

Metabolic syndrome in children (Review)

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Abstract. Metabolic syndrome (MetS) is a cluster of cardio-metabolic risk factors, including central obesity, insulin resistance, glucose intolerance, dyslipidemia and increased blood pressure. The prevalence of MetS is on the increase worldwide owing to the epidemic of overweight and obesity. The risk of prevalence of MetS greatly increases during adulthood for those children exposed to cardiometabolic risk factors in their early lives. MetS has also been associated with liver fat accumulation in children. Elevated levels of plasma alanine aminotransferase and γ -glutamyl transferase have been associated with liver fat accumulation. The present review aimed to expand knowledge on the clustering of cardiometabolic risk factors responsible for the widespread occurrence of metabolic disease in children.

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1. Introduction

Metabolic syndrome (MetS) is a cluster of cardio metabolic risk factors, including central obesity, insulin resistance, glucose

intolerance, dyslipidemia and raised blood pressure (1,2). The prevalence of MetS is on the increase worldwide due to the epidemic of overweight and obesity (3). Children with MetS have an increased risk of adulthood MetS, type 2 diabetes and cardiovascular disease (CVD) (4,5). MetS also predicts type 2 diabetes, CVD and all-cause mortality in adults (6,7). Thus, gaining a better understanding of the pathophysiology and determinants of this risk factor clustering as early as childhood is crucial.

In previous studies conducted on children continuous variables were used for the components of MetS and a continuous cardiometabolic risk score was calculated instead of using a definition based on dichotomous variables (8,9). Despite abundant research on MetS using a continuous cardiometabolic risk score or factor analysis, to the best of our knowledge, there are no previous studies in which the cardiometabolic risk score has been validated by confirmatory factor analysis (CFA) in different age groups. Furthermore, few studies have investigated the long-term health consequences of a high cardiometabolic risk score (10). In addition to traditional cardiometabolic risk factors, several other metabolic disorders, such as liver fat accumulation, have been associated with MetS in children (11). The epidemic of pediatric overweight and obesity has markedly increased the number of children affected/diagnosed with non-alcoholic fatty liver disease (NAFLD) (12,13). The plasma concentrations of liver enzymes, such as alanine aminotransferase (ALT) and γ -glutamyl transferase (GGT) are potentially useful tools in the screening of pediatric NAFLD (14). The present review focused on the recent aspects of MetSs in young infants.

2. Genetic factors responsible for MetS

Several genome-wide scans performed in families with clustering of cardio metabolic risk factors have strongly supported an inherited component to MetS (15,16). In a study of 357 children and 378 parents, children who had at least one parent with MetS, defined by the Adult Treatment Panel III criteria, had higher levels of obesity and insulin resistance than children in whom neither parent had MetS (17). Additionally, the Bogalusa Heart Study has shown that offspring of parents with early coronary heart disease were overweight beginning in childhood and developed an adverse cardiovascular risk factor profile at an increased rate (18). Other family and twin studies have identified a strong familial aggregation for cardio=metabolic risk factors (19).

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3. Low physical activity, sedentary behavior and poor cardiorespiratory fitness

The current epidemic of overweight and MetS is mainly due to an imbalance between energy intake and energy expenditure. Low levels of physical activity increase the risk of MetS, type 2 diabetes, CVD and all-cause mortality in adults (20). The prevalence of these diseases may be controlled by the elevation of physical activity and cardiorespiratory fitness (21). Low levels of physical activity and cardiorespiratory fitness have been associated with increased levels of independent and clustered metabolic risk factors among adolescents and children (22,23). A sedentary lifestyle has also caused a decrease in cardiorespiratory and musculoskeletal fitness. Although, the independent role and relative importance of physical activity and sedentary lifestyle in the development of childhood overweight is well known, MetS and associated adverse health consequences, as well as underlying biological mechanisms remain to be determined.

4. Dietary factors and MetS

The role of diet in the development of MetS is not well understood. Western dietary patterns and the consumption of meat and fried foods have been directly related to the risk of MetS, whereas the consumption of whole-grain products, fruit, vegetables and dairy products have been inversely associated with MetS (24). Weight loss has been observed to be effective in the treatment of the components of MetS, including excessive body adiposity, insulin resistance, dyslipidemia and elevated blood pressure (25). The Finnish Diabetes Prevention Study revealed that even modest weight loss reduced the prevalence of MetS in 522 middle-aged overweight men and women with impaired glucose tolerance (26). The Diabetes Prevention Program in the USA showed that an intensive lifestyle intervention reduced the incidence of MetS by 41% in 3,000 adults (27). Results from the Physical Activity and Nutrition in Children (PANIC) Study suggested that promoting regular consumption of main meals, decreasing the consumption of sugar-sweetened beverages and low-fat margarine and increasing the consumption of vegetable oils should be emphasized to reduce metabolic risk among children (28).

5. Other factors

Other potential risk factors underlying MetS include epigenetic factors as well as the overnutrition of the fetus resulting in increased birth weight and low birth weight associated with rapid catch-up growth (29). Exposure of the fetus to gestational diabetes of the mother increases the risk of MetS (30). Cigarette smoking and excess alcohol consumption have been connected with increased cardiometabolic risk (31). A poor socioeconomic status and psychosocial background have also been associated with MetS (32). Furthermore, health-related policies such as the focus on early prevention, plays a fundamental role in reducing overweight and obesity and related clustering of cardiometabolic risk factors.

6. Insulin resistance and hyperglycemia

Insulin resistance is increased in overweight and obese individuals and is often seen as the core feature of MetS (33). The main physiological effects of insulin include an increase in skeletal muscle glucose uptake and suppression of hepatic glucose production and adipose tissue lipolysis. Insulin resistance is a general term meaning that insulin does not exert its normal effects in insulin-sensitive target tissues, such as skeletal muscle and adipose tissue (34). As previously discussed, insulin resistance in adipose tissue manifests itself as the inability to suppress lipolysis, which leads to an influx of FFAs to the liver, skeletal muscle and other organs leading to insulin resistance in these tissues (35). The large number of adipokines secreted by adipose tissue modulates insulin sensitivity. Insulin resistance in the liver increases gluconeogenesis and decreases glycogen synthesis resulting in fasting hyperglycemia (36).

The majority of peripheral glucose uptake and further metabolism occurs in the skeletal muscle. Increased plasma FFA levels disrupt the glucose-fatty acid cycle and insulin-mediated glucose uptake in the muscle. However, in non-diabetic state, this resistance is compensated by increased insulin secretion from the pancreatic β -cells. If pancreatic insulin secretion fails, insulin resistance in skeletal muscle increases hyperglycemia. The more insulin resistance the body experiences, the more insulin is secreted to prevent decompensation of glucose tolerance (37). If the compensatory mechanisms fail, the subsequent hyperglycemia and glucotoxicity may exacerbate the insulin resistance and islet β -cell insulin secretion. Insulin resistance further worsens the low-grade inflammatory state, induces endothelial dysfunction in the arteries and elevates blood pressure. In addition, insulin resistance decreases signaling in the hypothalamus which leads to increased food intake and weight gain (38).

7. Dyslipidemia

It is currently unknown whether insulin resistance induces dyslipidemia or whether these risk factors are associated via a common underlying cause. Increased hepatic FA intake stimulated by insulin resistance leads to the increased production of VLDL-triglycerides and apolipoprotein B. Apolipoprotein B is a marker of triglyceride-rich lipoproteins and retards triglyceride clearance (39). Increased liver fat content is associated with the overproduction of VLDL from the liver due to a lack of insulin-induced suppression of VLDL production (40). In addition to the overproduction of VLDL by the liver, alterations in lipoprotein lipase activity have been associated with MetS. Circulating HDL cholesterol levels are decreased owing to overconsumption, while the density of low-density lipoprotein (LDL) increases in MetS. The small dense LDL is potentially atherogenic owing to its low affinity to the LDL receptor and long retention time in the circulation (41).

8. Elevated blood pressure

The role of blood pressure in the pathophysiology of MetS is not fully understood but several mechanisms have been suggested. Obesity has been associated with increased

sympathetic tone, which raises blood pressure. Furthermore, insulin and leptin appear to increase sympathetic nervous activity. In the setting of insulin resistance, the vasodilatory effect of insulin can be lost, resulting in endothelial dysfunction and vasoconstriction (42). Hyperinsulinemia leads to increased sodium absorption in the kidneys, which increases blood volume and thereby blood pressure (43). It has also been hypothesized that LDL cholesterol and triglycerides may damage the endothelium, impair nitric oxide release and cause endothelial dysfunction. This hypothesis suggests that dyslipidemia causes hypertension by mechanisms only partly related to obesity and insulin resistance (44,45).

9. Consequences of MetS

Type 2 diabetes and its complications. MetS is associated with a marked increase in the risk for type 2 diabetes, which is characterized by chronically elevated blood glucose concentrations resulting from insulin resistance and reduced insulin secretion (46). A typical situation is relative insulin deficiency due to the inability of body to adequately compensate for insulin resistance. Type 2 diabetes is a heterogeneous disease and its clinical expression requires genetic and environmental factors (47). Nevertheless, most patients have insulin resistance and MetS prior to the onset of type 2 diabetes. Overweight, obesity, insulin resistance and dyslipidemia in 75-85% of patients precede the progression of type 2 diabetes (48). The risk of CVD events is much higher in patients with type 2 diabetes than in non-diabetic subjects (49). Other common complications of type 2 diabetes included retinopathy, nephropathy and neuropathy, which also predict CVD (50). In recent years, the prevalence of type 2 diabetes in children as well as adolescents has been on the increase (51).

PNPLA3 gene variant and liver adiposity. Studies conducted on obese adults and children have suggested that the *PNPLA3* gene I148M variant is related to the severity of hepatic steatosis and the presence of NASH and fibrosis. The *PNPLA3* 148M allele has not been generally associated with the components of MetS, such as measures of body adiposity, as well as lipid and glucose metabolism (52). However, the results of previous studies in children have suggested that the 148M allele carriers have lower plasma levels of HDL cholesterol and a lower BMI than the non-carriers (53). It has been suggested that the increased amount of body fat may act as a stressor on the *PNPLA3* 148M carriers thereby influencing the susceptibility to increased circulating liver enzymes. Investigators hypothesized that the lack of association with ALT plasma levels may have been due to small sample sizes. Thus, an increased number of studies are needed to gain a better understanding of the biological functions and pathogenetic mechanisms of this genetic variant with regard to liver adiposity.

Atherosclerosis and atherosclerotic CVDs. In adults, MetS has been strongly associated with subclinical atherosclerosis, as estimated by carotid artery intima-media thickness (IMT) and atherosclerotic lesions using non-invasive ultrasonography (54,55). Previous findings have shown that cardiometabolic risk factors in childhood predict increased

adult carotid IMT (53) as well as decreased carotid artery elasticity (56,57).

MetS is associated with increased risk for CVD in the next 5-10 years and the lifetime risk is undoubtedly higher (58). MetS has also been associated with increased risk of acute ischemic stroke or transient ischemic attack. Individuals with MetS but without diabetes had a 1.5-fold higher risk of ischemic stroke or transient ischemic attack compared with patients without MetS. This risk was higher in women than in men (59). In the KIHHD study, middle-aged men without any previous history of CVD were followed up for 11 years, and those with MetS were three to four times more likely to succumb to coronary heart disease, about three times more likely to succumb to CVD and about two times more likely to succumb to all these causes. Despite the predictive value of MetS for type 2 diabetes, CVD and all-cause mortality in adults, it remains unclear whether MetS has prognostic value over its individual components (60). Furthermore, MetS is not an absolute risk indicator, because it does not contain many of the factors that determine absolute risk, for example, age, gender, cigarette smoking and LDL cholesterol levels.

10. Other manifestations of MetS

Other well-known manifestations of MetS include polycystic ovarian syndrome in women and obstructive sleep apnea. Polycystic ovarian syndrome is characterized by anovulation, androgen excess and insulin resistance (61). Women with polycystic ovarian syndrome have been found to have increased risk for developing type 2 diabetes and CVD. The pathophysiology of polycystic ovarian syndrome is unclear, but the ovary, hypothalamic-pituitary axis and insulin are likely to play a major role in MetS (62). Obstructive sleep apnea has been associated with excess body fat content, insulin resistance and other features of MetS (63,64). Individuals with obstructive sleep apnea are at increased risk for CVD morbidity and mortality (65). Several other disorders and symptoms such as dementia, depression, osteoarthritis, pulmonary embolism, gallbladder disease, asthma and many types of cancer have been associated with overweight and obesity (66).

11. Conclusion

It can be concluded from the above citations that MetS is a serious disorder associated with multiple diseased states. Extensive research is needed in the therapeutic as well as diagnostic areas for the improvement of affected pediatric patients.

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