Pediatric Endocrinology Diabetes and Metabolism
Endokrynologia, Diabetologia i Choroby Przemiany Materii Wieku Rozwojowego

Review Paper | Praca poglądowa
Pediatr Endocrinol Diabetes Metab 2015;23,1:32-36
DOI: 10.18544/PEDM-21.01.0022

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Metabolic syndrome in young patients

Zespół metaboliczny wśród młodych pacjentów

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Abstract
Metabolic syndrome (MS) is amajor problem in the population of children and adolescents. Genetic predisposition and environmental factors, such as physical inactivity and increased caloric intake, are responsible for the susceptibility to the development of the metabolic syndrome. Immunological aspects of obesity and MS, including the role of T regulatory cells, are also being investigated. The metabolic syndrome is defined as a cluster of risk factors (including abdominal obesity, dyslipidemia, insulin resistance, glucose intolerance or diabetes mellitus and hypertension) which increase the risk of accelerated development of cardiovascular diseases and other medical consequences.
Key words
metabolic syndrome, insulin resistance,glucose intolerance.

Streszczenie
Zespół metaboliczny jest poważnym problemem w populacji dzieci i młodzieży. Predyspozycje genetyczne oraz czynniki środowiskowe, jak np. brak aktywności fizycznej i zwiększona podaż kalorii, są odpowiedzialne za podatność na rozwój zespołu metabolicznego. Badany jest również wpływ immunologicznych mechanizmów otyłości i zespołu metabolicznego, włączając w nie rolę limfocytów T regulatorowych. Zespół metaboliczny określa się jako zbiór czynników (obejmujących otyłość brzuszną, dyslipidemię, insulinooporność, nietolerancję glukozy lub cukrzycę oraz nadciśnienie tętnicze), które zwiększają ryzyko przyspieszonego rozwoju schorzeń układu sercowo-naczyniowego oraz innych konsekwencji zdrowotnych.
Słowa kluczowe
zespół metaboliczny, insulinooporność, nietolerancja glukozy

Introduction

Insulin resistance lies at the core of the pathogenesis of the metabolic syndrome, therefore the condition is also referred to as the Insulin Resistance Syndrome (IRS) [1–3].

Insulin resistance is a condition in which tissues show a diminished response to the physiological blood concentration of insulin. It leads to disorders in carbohydrate, lipid and protein metabolism as well as a disruption of the anabolic effect of insulin in muscles. The reduction of peripheral tissues'sensitivity to insulin occurs mainly inthedirectly insulin-dependent ones.

The disturbance of the metabolism of fatty acids leads to an increased retention of lipids in certain organs. This process is referred to as „lipotoxicity" and results in the development of insulin resistance in muscles and liver as well as the dysfunction of beta cells. Fatty acids directly influence the activity of insulin-regulated glucose transporter 4 (GLUT4) and its translocationin muscles, adipose tissue and in the heart. Impaired transport of glucose may also be a result of serine phosphorylation in insulin receptor substrate 1 (IRS-1).

It is currently believed that the development of insulin resistance may be largely dependent on genetic factors. A common view is that insulin resistance occurs in genetically predisposed individuals, experiencing certain environmental factors – which shows its epigenetic base.

The main environmental factors associated with the development of insulin resistance include reduction in physical activity and access to diet rich in calories and foods with high glycemic index [4–6]. Among the environmental factors, disorders of fetal development have also been mentioned. Insulin

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Received: 2015-09-10.
Accepted: 2015-10-28.
Conflict of interests: none declared.

resistance and metabolic syndrome are a significant risk both among children who are small for gestational age (SGA) and large for gestational age (LGA) [7–12].

At present, much attention is focused on the immunological aspects of obesity and MS, including the role of T regulatory cells (Tregs). The role of Tregs in low-grade inflammation associated with obesity and atherosclerosis has been investigated. A substantial amount of data suggests that the decreased number and/or function of T regulatory cells can lead to a chronic inflammation present in patients with obesity and trigger formation of atherosclerotic plaque [13–15].

Assessment of Insulin Sensitivity

Hyperinsulinemic-euglycemicclamp is the "gold standard" for measuring insulin sensitivity. However, in clinical practice, it is more common to use simpler indirect methods based on the evaluation of relationship between insulin concentration and fasting blood glucose or glucose tolerance test: FGIR index (*fasting glucose-to-insulin ratio*) and HOMA-IR index (*Homeostasis Model Assessment – Insulin Resistance*).

During puberty, insulin resistance is increased and insulinsensitivity is reduced in both non-diabetic and diabetic children – it is a physiological condition.In high risk groups,the metabolic syndrome is diagnosed even in children under 10 years of age [16–21].

An excess of circulating FFA, TNF-α and other factors induce insulin resistance [22].

Recent years have brought information about the role of retinol binding protein 4 (RBP4) in the pathogenesis of the metabolic syndrome. It was found that RBP4 causes the development of insulin resistance in both liver and skeletal muscle [23,24]. This protein has been postulated to provide a new link between obesity and insulin resistance. Rhie et al. showed that the serum RBP4 level is related to the degree of adiposity and pubertal development in children and adolescents [25]. Various other authors believe that the association between RBP4 and insulin resistance is secondary to the underlying relationship to adiposity [26]. Boyraz et al. concluded that adiponectin, RBP4 and, in particular, resistin levels, may be used as suitable predictive biomarkers of the metabolic syndrome [27,28].

While considering the causes of the syndrome in children, attention should also be paid to the report of the Greek authors, who pointed out the role of chronic stress in the development of the metabolic syndrome [29].

Criteria for diagnosis of the metabolic syndrome

The criteria for diagnosis of the metabolic syndrome in young patients are still being discussed [30–37].

The presence of the metabolic syndrome is currently evaluated on the basis of the International Diabetes Federation's criteria for pediatric populations [38,39].http://pediatrics.aappublications.org/content/133/2/e386.full – ref-19. However, a widely accepted model of diagnosis looks at the presence of an increased waist circumference, triglycerides, HDL cholesterol, insulin secretion and blood pressure [40].

A truncal distribution of adipose tissue (even in children and adolescents) is related to harmful lipid, lipoprotein, cholesterol, and adipoprotein concentrations independently of the overall level of obesity [41]. Therefore, several investigators have concluded that the waist-to-height ratio (WHtR) is more strongly associated with cardiovascular disease risk factors than the body mass index (BMI).In general, WHt Rshowed slightly stronger associations with lipid and lipoprotein concentrations. It is a simple and effective screening tool that can be used to identify obese children with the metabolic syndrome and is also the simplest index to calculate and interpret – making it an ideal non-invasive screening tool for use in clinical practice [42–44]. However, some researchers believe that waist circumference is not a better predictor of metabolic risk factors than body mass index [45].

Metabolic-syndrome-related diseases

The metabolic syndrome is associated with the development of a number of complications, such as cardiovascular disease, diabetes mellitus, hypertension and dyslipidemia [46].

It has been suggested that metabolic abnormalities could be involved in the remodeling of the left ventricle of the heart. Left ventricular mass index (LVMI) is one of the markers helpful in the risk assessment of such complications – some pediatric studies have shown that it is related to insulin resistance syndrome characteristics in youth.Assessment of LVMI in obese children and adolescents may be used as a tool in predicting the presence of MS and its associated cardiovascular risk.

Atabeket al., in a study conducted on a group of obese children, found that insulin sensitivity indices derived from fasting samples and elevated basal insulin levels were significantly associated with increased LVMI [47]. They suggest that the assessment of LVMI in routine echocardiographic examinations of obese children and adolescents might be used to predictthe presence of MS and its associated cardiovascular risk. Bostanci et al. showed that LVH (left ventricle hypertrophy) occurs commonly in pediatric MS and is associated with systolic hypertension and insulin resistance [48].The authors believe that LVMI should be measured routinely for the prediction of cardiovascular risk in these patients.

In the field of cardiovascular risk assessment in adolescents with MS, the measurement of the carotid intima-media thickness (IMT) is a potential indicator of subclinical atherosclerosis. Epicardial adipose tissue thickness (EATT) is suggested as a new cardiometabolic risk factor. Assessment of EATT and carotid IMT in routine echocardiographic examinations is suggested as a feasible and reliable method for the evaluation of obesity with MS and its related cardiovascular risk in children and adolescents [49].

Hypertension may be a sign of pathological changes in the cardiovascular system. However, it is important to remember that the elevation of blood pressure may be only slight and discreet. [50–52].Pressure measurement in children and adolescents requires great care, the results should be evaluated using centile charts [53].The results of blood pressure measurements in adolescent patients with type 1 diabetes presented by Pietrzak et al. showed a significant relationship between blood pressure and body mass index and the percentage of adipose tissue in the body [54].

Dysfunction of glucose metabolism causes worsening of cellular response to insulin associated with an increased cardiovascular risk.

Increased insulin resistance, illustrated by the elevation of HOMA index, causes a worsening of endothelial function in childhood and the development risk factors associated with the development of cardiovascular disease. Therefore, noninvasive methods of assessing atherosclerotic risk in youth need to be developed and standardized.The ability to use noninvasive methods to accurately measure vascular damage related to atherosclerotic processes in youth will substantially improve our ability to risk-stratify individuals by traditional assessment, especially in the juvenile population [55].

The metabolic syndrome in children is often associated with the occurrence of non-alcoholic fatty liver disease (NAFLD). This disease is linked with a significantly higher mortality, as well as an increase in incidence of cardiovascular system diseases [56]. Monteiro et al.,in a trial conducted in a sample composed of 145 subjects aged 11 to 17 years, pointed out the usefulness of indicators such as assessment of waist circumference (WC), truncal fat mass (TFM) and fat mass (FM) by dual-energy X-ray absorptiometry (DXA) and ultrasound (US) for risk evaluationof NAFLD [57]. Their findings indicated that TFM, intraabdominal adipose tissue (IAAT) and WC present a high potential to identify NAFLD in obese children and adolescents.

During the last decade, pediatricians have observed a dramatic increase of the metabolic syndrome and NAFLD incidence in children. Central obesity and consequent adipose tissue inflammation are critical to promote both MS-associated metabolic dysfunctions and NAFLD-related hepatic damage [58].

Another disorder also often associated with the occurrence of the metabolic syndrome is polycystic ovary syndrome (PCOS). Its characteristic feature is the presence of insulin resistance, which often leads to impaired glucose tolerance as well as to clinically overt diabetes [59–62].

The metabolic syndrome is associated mainly with type 2 diabetes mellitus – however, we now know that it can also occur in type 1 diabetes mellitus because insulin resistance is also present in this condition.

The prevalence of abdominal obesity in diabetic children is higher than in the general population. WHtR is associated with components of metabolic syndrome [63–68].

Obesity of patients with type 1 diabetes mellitus is often the result of iatrogenic hyperinsulinemia (or "over insulining"). The patients try to maintain normal blood glucose profile by increasing the dose of insulin. This creates a "vicious circle" – an increase of insulin doses without a reduction of caloric intake results in a buildup of adipose tissue mass and consequently in an exacerbation of insulin resistance.

Treatment

It is reasonable to suggest that an early intervention aimed at managing obesity could reduce the risk of developing the metabolic syndrome. At present, there is no specific treatment for this cluster of risk factors in children, other than reducing obesity, increasing physical activity and treating the various components of MS – like hypertension or hyperlipidemia. Weight control improves glucose tolerance, exercise training improves insulin sensitivity and endothelial vascular function beyond the benefits of glycemic control and blood pressure reduction. Metformin is the drug of choice in the pharmacotherapy of MS [69,70].

Conclusion

Recent years have brought an increasing number of reports about the threat of the metabolic syndrome in very young children. This problem is of particular importance in adolescents, where the risk factors of this syndrome associated with genetic determinants and a growing epidemic of childhood obesity go together with the so-called "physiological" insulin resistance associated with puberty.

A relatively new issue is the presence of the metabolic syndrome in adolescent patients with type 1 diabetes mellitus.

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