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A growing problem in childhood and adolescence: Metabolic syndrome and its relationship with physical activity and fitness

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ABSTRACT
Metabolic syndrome (MetS); is defined as a life-threatening endocrinopathy in which systemic disorders such as insulin resistance, abdominal obesity, glucose intolerance, diabetes mellitus, dyslipidemia, hypertension, and coronary artery disease are combined. Although, it is generally known as a problem of adults, it emerges as an essential problem in childhood and adolescence. MetS, closely related to obesity, is increasing due to bad eating habits and sedentary lifestyles. The pathophysiology of MetS has yet to be elucidated. Therefore, lifestyle changes, especially diet and physical activity, are the cornerstones of MetS treatment. In general, both physical activity and fitness; appear to be separately and independently associated with metabolic risk factors in children and adolescents. Although, studies show that activities that increase physical activity levels and improve aerobic fitness cause a decrease in the risk of MetS; a definitive prescription for exercise has not been established at this time. This review aimed to review the definition, classification, and factors playing a role in the pathogenesis of MetS, as well as to evaluate the relationship between MetS and physical activity and aerobic fitness in children.
Keywords: Metabolic syndrome, Physical activity, Physical fitness, Pediatrics, Adolescents.

1. INTRODUCTION

Metabolic syndrome (MetS); is an important public health problem that causes severe mortality and morbidity and is increasing all over the world with the realization that metabolic abnormalities such as insulin resistance (IR), obesity, dyslipidemia, and hypertension (HT) cluster in some patients; MetS was first described by Gerald M. Reaven in 1988 as Syndrome X, which is a syndrome that is combining metabolic abnormalities. It was emphasized that Syndrome X is a collection of cardiovascular risk factors, and IR is a factor underlying Syndrome X [1]. Afterward, the diagnostic criteria of MetS were revised many times over time [2]. It is essential to prevent and manage MetS, which causes serious health problems, impairs quality of life, and even threatens life [3]. Increasing physical activity and cardiorespiratory fitness are suggested to be essential in reducing the risk of MetS, but the relationship between MetS and physical activity has yet to be fully elucidated.

MetS and Diagnostic Criteria

Various updates have been made to the MetS diagnostic criteria over time. First, in 1998, the World Health Organization (WHO) determined the diagnostic criteria for the syndrome and accepted its name as MetS. WHO has emphasized the relationship between the main components of MetS and IR. They accepted impaired glucose tolerance, overt diabetes mellutis (DM), or IR as the first condition for diagnosis. Also, they determined that at least two other components, dyslipidemia, abdominal obesity, and microalbuminuria, were associated with IR as diagnostic criteria [4]. International Diabetes Federation (IDF), in addition to absolute abdominal obesity, MetS was defined as

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the combination of two high triglyceride (TG), low high-density lipoprotein (HDL), high blood sugar, and high blood pressure [5]. In contrast, abdominal obesity, an indicator of IR, is the first condition in IDF diagnostic criteria. Turkish Society of Endocrinology and Metabolism published a clinical guideline in 2009. It defined MetS as a fatal endocrinopathy that starts with IR, abdominal obesity, glucose intolerance, or systemic disorders such as DM, dyslipidemia, HT, and coronary artery disease (CAD). The guideline emphasized that no single genetic or environmental factor has yet been defined that explains all the components of MetS. This heterogeneous disease develops based on IR.

Although, MetS is often known as a health problem in adulthood, it has recently emerged as an essential problem in childhood and adolescence. It is known that an increasing number of children and adolescents are affected by MetS [6, 7]. A definite consensus has yet to be reached in the definition of childhood MetS as in adults [8]. Although, the criteria used in the studies are based on national recommendations, there may be various changes in cut-off values according to age, gender, and race [8].

MetS Pathophysiology

The pathophysiology of MetS is complex, and the exact mechanism has not yet been elucidated [9]. However, it is suggested that abdominal obesity and insulin resistance effectively develop MetS [10]. Macrophage infiltration occurs in adipose tissue with intra-abdominal obesity. Various cytokines such as TNF-α and IL6 released from macrophages cause inflammation. This inflammation leads to lipolysis in adipose tissue, increasing circulating free fatty acids, decreased insulin signaling, and decreased glucose transporter (GLUT4) synthesis, resulting in IR [11]. It also leads to increased IL6 caused by obesity, insulin resistance, and acute phase reactants such as C-reactive protein (CRP) synthesis. Various studies have shown a close relationship between high CRP levels and the development of MetS. It is also known that IL6 contributes to the thrombotic pathway by causing an increase in fibrinogen [11].

Increased adipose tissue with obesity; causes a decrease in adiponectin levels and an increase in leptin levels. As a result, pro-inflammatory cytokines released from adipose tissue, increased leptin, decreased adiponectin level and increased free fatty acids in circulation cause atherogenic dyslipidemia, atherosclerosis, and CAD [11].

Another effective pathway in the development of MetS is activating the renin-angiotensin system (RAS). Obesity and IR cause an increase in the production of angiotensin-2 secreted by adipose tissue [11].

Increased lipolysis in insulin resistance causes an elevation of free fatty acids in the circulation. Increased fatty acids in the blood are used to synthesize triglycerides in the liver. Very low-density lipoprotein (VLDL) production increases, leading to dyslipidemia [9].

In conclusion, although the precise mechanisms of MetS have not been fully elucidated, it has been shown that IR and obesity cause MetS by affecting various pathways [12]. Regarding the prevention of abdominal obesity and insulin resistance, the importance of physical activity has been mentioned in previous studies [13, 14].

MetS Prevalence

MetS, which has a 35-40% prevalence in adults, is also an increasing health problem in childhood and adolescence [3, 6]. In the 2016 UNICEF report, it was stated that the frequency of MetS in children and adolescents in Western Europe and the United States (USA) increased from 2% to 25% in the mid-1990s [15]. In the study performed by Ağırbaşlı et al., in Turkey, the frequency of MetS was determined as 2.2% in 1385 healthy children aged 10-17 years [16].

National Health and Nutrition Examination Survey I (NHANES I) study (1988-1994), conducted in the USA, demonstrated that MetS features were found in 3% to 14% of all children and adolescents. These rates were reported as 13% to 37% in obese patients in the study [6]. The prevalence of MetS increased with the severity of obesity and reached up to 50% in severely obese individuals. They also found that increased obesity was associated with increased CRP levels and decreased adiponectin levels.

In previous studies, while the frequency of MetS was between 1-23% in the pediatric population, the frequency of MetS in obese children and adolescents was found in a wide range, such as 3-60% [17]. The main reason for this wide range was reported as criteria used for the MetS in childhood; different criteria used in guidelines and age, gender, race, and ethnicity are the leading causes of difference [18].

Prevention and Treatment of MetS and Obesity

Many studies revealed that MetS has gradually become a public health problem, especially in childhood and adolescence, and obesity is related to an increased risk of MetS [3]. MetS and its components in childhood increase the risk of MetS in adulthood [19]. So, prevention of childhood obesity and MetS is essential [3]. In addition to preventive approaches, effective and permanent treatment options are required regarding the consequences that may occur due to the increasing obesity in the pediatric population. Each syndrome component should be treated as early as possible [20].

Diet and physical activity are the cornerstones of MetS treatment [3]. Evidence on the efficacy and safety of pharmacotherapy in children is scarce [3]. However, in cases where diet and physical activity are insufficient to reduce overweight, dyslipidemia, high blood pressure, and high blood sugar, pharmacotherapy is needed; In resistant cases, surgery is also required [3]. As a result, a multidisciplinary approach and individual treatment are required to treat the components of MetS and obesity [3]. Treatment of obesity aims to reach a healthy weight and to maintain it by ensuring the energy balance between calories taken and spent. All of the components of MetS can be improved by reducing fat mass [3]. Primary approaches and treatments according to the components of MetS are summarized in Table I [3, 21].

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Table I. *MetS components and related primary approaches and treatments [3, 21]*

Components	Primary approach	Treatment
Obesity	Lifestyle interventions: 1. Regulation of diet (caloric limitation, personal goals recommended by dietitians) 2. Physical activity (60 min of moderate/vigorous physical activity every day, including vigorous activity three days per week)	1. Pharmacologic treatment, e.g., orlistat 2. Surgical treatment, e.g., bariatric surgery
Dyslipidemia	Lifestyle interventions: 1. Regulation of diet (reducing simple carbohydrate intake, reducing cholesterol intake <300 mg/day and total fat between 25 and 30% of daily calories, possible use of stanol esters or plant sterols) 2. Physical activity	Pharmacologic treatment, e.g., statins
Glucose regulation disorders and type 2 diabetes mellitus	Lifestyle interventions: 1. Regulation of diet 2. Physical activity 3. Sleeping habits	Pharmacologic treatment Although the use of metformin in glucose disorders is uncommon, for type 2 diabetes mellitus, e.g., metformin and/or insulin can be used.
Hypertension	Lifestyle interventions: 1. Regulation of diet (increasing intake of fruits and vegetables, increasing olive oil polyphenols, reducing sodium) 2. Physical activity (30-60 min of moderate/vigorous physical activity at least 3-5 days per week)	Pharmacologic treatment: Starting with a single drug (e.g., angiotensin receptor blocker, ACE inhibitör, long-acting calcium channel blocker, or thiazide diuretics) at the low end of the dosing range.
Non-alcoholic fatty liver disease	1. Lifestyle interventions and weight loss. 2.Omega-3 fatty acids and probiotics may ameliorate the progression of the disease. 3. Vitamin E can improve hepatocellular ballooning	

The Relationship of Physical Activity and Physical Fitness with MetS

Physical activity is any body movement created by skeletal muscles that cause energy consumption. Physical fitness is defined as the ability to create sufficient work in the muscle [3]. The metabolic equivalent of task (MET) is the ratio of a person's metabolic rate at work to his resting metabolic rate. One MET is the amount of oxygen consumed during rest, corresponding to 3.5 ml O_2/kg/min. It also allows the classification of physical activities according to their intensity and frequency. Physical activities below 3 METs, such as slow walking, and daily housework, as "Light-intensity activities"; activities between 3-5.9 METs, such as fast-paced walking, jogging, swimming, and dancing, as "Moderate-intensity aerobic physical activities (MPA)", activities between 6-8 METs such as high-paced running, volleyball, and basketball as "Vigorous-intensity aerobic physical activities (VPA)", and activities above 8 METs are called "Very vigorous-intensity aerobic physical activities" [22]. Maurice et al., reported that adult MET values are unsuitable for children and that the MET value should be taken as a reference as 1.5 to 2 METs for sedentary behavior [22]. Studies have shown that children with high physical fitness who are overweight and children with normal weight and low physical fitness have a similar risk of MetS [23].

There is an inverse relationship between physical activity and the risk of MetS. Increased physical activity in children and adolescents has positive metabolic effects independent of weight. It is also associated with the risk of MetS and its component [3, 24]. For example, physical activity contributes to body composition by reducing fat body mass and the risk of central obesity and its negative consequences [14].

Physical activity decreases insulin resistance and increases insulin sensitivity [1, 6, 25]. Physical activity also decreases the risk of hyperlipidemia by reducing LDL and TG levels and increasing HDL levels. It is also known that high TG leads to an increase in reactive oxygen species, leading to endothelial dysfunction [6]. Mendelson et al., had been performed a study on 20 obese adolescents, and they found a decrease in inflammatory markers after 12 weeks of an exercise program [26]. In a cross-sectional study on questionnaire-based physical activity reported from Brazil, which consists of participants who were not physically active in childhood and adolescence, it has been determined that the risk of high blood pressure, low cardiorespiratory fitness, and MetS is higher than those who are active. In addition, it was evaluated that adolescents who stated that they were only physically active during childhood had better cardiorespiratory compliance than those who were not physically active during childhood; Among interventions to prevent MetS, the importance of early physical activity participation was emphasized [27].

Amiri et al. studied for nine years at 3-year intervals and examined the effects of lifestyle interventions to increase healthy eating patterns and physical activity on MetS [28]. From the beginning, they divided the participants into three groups: fully intervened, partially intervened (interventions were interrupted occasionally), and the control group without any lifestyle intervention. As a result of the study, a significant decrease was observed regarding the prevalence of MetS in the short term in the partial intervention group compared to the control group. However, the decrease was not continued in the long term. A decrease was observed in the prevalence of MetS in both the long and short-term in the whole intervention group. This shows the importance of the positive effect of the continuity of lifestyle interventions such as physical activity and healthy diet on MetS [28].

Rognvaldsdottir et al. investigated the effects of physical activity and sleep patterns on metabolic profile in 256 adolescents, 146 of whom were girls [29]. Adolescents with variability and irregularity in sleep duration and bedtime were found to have a higher body fat percentage. Those who did less physical activity had higher insulin levels with a higher body fat percentage. As a result, they emphasized that regular sleep and sufficient physical activity positively affect the adolescent metabolic profile [29].

In contrast, some studies in the literature could not find a relationship between physical activity and MetS. For example, when Pan and Pratt examined the relationship between physical activity and MetS according to the NHANES 1999-2002 survey data, they could not find a significant relationship between them [30]. McMurray et al., included these two studies in their meta-analysis [1]. They stated that this might be due to methodological problems, such as assessing physical activity in the pediatric population based chiefly on questionnaires and self-reports.

Physical fitness has been reported to have a positive protective effect on cardiometabolic risk [31]. Anderssen et al., performed a study in a group of 9-15 age years old participants and found that those with a physical fitness level in the lowest quartile were 13 times more at risk for MetS than those in the upper quartile [32]. In another study including 223 girls and 223 boys adolescents, MetS was more common in inactive adolescents and adolescents with low physical fitness [33]. In the study of Martinez-Gomez et al., in which they examined the relationship between physical activity and physical fitness on MetS in 202 adolescents, 99 of whom were girls, a positive correlation was found between high physical fitness alone and low MetS risk, but this relationship could not be found with physical activity alone [34]. However, VPA and moderate-vigorous physical activity (M-VPA) were found to be associated with high physical fitness. Therefore, they emphasized that physical fitness may play a key role in the relationship between physical activity and MetS [34].

Various studies have been conducted on the intensity, duration, and type of physical activity. The relationship between physical activity intensity and MetS is still being determined [35]. Although studies show that high-intensity physical activity for only a few minutes a day positively affects body composition and metabolic risk, how low-intensity physical activity affects body composition has yet to be clarified [6]. Renninger et al., examined the relationship between physical activity duration and MetS in a meta-analysis of 8 studies, 6009 children and adolescents, based on IDF criteria [36]. Even a 10-minute increase in M-VPA and VPA was found to be negatively associated with MetS. On the contrary, Martinez-Gómez et al. found no relationship between physical activity level and MetS score in 202 adolescents aged 13-17 years [34]. Similarly, a study conducted by Dubose et al., with 72 male and female participants found no clear relationship between physical activity levels and MetS; they determined that high physical activity levels were associated with lower diastolic blood pressure [19].

Although, there is no clear information about the level of physical activity required to prevent the risk of MetS in children, there is no definite information about the duration of physical activity, but there are various suggestions. In 2000, the US Department of Agriculture recommended that children and adolescents be on M-VPA for 60 minutes daily [37]. In 2010, this recommendation was re-accepted and approved by the American Dietary Guidelines [38]. In the study of Ekelund et al., an inverse relationship was found between the time spent in light, moderate, and vigorous physical activity and the risk of MetS [39]. Andersen et al., suggested that 90 minutes of physical activity per day is required to prevent the clustering of metabolic risk factors [40]. Unlike other studies examining the MetS and duration of physical activity, in a study conducted by Andaki et al., it has been reported that taking 7872 steps per day in Brazilian boys would be protective against MetS [8]. The study determined that all children classified as MetS remained below 7872 steps per day [8].

Regarding the type of exercise, studies in the literature show that aerobic and resistance exercises reduce the MetS score [41-43]. Dias et al., investigated the effect of resistance exercises on non-diabetic obese adolescents [41]. While the exercise group consisted of 24 non-diabetic obese adolescents, the control group consisted of 20 non-obese adolescents and included the exercise group in a program consisting of 12-week resistance exercises. The groups were evaluated regarding body composition, 24-hour ambulatory blood pressure, adipocytokines, skin endothelial reactivity, metabolic profile, and aerobic and strength fitness before and after the program. They found significant improvements in endothelial function, hemodynamic-metabolic profiles, body composition, and physical fitness, independent of BMI, in non-diabetic obese adolescents with only resistance exercise at the 12^{th} week. Similarly, Son et al., divided 40 obese adolescent girls into two groups control and exercise arms [42]. While those in the control group continued their daily physical activities, the exercise group received a resistance and aerobic exercise program for 12 weeks. At the end of 12 weeks, they observed a significant difference in IR and body composition in the exercise group compared to the control group. As a result, they stated that resistance and aerobic exercise might be beneficial in reducing obesity and MetS risk factors. Marson et al., reviewed the effects of aerobic, resistance, and combined exercises on insulin resistance, fasting glucose, and fasting insulin in overweight, obese children and adolescents in their meta-analysis [43]. They stated that aerobic exercise was associated with decreased fasting insulin levels and HOMA-IR and that MetS and Type 2 DM could be prevented with aerobic exercise.

The last point is that reducing sedentary life is as important as increasing physical activity and physical fitness to reduce the risk of obesity [44]. Cadenas-Sanchez et al., compared participants with overweight and obesity in the Adolescent Nutrition and Lifestyle Study in Europe (n:3528, participation rate: 61.3%) with and without a healthy metabolic profile of physical activity and duration of inactivity [45]. While the duration of inactivity was high in the group with a poor metabolic profile, MPA and M-VPA were found to be low. Peplies et al., found that a sedentary lifestyle was associated with IR, independent of weight, in a study of the IDEFIC cohort of 3348 children aged 3 to 10.9 years [46]. In the study of Broadney et al., children who interrupted sedentary behavior at regular intervals, with short bouts of physical activity, observed lower insulin resistance than those who did not interrupt. Television (TV) is one of the leading causes of sedentary activity in children [47]. In the review by Carson et al., they found that more prolonged screen exposure and TV viewing time adversely affected body composition in 162 studies in the literature [48]. In 32 studies, it was stated that there is a relationship between longer TV watching time and higher cardiometabolic risk. Finally, studies have shown that the obesity rate increases as screen exposure (TV, computer, telephone, etc.) increases [49].

Family and school environments also play an essential role in increasing childhood physical activity and reducing sedentary life. Families need to be adequately informed, and their awareness has to be increased. In addition, necessary interventions should be taken so that children who spend most of the day at school due to education can engage in physical activity in the school environment [50].

Conclusion

MetS is a severe public health problem that causes serious mortality and morbidity that increasingly affects the pediatric population, where metabolic abnormalities such as IR, obesity, dyslipidemia, and HT are clustered. In this respect, the prevention and treatment of MetS is crucial. In order to increase physical activity in the prevention of MetS, it is necessary to raise awareness of families and make various arrangements in schools. There are still some uncertainties and conflicting results regarding the relationship between MetS and physical activity in the pediatric population. It is necessary to perform new studies on the definition of MetS and its relationship with physical activity in the pediatric population to reduce the risk of MetS, a growing health problem.

Compliance with Ethical Standards

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