Metabolic Syndrome in Children: A Concern in Perspective

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Introduction:

Overweight & obesity in the paediatric population is an emerging public health concern. The rapidly increasing rates of childhood obesity have often been clustered with other metabolic abnormalities namely hypertension, insulin resistance &dyslipidemia, leading to an increased risk of cardiovascular diseases. The rising prevalence of paediatric obesity, metabolic syndrome (MetS) is now evident in children & adolescents which were traditionally reported only in adults (Higgins et al., 2017 [12]). Metabolic syndrome, also known as syndrome X, is a cluster of cardiovascular risk factors including hypertension, altered glucose metabolism, dyslipidemia , and abdominal obesity. Metabolic syndrome is known to predict the onset of cardiovascular diseases and type 2 diabetes mellitus along with other clinical conditions such as oxidative stress, chronic low-grade inflammation, hyperuricemia, hyperandrogenism, polycystic ovary syndrome, hepatic steatosis, obstructive sleep apnoea and non-alcoholic fatty liver disease (Weiss et al. 2011 [6], Weiss et al.2013[7]). Metabolic syndrome in adults is defined as the presence of 3 out of the 5 risk factors: central obesity, hypertension, hypertriglyceridemia, low HDL, hyperglycaemia (Al-Hamad et al., 2017 [2]). Several attempts have been made for defining metabolic syndrome in children. Although the pathogenesis of metabolic syndrome is not clearly understood, obesity-related inflammation and insulin resistance are known to be key underlying factors. Childhood obesity is an early risk factor for adult mortality and morbidity and 85% of obese children become obese adults. Paediatric obesity has often been linked to the development of metabolic syndrome and is a marker for metabolic dysfunction. The pattern of lipid partitioning is identified to determine the metabolic impact of obesity. (Weiss et al.,2011[6] ,Higgins et al., 2017[12]). The primary goal in preventing the onset of metabolic syndrome is to promote lifestyle modifications such as healthy diet, physical activity, pharmacological and surgical interventions (Higgins et al., 2017[12]).

Defining Metabolic Syndrome in Children: A clustering of risk factors

In adults at least 5 health organisations

have created clinical criteria for defining metabolic syndrome or insulin resistance syndrome. These include World Health Organization (WHO), the NCEP's ATP III, the American Association of Clinical Endocrinologists/American College of Endocrinology, the International Diabetes Federation (IDF), and the American Heart Association (AHA) in conjunction with the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (Magge et al., 2017[9]). Presently, more than 40 definitions have been reported so far but there is no consensus in the diagnostic criteria for metabolic syndrome in the paediatric population (Al-Hamad et al.,2017[2]). The variability in definitions has been attributed to various physiological and methodological limitations such as the development of transient physiological insulin resistance during puberty, variation in normal insulin levels by age, sex and race and also the lack of standardized central obesity measures in children (Weiss et al.,2013[7]).

In 2007, the International Diabetes Federation attempted to define paediatric metabolic syndrome using age-specific diagnostic criteria based on developmental changes as presented by age-related differences in children. Children younger than 6 years were excluded from the definition due to insufficient data in this age group. (Weiss et al.,2011[6]). Children aged 6-10 years who were obese (defined as waist circumference (WC) ≥90th percentile) and have other relevant risk factors (such as family history of cardiometabolic disease) and children aged 1016 years who were obese (defined as WC ≥90th percentile) and met the adult metabolic syndrome criteria for triglycerides (TGs), HDL-cholesterol (HDL-C), blood pressure (BP), and glucose concentrations were classified with metabolic syndrome (Weiss et al.,2013[7], IDF 2007[11]). Identifying children with multiple metabolic derangements allows targeting of focused interventions toward children at the highest risk for cardiometabolic disease. Thus, rather than focus on defining metabolic syndrome in youth, the American Academy of Pediatrics (AAP) recommends that paediatricians focus on the concept of cardiovascular risk factor clustering and associated risk factor screening (IDF,2007[11]).

Screening:

Obese and overweight children at risk of developing type 2 diabetes mellitus and cardiovascular disease should be screened for medical and behavioural risks, including co-morbid conditions. History and physical examination should be the first step for screening co-morbidities (Al-Hamad et al., 2017[2]).

Table 1: Screening guidelines for co-morbid conditions (Al-Hamad et al., 2017[2]).

Condition	Frequency
Liver disease: Fatty liver	Bi-annually from the age of 10 with obesity or are overweight with other risk factors
Type 2 Diabetes Mellitus	Obese & overweight children with any of the following risk factors: (i) family history with 1st or 2nd degree relatives (ii) at risk race or ethnicity (iii) signs of insulin resistance (iv) maternal history of diabetes or gestational diabetes.
Dyslipidemia	Universal screening between ages 9-11. Obese children: 2-8years Overweight adolescents: 12-16years

Determinants of Metabolic Syndrome in Children:

Multiple determinants exist for the 5 risk factors currently used to define metabolic syndrome in children and adults.

Familial influences: Familial influences include shared environmental & genetic factors that together form a strong heritability of the individual components of metabolic syndrome. Family history of cardiovascular diseases and obesity are well-known risk factors for elevated blood pressure, dyslipidemia and obesity in the offspring through shared environmental & genetic factors.

Health behavioural factor: Health behavioural factors may directly or indirectly contribute to risk factors associated with metabolic syndrome, chiefly obesity in youth. The causative factors include excessive screen time, short duration of sleep, sedentary lifestyle and tobacco smoke exposure.

Prenatal & early postnatal period: Prenatal and early postnatal period lays a foundation for several risk factors contributing to obesity & other components of metabolic syndrome. These include the presence of maternal gestational diabetes, low birth weight (especially with rapid catch-up growth), infant feeding practices and early adiposity rebound. (Magge at al.,2017[9])

Pathogenesis of Metabolic Syndrome:

The exact pathophysiological mechanisms of paediatric metabolic syndrome are incompletely understood. Complex interactions between obesity, insulin resistance, and inflammation are

known to play a central role in its development. The World Health Organization (WHO) hypothesizes that the association and clustering of Type 2 Diabetes, hypertension, dyslipidemia, and Cardiovascular Diseases (CVD) arises from a common antecedent - insulin resistance (Al-Hamad et al., 2017[2], Higgins et al., 2017[12])

Obesity, Lipid Partitioning & Insulin Resistance: The term lipid partitioning refers to the distribution of body fat in various organs and compartments. Along with the degree of obesity, the impact of obesity is determined by the pattern of lipid partitioning. Different lipid depots have different metabolic characteristics, depicted by the adipocytokine and cytokine secretion profile and sensitivity to hormones. Accumulation of visceral fat, independent of Body Mass Index(BMI) is strongly associated with both childhood metabolic syndrome and CVD in later life. Visceral-fat derived adipocytokines and cytokines are known to be directly associated with insulin resistance and obesity. A lipid-partitioning profile with larger visceral-fat depot & relatively smaller subcutaneous fat depot is considered to be associated with adverse metabolic outcome as compared to individuals with a larger subcutaneous fat depot, even if the latter has considerably greater BMI & percent body fat. Waist circumference is known to be an independent risk predictor of insulin resistance and intra-abdominal fat deposition. Moreover, waist circumference has also been strongly linked systolic and dialostic blood pressure, HDL cholesterol and triglycerides. Thus, waist circumference is considered to be the best anthropometric correlate of intra-abdominal fat, of the pediatric metabolic syndrome definition by the Internal Diabetes Federation. (Weiss et al.,2011[6], Wittcopp 2016[1])

The secretion profile of adipocytokines and its impact on the circulating concentration of inflammatory cytokines and free fatty acids flux depends on the pattern of lipid storage. The combined effect of these factors determines insulin sensitivity within target organs such as skeletal muscle, adipocytes, pancreas, and liver. Build up of free fatty acids in the liver, decreases its ability to regulate gluconeogenesis, which further gives rise to insulin levels. The resultant hyperinsulinemia causes a rise in the transcription of genes for lipogenic enzymes in the liver, leading to increased triglyceride synthesis. (Weiss et al.,2011[6], Weiss et al.,2013[7], Al-Hamad et al.2017[2], Wittcopp 2016[1]). Additionally, the increased hepatic insulin insensitivity also is known to increase triglyceride-rich VLDL particles. (Al-Hamadet al.2017[2]).

At the adipocyte level, insulin resistance leads to amplified lipolysis & lipid deposition in the bloodstream. Adipocyte dysfunction is a major contributing factor to the pathogenesis of type 2 diabetes mellitus and obesity. Adipocyte dysfunction leads to the release of pro-

inflammatory cytokines, such as monocyte chemoattractant protein-1, tumor-necrosis factor alpha, promotes macrophages migration towards adipose tissue further contributing to cytokine production. This increase in inflammatory biomarkers indicates the presence of an activated subclinical inflammatory process in individuals with metabolic syndrome. A decrease in adiponectin level as seen in obesity results in an additional increase in inflammatory processes in the adipose tissue. This increase in inflammatory cytokines and reduced levels of adiponectin seem to be factors associated with the classical symptoms of the syndrome. These cytokines can affect insulin action in various tissues, such as liver & muscle & local insulin resistance. Insulin resistance increases lipolysis, leading to increased free fatty acids in the bloodstream. Thus, insulin resistance further promotes a pro-inflammatory state as its anti-lipolytic and anti-inflammatory effects are negated. (Weiss et al.,2011[6], Al-Hamad et al.2017[12], Higgins et al., 2017[12], Wittcopp 2016[11]).

The combination of insulin resistance and early atherogenesis (manifested as endothelial dysfunction) drives the development of altered glucose metabolism and of cardiovascular disease.

Genetics, Epigenetics & Maternal health: The role of genetics and maternal health in relation to metabolic outcomes of the offspring is well established. Epigenetic mechanisms may account for the majority of metabolic syndrome initiation. These are now considered to be mechanisms linking early environmental exposures during pregnancy with programmed changes in gene expression, resulting in an alteration of growth & development. It has been suggested that 10% of obesity cases could be attributed to genetics and 90% to environmental factors. Intrauterine environment, maternal, genetic, lifestyle factors & low and high birth weight leads to an increased predisposition of developing obesity during childhood and later in life. The hormonal, nutritional and metabolic environment during gestation alters organ structure, cellular responses and gene expression that impact the offspring's physiology and metabolism. These epigenetic alterations are mediated by DNA methylation, histone modifications, chromatin remodeling, and/or regulatory feedback by micro RNAs. It was noted in the Bolgalusa Heart Study that obesity during childhood tracks into adulthood. Also, it has shown that overweight/obesity or any metabolic abnormality between the age group of 9-24 years predicts a greater risk of developing metabolic syndrome, type 2 diabetes mellitus, and adverse cardiovascular outcomes 21-25 years later. (Arora et al., 2017[10], Bussler et al.,2017[8])

Maternal health, both before and during pregnancy has a direct impact on the metabolic profile of the offspring. It is a

key factor for the health and development of intra-uterine growth of the fetus. Gestational Diabetes, even when less severe has been associated with large-for-gestational-age (LGA)& larger birth weights. Nutrition and maternal health is a concern, even ahead of conception. It was observed in Project Viva, that each 5-unit increase in maternal BMI pre-pregnancy was associated with a 0.92 kg increase in total fat and 0.39 kg trunk fat in the offspring at birth. Each 5 kg of weight gained during pregnancy was positively and significantly associated with greater total and trunk adiposity. Thus, children born to mothers with a greater BMI have greater overall and central fat increases the risk of cardiometabolic diseases. Offspring of women with higher Greater Gestational Weight Gain had greater adiposity and higher leptin. The long-term consequences of children born LGA include imbalances in glucose homeostasis with higher insulin resistance pre-pubertally compared to normal for gestational age counterparts. (Bussler et al.,2017[8], Perng et al.2014[4])

Health Behavioural Factors: Negative health habits of parents are commonly mirrored in their offspring. Repeated exposure to negative health behaviours observed in childhood has been linked to the subsequent development of unhealthy lifestyle behaviours. The most important negative health behaviours predicting the development of metabolic syndrome in paediatrics include lack of sleep, screen time, lack of physical activity and incorrect eating habits.

Figure 1 shows the co-relation between irregular sleep and increased screen time with the development of Metabolic Syndrome.

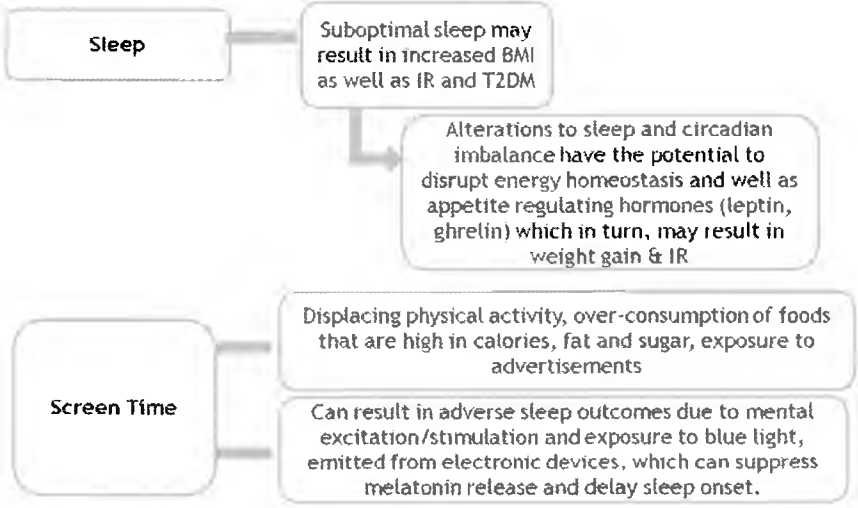


Figure 1: Association between irregular sleep, screen time and the development of Metabolic Syndrome (Arora et al.2017[10]).

In the Health Growth Study, it was observed that children aged 9-13 years having a lifestyle pattern characterised by screen time, shorter sleep duration and higher consumption of sugared beverages was positively associated with Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), whereas the pattern characterized by more time spent on moderate-to-vigorous Physical Activity (MVPA) and more frequent eating occasions was inversely associated with HOMA-IR. It was thus observed that a lifestyle pattern of 472 min of MVPA and 5 eating occasions/day was associated with reduced likelihood of IR in children (O Androutsos et al.2014[3]).

Dietary Factors: The recent exposure to an 'obesogenic' environment in early and adolescence has contributed to the rise in obesity and predisposition to insulin resistance, both playing a key role in the onset of paediatric metabolic syndrome. Rapid changes and increased exposure to food availability, including processed, ready-made and fast foods, has been purported to influence dietary intake. These modified foods tend to have higher sugar, salt and calorie contents. Over-consumption of these food items is likely to result in positive energy, which in turn, promotes obesity and/or insulin resistance if levels of energy expenditure are insufficient to counteract energy imbalance. (Weiss et al 2013[7], Magge et al. 2017[9], Arora et al 2017[10])

Co-morbid conditions associated with Metabolic Syndrome:

Non-Alcoholic Fatty Liver Disease (NAFLD): NAFLD is an important metabolic complication in the obese pediatric population. It includes a range of liver conditions from asymptomatic steatosis to non-alcoholic steatohepatitis to advanced fibrosis with cirrhosis. The intra-hepatic fat accumulation that is apparent in this disease is believed to be associated directly with insulin resistance and, therefore, is also strongly associated with MetS. Children with a diagnosis of NAFLD often have many clinical features that overlap with MetS, increasing their risk for CVD. Definitive diagnosis can be difficult and requires a liver biopsy, but elevated aminotransferase values in an obese child should prompt the clinician to investigate further for NAFLD. (Bussler et al.,2017[8])

Obstructive Sleep Apnoea (OSA): OSA is a very common condition among obese adults and children. OSA is characterized by repetitive pharyngeal narrowing and closure during sleep, snoring, and frequent nocturnal awakenings leading to recurrent oxyhemoglobin desaturation, sleep fragmentation, and hypercapniaIt is well recognized that obesity and specific fat depots (upper airway, tongue, andabdominal adipose deposition) predispose to OSA. Moreover, OSA may also predispose to obesity due to daytime somnolence, decreased activity, and decreased sleep duration, as well as due to neurohumoral changes, such as resistance to the anorexigenic hormone leptin. OSA is associated with MetS in children and adolescents. A study reported that MetS is present in 16% of children without OSA, but in 59% of those with OSA. Likewise, all single components of MetS are associated with OSA. (Bussler et al.,2017[8])

PCOS: Polycystic ovary syndrome

(PCOS) is a common disorder affecting obese adolescent girls that is characterized by hyperandrogenism and associated with insulin resistance. Adolescent girls with PCOS have an increased risk of MetS independent of obesity or insulin resistance, and the combination of PCOS and MetS may increase the risk for CVD and T2D more than just MetS alone.Young women with PCOS should be screened routinely for the components of MetS and impaired glucose metabolism.(Bussler et al.,2017[8])

Tackling Metabolic Syndrome in Children:

In general, treatment of childhood metabolic syndrome currently focuses on several areas that include weight reduction via dietary intervention, increased physical activity, lifestyle modifications, and management of various disease-specific components. Other available options to manage obesity include behavioural intervention, pharmacological therapies, and bariatric surgery. Weight reduction or, in younger children, a decrease in BMI percentile, is a critical component of MetS treatment. Even a small reduction in BMI percentile can have beneficial effects. Before engaging a patient and family in a weight reduction program, clinicians should assess them for readiness to change. Dietary recommendations continue to focus on a moderately reduced calorie intake while maintaining a well-balanced diet. Obese children with the components of MetS should be engaged in comprehensive behavioural modification programs that focus on nutrition and physical activity. Interventions that offer more contact hours (>26 hours) have more success with weight loss over both the short and long term.

Dietary interventions recommended in the recent Endocrine Society guidelines based on the AAP and the US Department of Agriculture include: elimination of sugar-sweetened beverages; decrease consumption of fast food; less added table sugar; avoidance of high fructose corn syrup; less high sodium processed food; and less saturated dietary fat in adolescents and children older than 2 years of age. Further, consumption of whole fruits, vegetables, and dietary fibre are encouraged in addition to portion control education, enhancing food labelling, and encouraging eating regular meals to avoid grazing. It is essential that dietary interventions and calorie reduction in children and adolescents are supervised by an experienced dietician in growing children's needs. (Weiss et al.2013[7], Wittcopp 2016[1], Al-Hamad et al., 2017 [2]).

Physical activity

It is recognized that inactivity can lead to lower insulin sensitivity in skeletal muscle and this can be reversed with increased physical activity A minimum of 20 min of moderate to vigorous physical activity daily, with a goal of 60 min daily is recommended in the context of a calorie-controlled diet. Physical activity is helpful in improving the lipid profile by increasing HDL concentration and decreasing both LDL and triglycerides concentrations. It is shown to improve insulin resistance and is correlated with lower fasting insulin levels. Exercise may result in improvement of endothelial function with a reduction in systolic and

diastolic BP in addition to its abdominal fat reduction effect. Physical activity is also found to have anti-inflammatory effects.(Weiss et al.2013[7]Al-Hamad et al., 2017 [2]).

Conclusion:

MetS in children and adolescents continues to be a challenge for clinicians, and families. It is clear that the lifecycle approach to combat obesity at critical phases of growth starting from pregnancy to infancy, early childhood and adolescence are critical. Dietary, lifestyle changes and behavioural modifications are the mainstays of the treatment. Concerted efforts of all stakeholders including parents, home environment, school environment, peer pressure, media, and food industry are of importance. The focus of the dietary intervention should be on High Fat Sugar and Salt Foods (HFSS). There is a felt need to undertake action research on behavioural changes to achieve success in curbing childhood obesity which can dramatically impact metabolic health.

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