METABOLIC SYNDROME IN CHILDREN (LITERATURE REVIEW)
Gaybiyeva Sh.A.

Gaybiyeva Shaxnoz Abdulloyevna – Assistant,
DEPARTMENT OF PROPAEDEUTIC OF CHILDHOOD DISEASES,
BUKHARA STATE MEDICAL INSTITUTE, BUKHARA, REPUBLIC OF UZBEKISTAN

Abstract: *the article raises the question of modern views on the pathogenesis and algorithms for diagnosing metabolic syndrome in children. The close relationship of violations of the morpho functional state of the hepatobiliary system and the pancreas with the development of hormonal and metabolic disorders is shown.*
Keywords: *metabolic syndrome, obesity, children.*

Metabolic syndrome (MS) is not a disease or a diagnosis, it is a complex of metabolic, hormonal and clinical disorders that are closely associated with type 2 diabetes mellitus and are risk factors for the development of cardiovascular diseases, which are based on insulin resistance (IR) and compensatory hyperinsulinemia (CH) [13; 16; 20]. It was first described in the 1960s and included a combination of insulin-dependent diabetes mellitus, gout and hyperlipidemia. Initially, obesity was not the main factor in the development of MS, although a close relationship between body weight gain and the development of IR was noted [30; 35].

The list of pathological conditions united by this term is steadily growing.

The relationship of MS with such pathological conditions as abdominal type of obesity, arterial hypertension, atherogenic dyslipidemia, hyperuricemia and/or gout, non-alcoholic fatty liver disease (NAFLD), hyperandrogenism and polycystic ovary syndrome in women, hypoandrogenism in men, microalbuminuria, violation of fibrinolytic activity of the blood, etc.

In recent years, many attempts have been made to systematize and develop unified diagnostic criteria for MS. Various classifications are presented in the literature, while the emphasis on the leading components of the symptom complex in them differs significantly.

In 1999, the WHO Working Group proposed the criteria for the first time, highlighting IR as the leading component. According to them, the main or "big" signs of MS include type 2 diabetes mellitus and/or other disorders of glucose metabolism and / or IR with relative CH. "Small" signs are: arterial hypertension, abdominal-visceral obesity, decreased fibrinolytic activity of the blood, atherogenic dyslipidemia, microalbuminuria. An incomplete MS is distinguished, which consists of a combination of three signs (one main and two of any of the listed small signs) [20].

According to the Working criteria of the US National Institutes of Health (NCEP/ATP III, 2001) [2; 9], the presence of MS in adults can be assumed with a combination of three or more of the following symptoms: abdominal type of obesity (waist size greater than 88 cm in women and more than 102 cm in men).

The main emphasis in this classification is made by the American Association of Cardiologists on the risk factors of cardiovascular diseases and, first of all, on arterial hypertension and lipid metabolism disorders.

In 2005, the International Diabetes Federation (IDF) proposed a new diagnostic algorithm, while tightening the requirements for the threshold values of some indicators [32]. According to the IDF recommendations, abdominal obesity (waist circumference greater than 94 cm in men and more than 80 cm in Caucasian women) is a mandatory criterion for MS in combination with at least two of the following factors: an increase in triglycerides greater than mmol/l, a decrease in high-density lipoproteins less than 1 mmol/l in men and 1.03 mmol/L in women, an increase in blood pressure greater than 130/85 mmHg. for example, an increase in the level of fasting venous plasma glucose greater than 5.6 mmol/l or detected type 2 diabetes mellitus.

Previously, it was believed that MS is a problem of middle-aged people and mainly women. However, studies conducted under the auspices of the American Diabetes Association indicate that over the past two decades, MS has shown a steady increase among adolescents and young people. According to scientists from the University of Washington (Seattle), in the period 1994-2000, the frequency of detection of MS among adolescents in the United States increased from 4.2 to 6.4%. The development of this syndrome in 32% of the observed patients from this age subgroup was associated with obesity [5].

According to epidemiological studies conducted in six federal districts of our country, about 12% of adolescents aged 12 to 17 years are overweight, 2.3% of them are obese, while every third obese teenager shows signs of metabolic syndrome [8]. According to other literature sources, MS is diagnosed in half of children with adolescent obesity [15; 31].

Unfortunately, to date, no uniform criteria have been developed to diagnose MS in children. One of the most universal classifications proposed for use in pediatric practice is the IDF classification, developed in 2007 on the basis of similar MS criteria for adults [33].

I would like to note that in the presented criteria (NCEP/ATP, IDF), the main component is abdominal (visceral) obesity. This trend is based on numerous data confirming the key role of obesity in the genesis of both individual symptoms included in MS and the syndrome itself [8; 31; 32; 24; 25]. In addition, it reasonably

simplifies the diagnosis and allows you to abandon technically complex laboratory methods for determining the level of insulin, calculating and interpreting insulin resistance indices (IR NOMA, QUICKI, clamp test, etc.) in the conditions of the polyclinic level.

Nevertheless, there is an alternative point of view. A number of authors consider it insufficiently justified to limit the problem of MS only to obese patients [15; 18; 28]. Alternative diagnostic models are proposed, in which, in particular, the main components are IR, CH, dyslipidemia and arterial hypertension, and obesity is considered as an additional criterion. Concomitant components also include hyperuricemia, microalbuminuria, hyperfibrinogenemia, increased C-reactive protein, tumor necrosis factor (TNF-a), etc. [28].

The development and adoption of a unified diagnostic algorithm in pediatric practice is influenced by differences in the assessment of extreme values (85, 90 or 95 percentile), taken as an increased indicator in determining BMI, abdominal obesity, blood pressure, etc. There is also no single universally recognized test for the detection of IR, and the threshold values of insulin due to the high variability of this indicator, especially in adolescence, have quite wide limits (from 10 to 20 μU / ml).

Despite numerous studies, the pathogenesis of MS has not been fully deciphered. The results of scientific works of recent years indicate that the common pathogenetic mechanism for the formation of the main components of MS is insulin resistance — a decrease in the sensitivity of target tissues to insulin, leading to a decrease in insulin-dependent glucose utilization by organs (liver, muscles). There are three types of IR, depending on the level of violations [30, 34].

There is evidence that the main defects leading to the development of IR are localized at the post-receptor level [8].

Although there is a close relationship between obesity and IR, there is still no answer to the question — which of them is primary [1; 19; 23]. According to some authors, the root cause is a hereditary predisposition to IR, which is realized in conditions of low physical activity and excessive nutrition. As a result of the formation of compensatory CH, insulin receptors are blocked, exogenous carbohydrates and fats are deposited by adipose tissue, lipolytic processes slow down and obesity progresses. Another hypothesis puts visceral obesity in the foreground. Adipocytes of visceral adipose tissue secrete free fatty acids (FFA), which prevent the binding of insulin to the receptor and disrupt the signal transmission from the receptor to the cells, which leads to the development of IR and compensatory CH [20].

It is important to note that it is not by chance that most researchers consider abdominal (visceral) obesity as the fundamental criterion for the development of MS [7; 15; 20]. Visceral adipose tissue has endocrine and paracrine activity. Visceral adipocytes have an increased sensitivity to the lipolytic action of catecholamines and a reduced sensitivity to the anti-lipolytic action of insulin. In abdominal fat depots, the rate of lipolysis is significantly higher than in subcutaneous fat. Adipocytes, along with FFA, produce adipocytokines — tumor necrosis factor (TNF-a), tissue growth factor-b1 (TGF-^1), interleukin-6 (IL-6), leptin, resisting, adiponectin, inducible NO synthase, etc., which also affect the sensitivity of tissues to insulin [11; 22].

Due to the fact that the most frequently combined components of MS are obesity, arterial hypertension and atherogenic dyslipidemia, the mechanism of their formation is currently the most studied. So, with obesity, as a result of increased lipolysis, a huge amount of FFA enters the bloodstream from visceral fiber, and then into the liver, as a result of which the process of their oxidation is disrupted, gluconeogenesis is activated and an excessive amount of glucose is formed. Against this background, the synthesis of triglycerides and their secretion in the form of very low-density lipoproteins (VLDL) increase in hepatocytes. This leads to excessive deposition of lipids in tissues and a decrease in the activity of enzymes involved in glucose metabolism. With hyperglycemia, the protein kinase-C enzyme is activated in the vascular endothelium, which increases vascular permeability and peroxidation processes, and the synthesis of nitric oxide by the endothelium, which has an antiplatelet and vasodilating effect, is inhibited, which ultimately leads to the development of arterial hypertension. In addition, as a result of an increase in glucose uptake in the insulin-sensitive cells of the ventromedial nuclei of the hypothalamus, the central activity of the sympathetic part of the ASP increases. This contributes to the maintenance of both vasoconstriction and hyperglycemia by reducing the capillary network and the number of slowly contracting fibers in the skeletal muscles, which is the main consumer of glucose. In addition, hypersympathicotonia stimulates the processes of lipolysis in adipose tissue, thereby contributing to the progression of IR [2; 20; 24].

Currently, the point of view has been convincingly confirmed, according to which the digestive organs play a direct role in the pathogenesis of hormonal and metabolic disorders, leading to the development of obesity, IR, atherogenic dyslipidemia, while they themselves become target organs [9-14].

As already mentioned above, one of the main organs regulating carbohydrate and lipid metabolism is the liver. It was found that almost every component of MS in adults is accompanied by secondary liver damage of the type of non-alcoholic fatty liver disease (NAFLD) [10-14]. If the average prevalence of NAFLD in the population is 10-40%, then among overweight people it reaches 74-100%. At the same time, 20-47% of the examined patients are diagnosed with steatohepatitis (NASH) [29]. It is no coincidence that in 2003 the American Association of Clinical Endocrinologists recognized NAFLD as one of the integral components of

MS. According to a number of authors, NAFLD is registered in 68% of obese children, in the presence of MS, this figure increases to 84% [5]. There is information about the detection of non-alcoholic steatohepatitis already at the age of 10-20 years. In the EU countries, it is found in 2.6% of the child population, while in overweight children-22.5-52.8% [10]. According to our data, NAFLD is diagnosed in 70% of children with MS, of which one in four (27%) has signs of NASH [3].

Convincing data indicate that the main link in the development of NAFLD, as well as the main components of MS, is IR. At the same time, the main causes of the development of the pathological process are fatty damage to hepatocytes and the processes of lipid peroxidation occurring with the participation of FFA and adipocytokines [6].

Another digestive organ that has exocrine and endocrine activity and directly affects the process of formation of IR and CH is the pancreas.

In the modern literature, there is evidence that adults with overweight, with a high frequency, are diagnosed with a similar NAFLD lesion of the pancreas — pancreatic steatosis (PS), which has recently been of increasing interest to scientists from the standpoint of the development of MS [9]. In addition, the absolute majority of children (up to 100%) with signs of MS also show characteristic changes in the pancreas [4].

It was found that an increase in the level of FFA has a toxic effect on the pancreatic cells and leads to a violation of their secretory activity. The early phase of stimulated secretion falls out and the impulse secretion of insulin is disrupted: The 1st (fast) phase of insulin secretion, in which vesicles with accumulated insulin are emptied, is absent, and the 2nd phase of basal secretion is carried out in a monotonous mode [27; 35]. At the same time, despite the CH, the glucose level does not normalize.

It should be emphasized that there is a relationship between the endocrine and exocrine parts of the pancreas through the insouciant portal system, which can have a direct impact not only on the pathogenesis, but also on the clinical symptoms of MS [17; 34].

Thus, the etiopathogenesis of MS is currently complex and not fully understood. The high frequency of atherogenic, diabetogenic, thrombogenic complications in adolescence allows us to consider this symptom complex as an important pediatric problem. Its interpretation requires a comprehensive approach with the involvement of specialists from various fields of medicine. Only the joint activity of pediatricians with endocrinologists, gastroenterologists, cardiologists will allow us to fully study the main pathogenetic mechanisms of the formation of MS in childhood, to identify the range of clinical manifestations, while focusing on earlier symptoms that are predictors of its development in children. This will allow us to develop methods of targeted prevention of cardiovascular pathology and type 2 diabetes mellitus, diseases of the hepatobiliary and reproductive systems, and thereby reduce the risk of early disability and premature death.

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