Evaluate the effects of metabolic syndrome in adolescents and children

Discussion

Rui-Min Jia^{a,*}, Xiao-Ning Yan^b, Jing Sun^a

^aNursing College, Shanxi University of Chinese Medicine, Jinzhong, Shanxi 030619, China

^bClinical Practice of the Fourth College, Shanxi University of Chinese Medicine, Jinzhong, Shanxi 030619, China

Received: 1 February 2020; Accepted: 26 February 2019; Published: 20 September 2020

Abstract: The metabolic syndrome (MS) in adolescents and children can cause serious consequences that lead researchers to pay efforts to study in such area. Presently, MS definition is still not standardized. Different versions of MS definition have been used by numerous studies, which may be a problem to identify MS and then to predict and prevent clinical diseases. The pediatric literature shows that insulin resistance and obesity might be the key underlying pathophysiology of MS to cause many related diseases. High prevalence of MS is in overweight and obese children and adolescents. This article focuses on such above issues and also effects of MS on two main disease outcomes: cardiovascular disease and type 2 diabetes.

Keywords: *metabolic syndrome • children/adolescents • type 2 diabetes • cardiovascular disease • metabolic syndrome definition • insulin resistance • obesity*

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1. Introduction

The interest of metabolic syndrome (MS) has been increased since the last century. This concept was first exposed in the 1920s and the publication indicated that MS was associated with hypertension, gout, and diabetes. Following, in the 1940s, some ground-breaking research by Vague were conducted on the correlation between central body fat distribution and several risk factors of cardiovascular disease (CVD). Later, in the 1990s, the lecture of Reaven's Banting started the modern era of MS. He drew new attention to the correlation between insulin resistance and many metabolic abnormalities linked to MS also named as "syndrome X."¹

Recently, the definition of MS is a cluster of risk factors for atherosclerotic CVD and type 2 diabetes mellitus (T2DM) which consist of obesity, glucose intolerance, abnormal lipid profile, and hypertension.² In the Ozanne and Hales' study, the possible mechanisms of developing T2DM and MS in regard to fetal development were reviewed.³ It indicated that MS development may be associated with early growth restriction in utero which might lead to onset of the pathological processes of T2DM in early childhood. Childhood MS might raise the risk of T2DM, CVD, and other related diseases, for instance, nonalcoholic fatty liver disease and polycystic ovary syndrome in life.⁴ Additionally, MS in childhood may likely track into adulthood, but the evidence

How to cite this article: Jia RM, Yan XN, Sun J. Evaluate the effects of metabolic syndrome in adolescents and children. *Front Nurs.* 2020;3:287-292.

* Corresponding author.

E-mail: beijing2008_hihi@163.com (R.-M. Jia).

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is limited, owing to limited studies that track participants during childhood to adulthood period and always use secondary data that may not be strong enough to reveal such tracking. Until at present, little has been known how well MS in children can predict adult disease.⁵

Recently, the common recognitions about the components of pediatric MS and its important predictability in the risk of T2DM and CVD development have been made during the accumulation of research evidence. This article aims to discuss those two diseases as the consequence of MS through MS definition and the major underlying pathophysiology.

2. MS definitions in adolescents and children

The definition of MS in children and adolescents has not been unified, and it is usually based on the adult standards (such as the International Diabetes Federation (IDF) guidelines) and varies with different ethnic populations by different criteria and cutoff points.⁶ Five similar studies were chosen and examined their MS definition, among which some criteria for defining MS were used in later studies. Those studies were conducted among the American adolescents to predict the prevalence of MS. Four of them used the modified adults version to define MS (the National Cholesterol Education Programme—Adult Treatment Panel III) (NCEP-ATP III) (see Table 1

for specific criteria of NCEP-ATP III).⁷⁻¹¹ Another study used MS definition derived from the 2007 child IDF.^{11,12} Findings showed that several cutoff points of variables are different and ambiguous, even using the same resource to classify MS.

Specifically, for defining variables with varied levels, fasting triglyceride (TG) was defined as ≥ 150 mg/dL by Park et al.⁸; however, defined as ≥ 100 mg/dL by de Ferranti et al.⁷ and Cook et al.⁹; and defined as ≥ 110 mg/dL by Duncan et al.¹⁰ For defining variables whether considering gender's difference, waist circumference (WC) was defined as >75 th percentile by de Ferranti et al.⁷ and defined as ≥ 90 th percentile by Cook et al.,⁹ Duncan et al.,¹⁰ and Ford et al.,¹¹ but defined separately in genders: >102 cm for male and >88 cm for female in Park et al.⁸

Furthermore, some studies defined MS by using specific ethnic or race criteria. However, which level should be selected as criteria for MS in children does not have a universal agreement.⁵ Different thresholds for some of the essential variables are used by studies, which may lead to the difficulty of diagnosing MS, estimating MS prevalence and the clinical consequences. According to those studies, a standardized definition of children may be needed even though they had a common disadvantage that was measured body mass index (BMI) instead of WC. Tables 2 and 3 show the specific range of characteristics and measures used commonly for diagnosing MS in children.

Items	All	Female	Male
Central obesity		Waist ≥ 102 cm	Waist ≥ 88 cm
Blood pressure	Systolic ≥ 130 mmHg; Diastolic ≥ 85 mmHg		
Triglycerides		≥ 1.7 mmol/L	≥ 1.7 mmol/L
HDL-C		< 1.3 mmol/L	< 1.0 mmol/L
Fasting glucose		≥ 6.1 mmol/L	≥ 6.1 mmol/L

NCEP-ATP III, National Cholesterol Education Programme—Adult Treatment Panel III; MS, metabolic syndrome; HDL-C, high-density lipoprotein cholesterol.

Table 1. NCEP-ATP III definition of MS in adults.

Risk factors	de Ferranti et al. ⁷	Cook et al. ⁹	Cruz et al. ¹²
Abdominal obesity	> 75 percentile	≥ 90 percentile	≥ 90 percentile
HDL-C	Female < 50 mg/dL; male < 45 mg/dL	≤ 40 mg/dL	≥ 10 percentile
Triglycerides	≥ 100 mg/dL	≥ 110 mg/dL	≥ 90 percentile
Fasting glucose	≥ 110 mg/dL	≥ 110 mg/dL	IGT:ADA criterion
Blood pressure	> 90 percentile	> 90 percentile	> 90 percentile

MS, metabolic syndrome; HDL-C, high-density lipoprotein cholesterol; ADA, American Diabetes Association; IGT, impaired glucose tolerance.

Table 2. Published definitions of MS in pediatrics.

Items	Age group		
	6–10 years	10–16 years	> 16 years
Obesity (WC)	≥90 percentile	≥90 percentile (or adult cutoff)	Using adult criteria
Triglycerides	MS cannot be diagnosed	≥150 mg/dL	Using adult criteria
HDL-C	MS cannot be diagnosed	<40 mg/dL	Using adult criteria
Blood pressure	MS cannot be diagnosed	Systolic: ≥130 mmHg; diastolic: ≥85 mmHg	Using adult criteria
Glucose	MS cannot be diagnosed	OGTE: ≥5.6 mmol/L; or known type 2 diabetes	Using adult criteria

IDF, International Diabetes Federation; MS, metabolic syndrome; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; OGTE, oral glucose tolerance test.

Table 3. IDF definition of MS in adolescents and children

However, a single MS definition to adolescents and children might not be proper to show problems in this age, owing to the unique physical development during childhood.¹⁰ Endocrine levels may be influenced by pubertal development and genders. A typical previous study indicated that the adverse association existed among puberty, body fat, age, insulin resistance, and adiponectin. Compared with prepubertal children, pubertal children had apparently lower adiponectin level ($P < 0.001$). Especially, adiponectin was shown to be at lower level in pubertal girls, and no difference of adiponectin had been found between prepubertal girls and boys. The negative association had been observed among body fat ($r = 0.44$; $P = 0.002$), age ($r = 0.41$; $P = 0.003$), insulin resistance ($r = 0.33$; $P = 0.016$), and adiponectin.¹³ Hence, for adolescents and children, to define abnormalities by using single cutoff point might not be suitable. A recent study combined clinical indicators and diseases as criteria. Specifically, five criteria were: TG serum concentration ≥150 mg/dL/treating TG; in male high-density lipoprotein cholesterol (HDL-C) <40 mg/dL/in female <50 mg/dL/treating HDL-C; BMI > age and 95th percentile; glucose concentration ≥100 mg/dL/treating hyperglycemia; systolic blood pressure (SBP) ≥130 mmHg or/and diastolic blood pressure (DBP) ≥85 mmHg/treating hypertension.¹²

Additionally, there are also some other difficulties in determining a standardized definition of MS in children. For example, ethnic differences exist in developing MS.¹⁴ MS criteria may need consider ethnic variations and immigrant population.

3. Impact of MS on CVD and T2DM

MS is defined as a cluster of high TGs, obesity, low HDL cholesterol, high blood pressure, and insulin resistance which associate with the early progress of coronary atherosclerosis and T2DM.^{2,3} In the pediatric literature, lot of effort has been made to explore the relationship

among CVD, T2DM, and MS. MS in children may be an indicator of CVD and T2DM in their adult period, but limited data directly explore the impact of MS on disease outcomes in adolescents and children. The consistent finding was that there is a strong positive relationship between children with MS and the development of CVD in their later life. Youth with MS were at two- to three-fold risk of having subclinical atherosclerosis (carotid intima-media thickness) and T2DM compared with healthy youth.¹⁵

However, the correlation between the severity of MS and the level of adiponectin and fasting insulin has been not clear enough. One recent study pointed that childhood MS Z-scores had a positive association with insulin levels in adult ($P < 0.001$) and a negative association with levels of adiponectin ($P = 0.01$). For individual analyses, greater levels of insulin and MS Z-score during adulthood were significantly related to greater odds of occurrence CVD and diabetes over the following 11.2 years ($P < 0.001$).

Therefore, MS severity had a long-term link to the level of adiponectin and insulin, and it independently and consistently correlated with T2DM and CVD, which may be owing to the potential, environmental, and genetic influence over time. So, in the future, MS severity may be used as a risk predictor of these diseases.¹⁶

The correlation among MS, T2DM, and CVD varied with ethnicity and race. The black population with MS has a greater risk of CVD than the white population with MS. The reason may be that MS induces some nontraditional risk factors of CVD including C-reactive protein, high level of low-density homocysteine, lipoprotein oxidation, adiponectin, lipoprotein a, and plasminogen activator inhibitor-1, and so on. Therefore, to predict and examine CVD and T2DM caused by MS should consider ethnicity/race and also nontraditional and traditional risk factors. Researchers suggested that nontraditional risk factors need to be added in the definition of MS.¹⁷

4. Major pathophysiology of MS contributing to consequences of CVD and T2DM

4.1. Insulin resistance

Insulin resistance may be a core abnormality of a clustering of CVD and T2DM risk factors.¹⁵ Higher baseline insulin concentration in youth gradually develops MS, which provides the evidence that insulin resistance might precede and enhance the development of MS in childhood. Increased insulin levels had greatly adverse levels of other risk factors that subsequently led to MS, regardless of race, age, and sex. According to the report of WHO, in 2017 about 425 million people had diabetes worldwide, and by 2040 the number will increase to 642 million. Among diabetes, there will be about 70% people with MS, mainly at puberty age.¹⁸

Normally people with higher insulin concentration had lower level of HDL-C and higher level of DBP and SBP, very low-density lipoprotein (VLDL) cholesterol, low-density lipoprotein (LDL) cholesterol, total cholesterol, TGs, and glucose, compared with people with lower insulin level.¹⁹ Obesity (WC > 90 cm), triacylglycerol level >150 mg/dL, blood glucose >100 mg/dL, HDL-C <40 mg/dL, and blood pressure >130/85 mg/dL had a strong association with insulin resistance.²⁰

4.2. Obesity

According to a recent report study, approximately 44.3% of obese children have characteristics of MS, and lower percentage of normal weight children have only one risk factor of MS.²¹ Another study even showed a higher prevalence (70% obesity with SM) through modified guidelines of WHO.²²

Obesity, particularly, abdominal obesity may directly contribute to the progress of MS and cardiovascular risk. It has been known that childhood obesity is related to increased blood pressure, low HDL-C, increased TGs, abnormal glucose levels, reduced vascular function, and insulin resistance.¹⁷ Central obesity (WC > 90 cm) is strongly associated with MS, on which genetic variants may have an effect. Obese genes and lipid metabolism can drive genetic predisposition to MS. Examining genetic variants in MS polygenic scores may be a way to identify the child and subsequently the adult belonging to a high-risk group to early targeting interventions.²⁰

Central obesity induces MS that may also be due to modulating particular signaling pathways, the growth hormone/insulin-like growth factor-1 and ghrelin signaling axis, through which it regulates metabolic homeostasis and energy balance.²³

4.3. Both insulin resistance and obesity

Either in the adult or pediatric literature, insulin resistance and obesity are pointed to be always tightly connected with each other and to be as underlying etiological factors to develop MS that may then give rise to CVD and T2DM. The degree of body fat was significantly related to reverting impaired glucose tolerance to normal glucose tolerance and T2DM development. Change in body weight was negatively associated with changes in glucose level and insulin sensitivity. Further reduction of insulin sensitivity exists in youth with a developed T2DM, which was related to a continued weight gain and abnormal body composition profiles such as truncal subcutaneous fat, excess body fat, and abdominal adiposity.²⁴ According to a recent study, 53% obese children and adolescents have insulin resistance.²² Another study showed that MS with high triacylglycerol and central obesity were correlated with high risk of insulin resistance (OR: 24.4; 95% CI: 5.19e114.42) and (OR: 9.4; 95% CI: 3.09e28.68), respectively.²⁵

However, not all obese children or adolescents with impaired metabolism of carbohydrate develop MS and even CVD or T2DM. Probably, other elements such as pathological and metabolic factors and lifestyle factors are involved. Currently, it has been reported that the lead of urinary level was positively correlated to MS.²⁶ Unhealthy lifestyle (including smoking, low income, low physical activity, and alcohol intake) has a negative effect on diseases development.²⁷ Overall, the interaction between the elements of MS and between other metabolic factors may ultimately lead to disease.

5. Conclusions

There are several points that may need to be emphasized for the future study. First, the definition of MS may need to be standardized. Number of studies have been attempted to characterize MS in children. However, to date, there has been no universally accepted MS definition in children, which may lead to the situation where it is hard to diagnose MS and to estimate its clinical consequences, and subsequently hard to take early treatment. To define the standardized concept of MS may need complete understanding of the underlying pathophysiology and consideration of variations concerning related factors including age, ethnicity, sex, family history, and lifestyle behaviors. Second, the true picture of diabetic and cardiometabolic risk may be due to overweight/obesity and insulin resistance, but that may not mean that other traditional components of MS, pathological and metabolic factors, and genetic factors can be ignored to predict CVD and T2DM.

Ethical approval

Ethical issues are not involved in this paper.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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