of them are encoded by genes whose polymorphisms have been associated with MetS. The SNPs T1131C (rs662799) on the APOA-V gene was correlated, both in adults and children, with high levels of triglycerides resulting from a lower ability to activate lipoprotein lipase **(8)**.

The transcription factor 7-like 2 (TCF7L2) gene encodes for a protein that affects incretin-induced insulin secretion from pancreatic β cells and confers the strongest genetic predisposition to the development of T2D. A study conducted on Caucasian and Asian adolescents associated the C allele of rs10749127 SNP with different features of MetS. A meta-analysis of five studies showed that the rs7903146 T allele also increased the risk for MetS in an adult population. Although this allele is com mon among Europeans, studies in childhood and adoles cence are still lacking in European countries **(2)**.

The melanocortin-4 receptor (MC4R) gene is critical for energy balance; it regulates food intake as well as satiety in the hypothalamus and exerts its function at the peripheral level by preventing excessive fat deposition. The presence of the most common mutation rs17782313 (T/C) has been associated with several MetS traits (higher BMI and weight, higher triglycerides and lower HDL) as well as MetS itself in adults **(9)**, but only with BMI in children **(6)**.

The Arg389Gly (rs1801253) SNP of the ADRB1 gene, which encodes for the β1 adrenergic receptor, was found to be associated with childhood obesity and blood pressure control **(10)**.

It has to be noted that studies aimed at investigating associations of genes with single MetS disorders do not take into account that most genetic loci have a pleiotropic effect on more than one MetS component and thus explain more than a single phenotypic trait; for example, a quantitative genetic analysis conducted on Hispanic children with metabolic disorders found a pleiotropic effect among genes encoding for systolic blood pressure, waist circumference and glucose, whereas a negative correlation was observed between HDL and waist circumference genes. More over, Kraja AT et al. identified 25 genes whose SNPs are associated with at least two metabolic traits of MetS and at least one marker of inflammation **(2)**. These findings suggest the importance of considering the disease as a whole; however, the lack of defined diagnostic criteria for MetS is a severe limitation, as data are often not comparable between studies. In this scenario, assessing each SNP's impact on MetS risk would help quantify the role of genetic predisposition. Another limitation in estimating the herit ability of MetS is the difficulty in identifying rare or minor SNPs (defined by a minor allele frequency lower than 5% and 0.5%, respectively) that appear to be prevalent in children with obesity **(9)**.

Modifiable risk factors of MetS in childhood and adolescence

Early in life

Environmental factors, including behaviour of the mother during pregnancy and children lifestyle, can contribute to the early development of MetS. Susceptibility for MetS already begins before birth, as high maternal weight during pregnancy and associated gestational diabetes mellitus increase the risk to develop obesity and type 2 diabetes in the offspring.

Obesity, insulin resistance and sedentariness

A sedentary lifestyle, obesity and insulin resistance (IR) trigger MetS. The World Health Organization indicates that IR is the common antecedent to all manifestations of MetS; other studies suggest that obesity is the trigger of MetS. Considering that obesity and IR are closely related and most often occur together, it is correct to

assume that both play an essential role in the pathogenesis of MetS and that neither factor is sufficient by itself to determine all the metabolic complications. The Bogalusa Heart Study revealed that both childhood obesity and IR can predict adult MetS development, but after adjustment for insulin and BMI respectively, only obesity maintained a significant association. Two different obesity-associated metabolic conditions, namely metaboli cally healthy obese (MHO) and metabolic unhealthy obese (MUO) have been described in children as well as in adults **(2)**.

An MHO phenotype during childhood is more likelyto be retained during adulthood. Furthermore, the conversion of MHO children to MUO is determined by the loss of insulin sensitivity **(11)**, thus corroborating the hypothesis that MetS begins with obesity but requires IR to develop. It is important to note that a physiological and transient IR occurs during pubertal development, and it could accelerate the onset of MetS in a pre-existing state of obesity-dependent IR. The causal link between obesity and IR lies in the elevated levels of proinflammatory adipokines, such as IL-6 and TNF-α, released by adipose tissue following fat accumulation, which worsens tissue responses to insulin, thus resulting in T2D, dyslipidemia and hypertension **(12)**.

Sedentariness and high fat diet take part in the development of obesity while elevated consumption of fructose and branched-chain amino acids contributes to a state of IR through the serine phosphorylation of the insulin receptor substrate-1 (IRS-1) and the resulting decrease in hepatic insulin sensitivity. In children, the most common metabolic alterations are obesity and dyslipidemia with low HDL levels, whereas hypertension and glucose intolerance develop later in life and are typical of adult MetS. Obesity and dysli pidemia are consequences of poor dietary habits, whereas the age-specific decrease in HDL levels could be due to an androgen-sensitive increase in hepatic lipase activity and the consequent increase of HDL catabolism **(2)**.

Vitamin D deficiency, sleep disturbances and hypercortisolism

Vitamin D deficiency in youth has been associated with the presence of MetS **(13)**; emerging evidence suggests that adequate vitamin D levels may offer potential protection against the onset of metabolic complications. This includes fostering improved glycemic control, enhancing vascular function and regeneration, and reducing reactive oxygen species, thereby mitigating the risk of T2D and cardiovas cular events **(14)**. Despite these promising indica tions, a recent meta-analysis examining the impact of vitamin D supplementation in overweight and obese children revealed that elevated 25(OH)D levels did not translate into clinically significant outcomes **(15)**. As a result, the controversy surrounding the effectiveness of supplementation treatment persists.

Moreover, sleep disturbances, namely insufficient sleep, poor sleep quality and/or insomnia and obstructive sleep apnea, induce cortisol production by the adrenal cortex, which leads to a higher caloric intake and fat accumulation in children **(16)**.

Systemic and tissue inflammation

MetS is accompanied by a chronic low-grade inflammation that is ascribable to obesity and could increase the risk of cardiovascular diseases later in life, as children appear to be more sensitive to oxidative stress than adults **(2)**. This is supported by the evidence that diet-induced weight loss exerts anti-inflammatory effects, resulting in improvements in metabolic parameters, lipid levels, and cytokine profiles **(17)**. A central role in the development of inflammation is associated to the activation of Toll-like receptors (TLRs), which triggers inflammatory signaling pathways and leads to the release of cytokines **(4)**. Obesity in children exhibits similar inflammatory-mediated mechanisms as in adults, with similarly altered levels of cytokines and adipokines and increased expression of TLR2 and TLR4 **(2)**. Here, we will focus on the description of inflammatory markers that have shown changes in children with single or multiple MetS traits.

Alteration of the gut microbiota

The human intestinal microbiota is composed by a large number of microorganisms with the vast majority of bacteria belonging to the Firmicutes, Bacteroidetes, Actino bacteria, Proteobacteria, Fusobacteria and Verrucomicrobia phyla **(18, 19)**. Metabolic syndrome has been associated with a higher Firmicutes/Bacteroidetes ratio (F/B) **(20)**. In studies conducted by **Gallardo-Becerra et al. (20)** in children, a higher abundance of Firmicutes and a lower abundance of Bacteroidetes were found in patients with MetS. These differences were

statistically significant when obese patients with MetS were compared with normal-weight subjects; however, obese patients without MetS also showed an increase in the F/B ratio **(20)**. Given that obesity plays a central role in the development of MetS, it's not surprising that dysbiosis goes in the same direction. However, as both obesity and IR have been independently associated with an increased F/B ratio in children **(21)**, the timing of changes in gut microbiota composition during the natural history of MetS is unclear.

Screening

Clinicians should recognize children who are obese and overweight and at risk for T2DM and CVD. It is important to screen these children for behavioral and medical risks, including persistent obesity, as well as its associated co-morbidities. A significant risk factor for childhood obesity that needs to be considered during the screening evaluation is the presence of obese parents. The history and physical examination are the first steps in the comorbidity screening process. Clinicians should request information about the signs and symptoms for associated comorbidities that may be present, such as PCOS, liver disease, and obstructive sleep apnea, which can be confirmed as a comorbidity with polysomnography. Serum alanine aminotransferase and aspartate aminotransferase levels are respectably effective screening tests for fatty liver disease. When values are double the upper limit of normal, a pediatric hepatologist should be consulted. Bi-annual liver disease screening is recommended starting at the age of 10 years for children with obesity or those who are overweight with other risk factors **(22)**.

Screening for T2DM is recommended in overweight (≥85th percentile) or obese (≥95th percentile) children and adolescents with ≥1 of the following risk factors: (I) Family history of T2DM in first- or second-degree relatives; (II) at risk race or ethnicity (Native American, African American, Latino, Asian American, and Pacific Islander); (III) signs of insulin resistance or associated conditions, such as acanthosis nigricans, hypertension, dyslipidemia, PCOS, or a history of being born small for gestational age; and (IV) maternal history of diabetes or gestational diabetes during the child's gestation. The ADA recommends starting screening at the age of 10 years or at the onset of puberty, whichever arrives earlier, and be repeated every three years. Generally, fasting plasma glucose, 2-hour plasma glucose measured during the 75-gram oral glucose tolerance test, and the glycated hemoglobin test are equally appropriate for diagnostic screening **(22)**.

Starting at age 3 years, blood pressure should be obtained annually at all regular health check-ups, and results should be compared to reference ranges from tables issued by the NHLBI. Finally, children should be routinely screened for dyslipidemia with universal lipid screening between 9–11 years of age with a non fasting, non-HDL lipid profile. Screening children 2–8 years of age with fasting lipid profiles is recommended for obese children since obesity is considered a moderate- to high-risk factor. The NHLBI recommends repeating lipid profiling in overweight adolescents at 12–16 years of age. The level of abnormality, the presence of additional known risk factors, and the presence of high-risk diseases should determine whether to pursue dietary or medicinal intervention **(22)**.

Prevention of Metabolic Syndrome

Pediatric obesity prevention involves promoting healthy diet and increasing physical activity as the primary prevention strategies in order to avoid MetS in children. Lifestyle modifications to achieve a healthy diet include increasing consumption of vegetables and fruits; increasing fiber intake while reducing dietary fat; and avoiding carbonated beverages, refined carbohydrates, high-fructose corn syrup, high sodium, and processed foods. Fruit juice should be replaced with whole fruits for additional nutritional value. Physical activity is also recommended 3–5 days per week with ≥20 min of vigorous short bursts to improve metabolic measures in children and adolescents, which may prevent obesity. Adopting healthy sleep habits, limiting non-academic screen time, involving the entire family and community in prevention efforts, and using school-based programs and community engagement for the prevention of pediatric obesity are additional lifestyle changes that can lower the risk of developing obesity **(22)**.

Treatment of Metabolic Syndrome

In general, childhood MetS is treated through weight reduction by lifestyle modifications, including dietary intervention, increased physical activity, and the management of various disease-specific factors. Pharmacological treatments and bariatric surgery are other alternatives for managing obesity.

1) Lifestyle modifications and behavioral treatment

For the first step to change, clinicians should assess patients and families. In this way, family and patient interventions will be more easily incorporated. When compared to programs focused solely on the child, those that involved the entire family in lifestyle change were found to have favorable outcomes for lowering BMI. Comprehensive weight reduction programs, including nutritional, physical activity, education, and behavioral therapy, have been linked to improvements in a number of metabolic parameters, including blood pressure and lipid profile indices in obese children and adolescents. Obese children and adolescents should be screened for mental health, including eating disorders, depression, and other mood disorders. Support and referral to available behavioral health resources for those disorders are essential.

a- Dietary intervention

Basic dietary recommendations are mostly based on low-fat diets and, recently, low carbohydrate diets are gaining popularity. Recent Endocrine Society guidelines recommended avoiding beverages sweetened with sugar, elimination of fructose-rich corn syrup, and decreased consumption of processed foods high in salt and saturated dietary fat in children over 2 years of age and adolescents. Furthermore, consumption of dietary fibers, vegetables, and whole fruits other than fruit juice or carbonated drinks is encouraged. Additionally advocated for nutritional intervention are education about portion control, improved product labeling, and the consumption of frequent meals to prevent snacking. In addition, because eating fast and the risk of developing T2DM are highly associated, slow eating should be taught as an important eating habit **(23)**.

b- Physical activity

The second-most important behavioral intervention is physical activity. The AAP and the European Society for Pediatric Endocrinology advise engaging in physical activity regardless of weight status, aiming for at least 30 minutes of daily moderate to vigorous activity, and keeping non-academic screen time to no more than one to two hours per day **(24)**. It is recognized that inactivity can decrease insulin sensitivity in skeletal muscle, which can be reversed by increasing physical activity. Physical activity is also helpful in improving the lipid profile by lowering LDL and triglyceride concentrations and increasing the HDL concentration. Regular physical activity increases cardiorespiratory fitness by reducing blood pressure, arterial stiffness, and abdominal fat. Most children, including children with obesity, do not achieve these recommendations. Exercise physiologists and physical therapists can help these children by developing individual exercise plans, especially when movement is limited by gross motor delay or musculoskeletal pain **(24)**.

2) Pharmacological therapies

As previously stated, lifestyle modification therapy is the primary form of treatment for MetS. When patients are unable to achieve their weight loss objectives with lifestyle modification therapy alone, pharmacotherapy is the next logical treatment option to consider **(25)**. The indication for pharmacotherapy to treat pediatric obesity includes an age of ≥10 years and a BMI in the ≥95th percentile with weight-related co-morbidities or a BMI that is ≥120% of the 95th percentile, regardless of comorbidities, without an appropriate response to lifestyle modification. Intense lifestyle modification programs should be considered along with pharmacotherapy.

Options for pharmacotherapy to treat pediatric obesity are limited. Orlistat, a lipase inhibitor that blocks the absorption of fats from the human diet, is the only medicine recognized by the American Food and Drug Administration (FDA) for long-term use in the treatment of pediatric obesity (≥12 years of age). However, due to its modest efficacy (2.61-kg weight loss after one year of treatment), its therapeutic application is somewhat limited, and many adolescents may find its side effects unpleasant (flatulence; oily, spotty stools; and diarrhea) **(22)**.

Glucagon-like peptide-1 receptor (GLP-1) agonists include exenatide and liraglutide. Exenatide has FDA approval for adult T2DM, and a liraglutide 3.0-mg injection has FDA approval for adult obesity. Recently, a liraglutide 3.0-mg injection received FDA approval for the treatment of obesity in adolescents (aged 12–17 years) with a body weight>60 kg and an initial BMI≥30 kg/m^2 combined with a reduced-calorie diet and increased physical activity. GLP-1 agonist–associated weight reduction appears to be related to decreased gastric emptying and increased satiety and appetite suppression. Recently, a randomized controlled trial of adolescent obesity with a 56-week liraglutide treatment period reported that the use of a liraglutide 3.0-mg injection combined with lifestyle modification led to significant reduction in BMI z-score **(26)**. In patients with syndromic and hypothalamic obesity with hyperphagia, GLP-1 agonist therapy has the potential for weight reduction and weight stabilization **(25)**.

Metformin, a biguanide primarily used for glycemic control, has been used off-label to achieve weight loss in children. Meformin is FDA-approved for children≥10 years of age for T2DM. Currently, in a systematic review of randomized controlled trials on children and adolescents. Several studies reported improvements in fasting plasma glucose and insulin resistance, but not in lipid levels. As compared to a placebo, metformin was associated with double the number of gastrointestinal adverse effects. By this finding, the question of whether metformin is an appropriate adjuvant therapy to lifestyle change for the treatment of pediatric obesity is raised **(22)**.

3) Surgical therapies

As a standard course of treatment, surgical intervention for childhood and adolescent obesity is still not approved. In children and adolescents, research on the effects of surgery on growth and development is limited. Thus, it should only be considered when growth and puberty are complete. Also, surgical treatment for children and adolescents in growing process should be limited to strict standards. Before considering surgical treatment, evaluation for previous treatment, such as multidisciplinary treatment and pharmacotherapy, should be conducted. Furthermore, adolescents and their families should have psychological stability and competence, availability for appropriate follow-up care, and a demonstrated ability to comply with healthy dietary and activity routines. It is also very important that the patient has a reliable caretaker who can provide physical and psychosocial support through the entire process. Recently, metabolic and bariatric surgery (MBS) has been shown to be an effective treatment for severe obesity in adolescences, and studies have reported significant improvements in co-morbidities associated with obesity **(22)**.

According to the most recent recommendations issued by the American Society for Metabolic and Bariatric Surgical Pediatric Committee, MBS could be considered for children ≥10 years of age with a BMI that is ≥120% of the 95th percentile who also have a weight-related co-morbidity, such as T2DM, hypertension, NAFLD, and/or obstructive sleep apnea, or those with a BMI that is ≥140% of the 95th percentile regardless of co-morbidities. According to the recommendations, treatment should be provided to adolescents who have previously attempted to reduce weight, have a low Tanner stage, and have immature bone growth. Lack of evidence, however, suggests that MBS may have a negative impact on a child's pubertal status as determined by Tanner staging, linear development, or height. The impact of MBS on children's pubertal development should therefore be the subject of additional research. MBS has the potential to result in both macro- and micronutrient deficit, therefore lifetime supplemental protein, iron, calcium, and vitamins are necessary to prevent deficiencies **(22)**.

References:

1. Flemming, Gunter Matthias Christian, Sarah Bussler, Antje Körner, and Wieland Kiess. 2020. “Definition and Early Diagnosis of Metabolic Syndrome in Children.” J Pediatr Endocrinol Metab 33 (7): 821–33. https://doi.org/10.1515/jpem-2019-0552.
2. Codazzi, Valentina, Giulio Frontino, Luca Galimberti, Andrea Giustina, and Alessandra Petrelli. 2024. “Mechanisms and Risk Factors of Metabolic Syndrome in Children and Adolescents.” *Endocrine* 84: 16–28. https://doi.org/10.1007/s12020-023-03642-x.
3. Reisinger, Carolin, Benedicta N. Nkeh-Chungag, Per Morten Fredriksen, and Nandu Goswami. 2021. “The Prevalence of Pediatric Metabolic Syndrome — a Critical Look on the Discrepancies between de Fi Nitions and Its Clinical Importance.” *International Journal of Obesity* 45: 12–24.

https://doi.org/10.1038/s41366-020-00713-1.

4. Fahed, Gracia, Laurence Aoun, Morgan Bou Zerdan, Sabine Allam, Maroun Bou Zerdan, Youssef Bouferraa, and Hazem I Assi. 2022. "Metabolic Syndrome : Updates on Pathophysiology and Management in 2021." *Int. J. Mol. Sci.* 23 (2): 786. https://doi.org/10.3390/ijms23020786.
5. Simunovic, Marko, Andrija Jukic, Martina Paradzik, Daniela Supe-domic, Lada Stanisic, Marina Degoricija, Anna Hummelvoll Hillestad, Veselin Skrabic, and Josko Bozic. 2022. "The Role of Urotensin-II in Obesity and Metabolic Syndrome in Pediatric Population." *Children* 9 (204). https://doi.org/10.3390/children9020204.
6. Dastgheib, Seyed Alireza, Reza Bahrami, Sepideh Setayesh, Seyedali Salari, Seyed Reza Mirjalili, Mahmood Noorishadkam, Jalal Sadeghizadeh-Yazdi, Elahe Akbarian, and Hossein Neamatzadeh. 2021. "Evidence from a Meta-Analysis for Association of MC4R Rs17782313 and FTO Rs9939609 Polymorphisms with Susceptibility to Obesity in Children." *Diabetes & Metabolic Syndrome* 15 (5): 102234. https://doi.org/10.1016/j.dsx.2021.102234.
7. Nagrani, Rajini, Ronja Foraita, Francesco Gianfagna, Licia Iacoviello, Staffan Marild, Nathalie Michels, Dénes Molnár, et al. 2020. "Common Genetic Variation in Obesity , Lipid Transfer Genes and Risk of Metabolic Syndrome : Results from IDEFICS / I . Family Study And." *Scientific RepoRtS* 10 (1): :7189. https://doi.org/10.1038/s41598-020-64031-2.
8. Hanh, Nguyen T H, Bui T Nhung, Le T Hop, Le T Tuyet, Duong T A Dao, Nguyen T. T. Thu, and Tran Quang Binh. 2020. "The APOA5 -Rs662799 Polymorphism Is a Determinant of Dyslipidemia in Vietnamese Primary School Children." *Lipids* 55: 683–91. https://doi.org/10.1002/lipd.12270.
9. Roberts, Karyn J., Adolfo J. Ariza, Kavitha Selvaraj, Maheen Quadri, Caren Mangarelli, Sarah Neault, Erica E. Davis, and Helen J. Binns. 2022. "Testing for Rare Genetic Causes of Obesity : Fi Ndings and Experiences from a Pediatric Weight Management Program." *International Journal of Obesity* 46 (8): 1493–1501. https://doi.org/10.1038/s41366-022-01139-7.
10. Cortés-martín, Adrián, Gonzalo Colmenarejo, María Victoria Selma, and Juan Carlos Espín. 2020. "Genetic Polymorphisms , Mediterranean Diet and Microbiota-Associated Urolithin Metabotypes Can Predict Obesity in Childhood-Adolescence." *Scientific RepoRtS* 10: :7850. https://doi.org/10.1038/s41598-020-64833-4.
11. Vukovic, Rade, Tatjana Milenkovic, Katarina Mitrovic, Sladjana Todorovic, Ljiljana Plavsic, & Ana Vukovic, and Dragan Zdravkovic. 2015. "Preserved Insulin Sensitivity Predicts Metabolically Healthy Obese Phenotype in Children and Adolescents." Eur J Pediatr 174 (12): 1649–55. https://doi.org/10.1007/s00431-015-2587-4.
12. Wang, Helen H, Dong Ki Lee, Min Liu, Piero Portincasa, and David Q Wang. 2020. *Novel Insights into the Pathogenesis and Management of the Metabolic Syndrome*. Vol. 23. https://doi.org/10.5223/pghn.2020.23.3.189.
13. Buchmann, Nikolaus, Nils Eckstein, Dominik Spira, Ilja Demuth, Elisabeth Steinhagen-Thiessen, and Kristina Norman. 2021. "Vitamin D Insufficiency Is Associated with Metabolic Syndrome Independent of Insulin Resistance and Obesity in Young Adults - The Berlin Aging Study II." *Diabetes Metab Res Rev. 2021;37:E3457.* 37: :e3457. https://doi.org/10.1002/dmrr.3457.
14. Tecilazich, Francesco, Anna Maria Formenti, and Andrea Giustina. 2021. "Role of Vitamin D in Diabetic Retinopathy : Pathophysiological and Clinical Aspects." *Reviews in Endocrine and Metabolic Disorders* 22: 715–27. https://doi.org/10.1007/s11154-020-09575-4.
15. Corsello, Antonio, Marina Macchi, Veronica D Oria, Chiara Pigazzi, Ilaria Alberti, Giorgio Treglia, Valentina De Cosmi, Alessandra Mazzocchi, Carlo Agostoni, and Gregorio Paolo Milani. 2023. "Effects of Vitamin D Supplementation in Obese and Overweight Children and Adolescents : A Systematic Review and Meta-Analysis." *Pharmacological Research* 192: 106793. https://doi.org/10.1016/j.phrs.2023.106793.
16. Jansen, Erica C, Helen J Burgess, Ronald D Chervin, Dana Dolinoy, Martha María Téllez-rojo, Alejandra Cantoral, Libni Olascoaga-torres, et al. 2023. "Sleep Duration and Timing Are Prospectively Linked with Insulin Resistance during Late Adolescence." *Obesity* 31 (4): 912–22. https://doi.org/10.1002/oby.23680.
17. Addio, L Montefusco F D, C Loretelli M Ben, M Garziano A Rossi, and I Pastore L Plebani. 2021. "Anti

- Inflammatory Effects of Diet and Caloric Restriction in Metabolic Syndrome." *Journal of Endocrinological Investigation* 44 (11): 2407–15. https://doi.org/10.1007/s40618-021-01547-y.

18. Carrizales-sánchez, Ana K, Tomás García-cayuela, and Carmen Hernández-brenes. 2021. "Gut Microbiota Associations with Metabolic Syndrome and Relevance of Its Study in Pediatric Subjects." *Gut Microbes* 13 (1): e1960135. https://doi.org/10.1080/19490976.2021.1960135.
19. Hassan, Nayera E, Salwa M El Shebini, Sahar A El Masry, Nihad H Ahmed, Ayat N Kamal, Ahmed S Ismail, Khadija M Alian, Mohammed I Mostafa, Mohamed Selim, and Mahmoud A S Afify. 2022. "Brief Overview of Dietary Intake , Some Types of Gut Microbiota , Metabolic Markers and Research Opportunities in Sample of Egyptian Women." *Scientific Reports* 12 (1): :17291. https://doi.org/10.1038/s41598-022-21056-z.
20. Gallardo-Becerra, Luigui, Fernanda Cornejo-Granados, Rodrigo García-López, Alejandra Valdez-Lara, Shirley Bikel, Samuel Canizales-Quinteros, Blanca E. López-Contreras, Alfredo Mendoza-Vargas, Henrik Nielsen, and Adrián Ochoa-Leyva. 2020. "Metatranscriptomic Analysis to Define the Secrebiome , and 16S RRNA Profiling of the Gut Microbiome in Obesity and Metabolic Syndrome of Mexican Children." *Microbial Cell Factories* 19 (1): :61. https://doi.org/10.1186/s12934-020-01319-y.
21. Yuan, Xin, Ruimin Chen, Ying Zhang, Xiangquan Lin, and Xiaohong Yang. 2021. "Gut Microbiota of Chinese Obese Children and Adolescents With and Without Insulin Resistance." *Front Endocrinol* 12: :12:636272. https://doi.org/10.3389/fendo.2021.636272.
22. Chung, Yoojin Lindsey, and Young-jun Rhie. 2022. "Metabolic Syndrome in Children and Adolescents." *Ewha Med J* 45 (4): :e13. https://doi.org/10.12771/emj.2022.e13 eISSN.
23. Gudi, Sai Krishna. 2020. "Eating Speed and the Risk of Type 2 Diabetes : Explorations Based on Real-World Evidence." *Ann Pediatr Endocrinol Metab* 25 (2): 80–83. https://doi.org/10.6065/apem.2040028.014.
24. Lobelo, Felipe, Natalie D Muth, Sara Hanson, Blaise A Nemeth, and Council On. 2020. "Physical Activity Assessment and Counseling in Pediatric Clinical Settings." *Pediatrics* 145 (3): :e20193992. https://doi.org/10.1542/peds.2019-3992.
25. Kim, Yoo-Mi, Yeoun Joo Lee, Soo Yeon Kim, Chong Kun Cheon PhD2, and Han Hyuk Lim. 2020. "Successful Rapid Weight Reduction and the Use of Liraglutide for Morbid Obesity in Adolescent Prader-Willi Syndrome." *Annals of Pediatric Endocrinology & Metabolism* 25 (1): 52–56. https://doi.org/10.6065/apem.2020.25.1.52.
26. Kelly, Aaron S., Pernille Auerbach, MargaritaBarrientos-Perez, Inge Gies, Paula M. Hale, Claude Marcus, Nandana Prabhu Lucy D. Mastrandrea, and Silva Arslanian. 2020. "A Randomized, Controlled Trial of Liraglutide for Adolescents with Obesity." *N Engl j Med* 382 (22): 2117–28. https://doi.org/10.1056/NEJMoa1916038.