SCIENTIFIC REVIEWS AND LECTURES

N.A. Danilov, T.E. Burtseva, Y.A. Munkhalova, M.P. Slobodchikova

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METABOLIC SYNDROME IN CHILDREN AND ADOLESCENTS

The article represents review of metabolic syndrome in children and adolescents. Obesity pandemic, which is common all over the world, outlines significant social issues, resulting in cardio-vascular disorders, the leading cause of mortality and disability. The concern of increasing tendency of cardio-vascular disorders among children and adolescents for the last decades is growing [5]. According to the National Medical Research Center for Endocrinology (2017) from 13-15% of children suffer from obesity in Russia, among them 5-8% school children.

This number of obese children is twice higher than in France, 1.5% higher than in England and is reaching the number of obese children in the USA (17%) [9]. Increase of obesity in children is doubling each 30 years resulting in a threat to national security [6].

Keywords: metabolic syndrome, obesity, children, adolescents.

Yakutia is referred to the regions with extreme conditions for living, resulting in high-energy consume taken in with food and nutrients and their high expenditure for normal activity of the organism. The traditional diet rich in protein and lipid is being substituted by the diet rich in carbohydrate and protein for the last decades [2, 7], moreover the motor activity of teenagers tends to decrease. The combined action of both factors leads to increase of obesity rate consequently resulting in cardio-vascular disorders.

Of greatest concern is the dangerous tendency to increase CVD mortality among children and young people, noted in recent decades [4]. According to the endocrinology research center of the Ministry of Health (2017), 13-15% of children in Russia are obese, 5-8% are students. This number exceeds 2 times the number of children with obesity in France, 1.5 times more than in England and approaches the number of children with obesity in the United States (17%) [9]. The rate at which the incidence is increasing, the number of sick children doubles every 30 years, and this suggests a threat to national security [5].

The prevalence of metabolic syndrome (MetS) in overweight children and adolescents is 30-50% worldwide [1]. The first description of metabolic syndrome is known to be introduced by a Swiss physician E. Kylin in 1923, named as 'a syndrome involving hypertension, hyperglycaemia and hyperuricaemia' [5]. The concept of metabolic syndrome was first suggested by Gerald Reaven in 1988 [11], the syndrome was defined as a complex of such metabolic and clinical disorders as abdominal obesity, arterial hypertension, dyslipidemia, insulin-resistance, glucose intolerance or diabetes mellitus type 2 [12]. Clear diagnostic criteria of metabolic syndrome in adolescents above 16 were constituted by the International diabetes federation in 2007, they were based on analogous adults' criteria [1]:

- Tryglycerides level ≥1.7 mmol/L;
- High-density lipoprotein level <1.03 mmol/L;
- An increase in arterial pressure ≥130/85 mm Hg;
- An increase value of venous plasma glucose on an empty stomach ≥5.6 mmol/L or diagnosed diabetes mellitus type 2 and/or other disorders of carbohydrate metabolism.

However, the representatives of different medical organisations disagreed the clinical and diagnostic significance of each component included in the diagnostic criteria. In 2009 the following international research associations: International diabetes federation (IDF), International heart, lung and blood institute (NHLBI), American heart association (AHA), World heart federation (WHF), International atherosclerosis society (IAS), and International association for the study of obesity (IASO) together represented unified criteria for diagnosis of metabolic syndrome in children and adolescents (Table), nowadays these criteria are used all over the world [4].

Obesity is not just esthetic problem, it is severe disease which affects physical, social and psychological well-being of children [8], and moreover, it results in such diseases as ischemic disease, diabetes mellitus, arterial hypertension, malignant neoplasms.

Despite high prevalence of metabolic syndrome there is still no unified classification of it. The following classification, based on the classifications of M.I. Balabolkin et al, G.A. Melnichenko et al, V.A. Peterkova et al, seems most relevant in pediatric practice [1]:

- Initial obesity:
- Exogenous constitutional or alimentary constitutional;
- monogenous forms (mutation of leptin gene mutation, the leptin gene receptor mutation, POMC deficiency, convertase 1 gene mutation, PPAR-y2 gene;
- Secondary obesity:
- genetic (resulting from Prader-Willi syndrome, Laurence–Moon–Biedl–Bardet syndrome, Cogan syndrome, Albright syndrom etc.)
- cerebral (tumours and traumas of CNS, infectious diseases, mental disorders etc.)
- endocrene (hypothyroidism, polycystic ovary syndrome, adrenal gland disorders etc.)
- iatrogenic (associated with medication intake)

By the character of fat accumulation:

- Abdominal (android) type when the fat is accumulated in the waistline or upper part of the waistline / the upper part of the trunk)
- Gynoid obesity when the fat is accumulated in thighs, hips, butt etc.
- Middle pattern when fat is distributed more or less evenly.

The abdominal (visceral) type of obesity leads to the development of metabol-

DANILOV Nikolai Andreyevich – a post-graduate student of the department of pediatrics and pediatric surgery, Medical institute of the North-Eastern federal university, +7-981-793-1727, danilov.na.94@mail.ru; **BURTSEVA Tatiana Yegorovna** – MD, professor of the department of pediatrics and pediatric surgery, Medical institute of the North-Eastern federal university, a head of the laboratory of the Yakutsk science center of complex medical problems, +7-914-294-3244, bourtsevat@yandex.ru; **MUNKHALOVA Yana Afanasievna** – PhD, associate professor, a head of the department of pediatrics and pediatric surgery, Medical institute of the North-Eastern federal university, +7-914-270-7107, tokmacheva@mail.ru; **SLOBODCHIKOVA Maya Pavlovna** – a senior lecturer of the department of foreign languages with the courses of Russian and Latin languages, St. Petersburg state pediatric medical university, limelight@mail.ru , +7-911-908-7772

ic syndrome. It is established that visceral fat tissue is characterized by endocrine and paracrine activity [1].

Metabolic syndrome associated with insulin resistance results in overstimulation thus leading to further exhaustion of pancreatic islets. This can result in impaired glucose tolerance and diabetes mellitus type 2 [1]. Persistent hyperglycemia or glucose toxicity may lead to beta-cell dysfunction and decreased sensitivity of beta-cells. It triggers the early stage of stimulated insulin secretion and impairs its impulse secretion. In developed insulin resistance the first stage, when vesicles empty the collected insulin, the insulin secretion is absent. In the second stage the basal secretion is monotonous. Thus, despite excessive insulin secretion the glucose level is not normalized, causing a viscous circle: hyperglycemia – hyperinsulinemia – insulin resistance – hyperglycemia – hyperinsulinemia. It results in glucose tolerance disorder thus causing diabetes mellitus type 2.

Arterial hypertension in metabolic syndrome is directly associated with the main pathogenic trigger, i.e. compensatory hyperinsulinemia, which develops on the preexisting insulin resistance background [10]. The investigations have shown that children with metabolic syndrome have high mean night-time systolic BP and diastolic BP, time index of hypertension at night, more decreased level of night-time systolic BP and diastolic BP [6]. Moreover, the mechanisms of arterial hypertension in metabolic syndrome associated with hyperleptinemia are being discussed last time; persistent dyslipidemias result in atherosclerotic changes of renal vessels causing renovascular hypertension [16].

It is necessary to underline that pathologic process in metabolic syndrome affects not only the heart but also the vessels of all kinds and levels, i.e. the cardiovascular pathology. Thus, cardiovascular syndrome including arterial hypertension is represented by the vegetative dysfunction (including heart beat rate variability), endothelial dysfunction and systolic and diastolic myocardial dysfunction. The level of expression of cardiovascular disorders in children and adolescents with metabolic syndrome mentioned above varies individually and depends on the degree of insulin resistance expression.

Dyslipidemia is considered as the decrease in the level of high density of lipoproteins (HDL) below minimum normal numbers and hyperglyceridemia more than >1.7 mmol/L. Dyslipidemia is one of the most important criterion in metabolic syndrome diagnosing. The development of dyslipidemia is directly associated with non-alcoholic fatty liver disease (NAFLD) and insulin resistance. Moreover, there is positive correlation between dyslipidemia, non-alcoholic fatty liver disease and development of atherosclerosis [16].

It is proved that insulin resistance promotes further development of hypertriglyceridemia. Hyperglycemia and hyperinsulinemia break the lipoprotein synthesis: liver starts producing excessive amount of tryglicerides from glucose. Moreover, the Bogalusa heart study revealed that insulin resistance is closely associated with increased sensitivity of LDL receptors to cholesterol. Protein glycation in hyperglycemia greatly contributes to the development of atherosclerosis. Glycated VLDL and LDL circulate in blood for a longer period of time, as receptors do not recognize them and have longer period of half-life. Glycated HDL are better metabolized, glycated collagen better bonds together with VLDL-cholesterol and LDL-cholesterol [1, 3].

The main hypothesis for non-alcoholic fatty liver disease (NAFLD) pathology is 'two-hit hypothesis', represented in 2002 [3]. According to the 'two-hit hypothesis' the liver damage is associated with two components. Firstly, the so-called 'first hit', is associated with obesity caused by fatty diet and insulin-resistance, that might be responsible for depositing of tryglicerides in hepatocydes. The 'second-hit' results in oxidative stress. The inflammatory cytokines, adipokines, mitochondrial dysfunction and endoplasmic reticulum stress trigger the condition to the non-alcoholic steatohepatitis.

For the last years it was modified into 'multiple parallel-hit hypothesis'. According to which NAFLD was determined as epiphenomenon of several metabolic mechanisms, including genetic and environmental factors, interactions between liver, fatty tissue, pancreatic gland and intestine [13].

Accumulation of lipids in the form of tryglicerides and free fatty acids is responsible for NAFLD development. Dyslipidemia is considered as the main component for metabolic syndrome according to IDF (International diabetes federation) criteria, constituted in 2007. It was considered as the main triggering factor for NAFLD development.

Diagnostic criteria for metabolic syndrome (2009)

Age	Obesity	Triglycerides (TG)	HDL	BP	Glucose (mmol / L)
6 to <10 years-old	≥90 percentile	MetS cannot be diagnosed, but the following investigations should be carried out if there is MetS in a family history; diabetes mellitus type 2, dyslipidemia, cardiovascular disorders, arterial hypertension			
Metabolic syndrome					
10-16 years-old	≥90 percentile	≥1.7 mmol/L (≥150 mg/dl)	<1.03 mmol/L (≤40 mg/dl)	Systolic BP≥130 mm Hg or diastolic BP≥85 mm Hg	≥5.6 mmol/L (≥100 mg/dl) or diagnosed diabetes mellitus type 2; If the concentration is ≥5.6 mmol/L peroral glucose tolerance test is recommended
Metabolic syndrome (Adults IDF criteria are used)					
>16 years-old	Central obesity: waist circumference ≥94 cm in Caucasian males and ≥80 cm in Caucasian females (racial/ethnic prevalence for other groups)	≥1.7 mmol/L (≥150 mg/dl	For males <1.03 mmol/L (≤40 mg/dl) For females <1.29 mmol/L (≤50mg/dl) or specific therapy of such disorders in anamnesis	Systolic BP≥130 mm Hg or diastolic BP≥85 mm Hg or previously diagnosed arterial hypertension treatment	≥5.6 mmol/L (≥100 mgdl) or diagnosed diabetes mellitus type 2; If the concentration is ≥5.6 mmol/L peroral glucose tolerance test is recommended

The diagnosis of metabolic syndrome is composed of several stages:

1 stage – the initial attendance of the doctor, including the collection of anamnesis of the current illness, family history (for genetic predisposition to obesity), diabetes mellitus type 2, the diseases of cardiovascular and hepatobiliary systems, social anamnesis checking the dietary habits, social and economic welfare of the family, physical activity; physical examination, including antropometry (height, weight, BMI, waist circumference, thigh circumference), arterial BP [1].

2 stage – laboratory and instrumental diagnosis – biochemical analysis of blood, detection of glucose, alanine transaminase and aspartate transaminase levels in blood, lipidogram; hormone tests - thyroid hormones, hypothalamo-pituitary-adrenal and gonadal axis (Adrenocorticotropic (ACTH) and somatotropic hormones, luteinizing hormone (LH), follicle-stimulating hormone (FSH), cortisol, aldosterone, renin, testosterone etc.; instrumental investigations like ECG, holter monitoring ECG, 24-hour monitor test, ultrasound investigation of the organs of abdominal cavity, echocardiography; if necessary – endoscopic investigations of the organs of gastrointestinal tract, CT-scan/MRI for the brain and abdominal cavity imaging; consultation of the related specialists [1].

The treatment of metabolic syndrome should have an integrated approach and consist of several procedures correcting complex of medical treatment and psychotherapy.

First of all, the lifestyle should be changed starting with the diet and increased physical activity. American academy of pediatrics recommends at least 60 minutes of daily moderate physical activity for children older than 5 [14]. Physical activity increases metabolism of hepatic mitochondrial substrate, and decreases substrate availability for lipogenesis and insulin resistance causing mitochondrial biogenesis in the liver and muscles. It is evidently shown that physical exercises stimulate decrease of insulin level on an empty stomach and insulin-resistance in children and adolescents. It is necessary for lipid profile improvement increasing the concentration of HDL and decreasing the concentration of LDL, and tryglicerides [14]. Moreover, physical activity improves the endothelium function with the following decrease of systolic and diastolic BP without any association with the kind of physical activity (aerobic or muscle-strengthening exercises).

Secondly, one of the most important components for metabolic syndrome treatment is the change of diet or dietary intervention. The main goal of dietary intervention is a decrease of calorie, the second goal is to achieve macronutrient balance decreasing the amount of carbohydrate intake, and achieving the balance of protein and fat intake to physiological norm according to the ratio 1:1:4 (in correlation of protein : fat : carbohydrate). Moreover, it is important to follow fractional nutrition to normalize metabolic process. The whole family of the patient should undoubtedly undergo dietary intervention, it is recommended to achieve psychological comfort of the patient that he/she is not discriminated because of his/her illness but improve dietary habits of all the family. If the child is subjected by overeating mental illness then it is necessary to have psychological therapy together with the specialist.

The medical treatment of obese children is restricted as there is high negative impact of anorectic drugs which is not recommended in most of the countries. The only recommended drug for pediatric use in the territory of the Russian Federation is orlistat, which is limited to the age of the patient and is recommended only for children above 12. It can be used only in such a case when one year of previous treatment including the change of a lifestyle was with no effect.

The effectiveness of surgical treatment is disputable. On the one hand, surgical operation can considerably reduce the weight at once, but on the other hand, there are strict requirements for surgical intervention [15], high price [11], absence of cogent data on the safety of bariatric appliances in a long-term perspective and high risk of complications [16] which limit such choice of treatment.

Treatment of arterial hypertension in children with metabolic syndrome is aimed at achievement maintenance of the arterial pressure equaling to ≤130/80 mm Hg in adolescents older 13 [14]. The approach is aimed at a lifestyle modifying, which are mentioned above. If the modification did not result in decrease of the arterial blood pressure, then the medical treatment is recommended. The medication starts with enalapril, inhibitor of angiotensin-converting-enzyme (ACE), which is administered in its minimum dosage. In 4-6 weeks after administration of hypotensive medication the patient should visit a doctor for therapy controlling and changing the dosage if necessary. If mono-therapy is inefficient, the combined hypotensive therapy is recommended, the lifestyle should undoubtedly be changed.

The treatment of diabetes mellitus type 2 caused by metabolic syndrome or glucose tolerance disorder should be treated according to the treatment protocol for such conditions.

Conclusion. Metabolic syndrome is complex and complicated issue for the healthcare. It is associated with many components and factors resulting in complex and high cost of diagnosis for the disease requiring multidisciplinary approach to the treatment and prevention of the condition. This thesis is confirmed by the information discussed in the article as the prevalence of metabolic syndrome is directly associated with obesity especially occurred in the last decades. Further research works are necessary, especially cooperated researches with medical specialists of the various fields to reveal the early symptoms or predictors of the condition prevent such severe conditions like primary hypertension or diabetes mellitus in adults, which can result in disability in its long-term perspective.

Ethno-geographic data for metabolic syndrome in each region are not less important, they can reveal genetic features for inhabiting population, traditional dietary habits and its quality, climate, physical activity and character of labour. All these factors should be taken into account in the further research of complex symptoms.

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