colloquium-journal

ISSN 2520-6990

Międzynarodowe czasopismo naukowe

Medical sciences
Technical science
Economic sciences
Physical and mathematical sciences

№34(157) 2022
Część 1

colloquium-journal

ISSN 2520-6990

ISSN 2520-2480

Colloquium-journal №34 (157), 2022

Część 1

(Warszawa, Polska)

«Colloquium-journal»
Wydawca «Interdruk» Poland, Warszawa
Annopol 4, 03-236
E-mail: info@colloquium-journal.org
http://www.colloquium-journal.org/

MEDICAL SCIENCES

UGC 612.35

Piddubna A.A.
ORCHID: 0000-0002-9143-9574
Candidate of medical sciences,
Docent of Endocrinology, Allergology and Immunology Department,
Higher State Medical Establishment «Bukovinian State Medical University»
Chernivtsi, Ukraine
Honcharuk L.M.
Candidate of medical sciences, Docent of the Department of Internal Medicine,
Higher State Medical Establishment «Bukovinian State Medical University»
Chernivtsi, Ukraine
Voncha K.V.
6th year student,
Higher State Medical Establishment «Bukovinian State Medical University»
Chernivtsi, Ukraine
Yunak V.V.
6th year student,
Higher State Medical Establishment «Bukovinian State Medical University»
Chernivtsi, Ukraine
Makoviichuk K.Y.
4th year student,
Higher State Medical Establishment «Bukovinian State Medical University»
Chernivtsi, Ukraine

DOI: 10.24412/2520-6990-2022-34157-39-42

SOME PATHOGENETIC FEATURES OF THE METABOLIC SYNDROME

Abstract:
The article discusses the features of pathogenetic mechanisms in metabolic syndrome. Almost all of its components are risk factors for the development of cardiovascular diseases, and in combination accelerate their development many times over. Moreover, the combination of individual components can be considered within the framework of the metabolic syndrome only in the presence of insulin resistance. Of course, not all components of the metabolic syndrome occur at the same time. The phenotype of metabolic syndrome depends on the interaction of genetic and environmental factors.

Key words*: metabolic syndrome, insulin resistance, hyperinsulinemia, hyperglycemia, arterial hypertension, hypodynamia, obesity, leptin resistance.*

Research in recent years shows a dangerous trend towards the "rejuvenation" of metabolic syndrome (MS). According to many authors, the incidence of MS among adolescents has increased from 4.2 to 6.4% over the past 10 years. Excess body weight was found in 12-14% of the child population of economically developed countries. The initial signs of metabolic disorders are revealed already in adolescence and young adulthood, and are more often registered in the group of children with burdened heredity and excess body weight. When examining adolescents with obesity that developed before the onset of puberty, a high prevalence of hyperinsulinemia and arterial hypertension (AH) was noted. At the age of over 18, an increase in body weight by 1 kg increases the risk of hypertension by 5%, and an increase of 8.0-10.9 kg increases the risk of cardiovascular diseases by 1.6 times. MS occurs in 35-49% of postmenopausal women, and the frequency of this syndrome is steadily increasing. MS or syndrome X is a kind of payback for our urbanization: hypodynamism, poor nutrition and a sedentary lifestyle, which can later turn into serious health problems. You can talk about the presence of MS if a person has at least three of the following symptoms: overweight; arterial hypertension; hyperglycemia; dyslipidemia; early atherosclerosis; coronary heart disease; gout; hyperandrogenism According to statistics, about 20% of middle-aged and elderly people suffer from X syndrome. And their number is growing every year. The development of MS largely depends on body weight and correlates with BMI in both men and women. Among people with excess body weight, the prevalence of MS varies between 22-28%, among people with obesity - 50-60%. In the near future, scientists predict an increase in the number of patients with MS, primarily due to obesity. The prevalence of this syndrome has a clear age dependence: among people from 20 to 29 years old, it is 7%, and among people over 60 years old it reaches 40%.

A hereditary predisposition is clearly visible in the development of MS. Genetic risk factors may lie in the constitutional features of the composition of muscle fibers, fat distribution, activity and sensitivity to insulin of the main enzymes of carbohydrate and fat metabolism. The genetic predisposition to the formation of MS is determined by several groups of genes. One of these groups includes genes whose products determine elevated glucose levels. The number of genes that can potentially affect the action of insulin is very large. Various proteins are involved both in the signaling chain of insulin action and in the processes of glucose capture and metabolism, any change in which can affect insulin sensitivity. However, to date, only the gene encoding

the receptor that is activated by the peroxisome proliferator type P2 (PPARG2) has been found to be reliably associated with reduced sensitivity of peripheral cells to insulin. In addition, this group should include genes associated with the development of type 2 diabetes, namely: genes that play an important role in the transport of insulin through the membrane of β-cells of the pancreas - KCNJ11 (encodes the Kir6.2 protein) and ABCC8 (encodes the sulfonylurea receptor SUR1); genes whose products calpain 10 and factor 2-like transcription factor 7 are involved in the regulation of glucose homeostasis through the Wnt-type signaling channel (CAPN10 and TGF7L2). A group of genes whose products regulate lipid metabolism and the development of obesity should be singled out separately. Currently, it is suggested that genes encoding AV apolipoprotein (APO A5), CD36 fatty acid transporter associated with cell membranes (FAT), a fatty acid-binding protein in intestinal cells may be associated with the development of MS (FABP2), microsomal TG fatty acid transporter (ATGL), adiponectin (ADIPOQ), and adiponectin receptor type 2 (ADIPOR2). Genes encoding angiotensinogen (AGT), β-protein subunit G 8 (GNB3) and NO-synthetase of vascular endothelial cells (NOS3) are included in the group of genes for which a reliable association with essential hypertension was found.

The most important environmental factor is excessive consumption of fatty foods, especially animal fats containing saturated fatty acids. In addition, about 30-40% of obese patients have eating disorders, among which hyperphagic response to stress, compulsive hyperphagia, carbohydrate craving and premenstrual hyperphagia are the most common. Hyperphagic reaction to stress as an eating disorder is manifested by the fact that during psycho-emotional stress, excitement or immediately after the end of the action of the factor that caused stress, a person's appetite increases sharply, and the desire to eat appears. Yes, nocturnal hyperphagia is an imperative increase in appetite in the evening and at night. To satisfy carbohydrate or food cravings, patients need both sweet and fatty food. In its absence, patients develop a severe depressive state, reminiscent of withdrawal. It is believed that the mechanisms of the occurrence of eating disorders are related to the disruption of serotonin transmission in the brain structures responsible for the regulation of eating behavior. Excessive fat consumption can be formed as a family eating habit, transmitted by upbringing. Unfortunately, the number of families with a high incidence of obesity is increasing. The tendency to develop obesity lies precisely in the reduction of the ability to oxidize fats. One of the possible reasons for this is the condition of the muscles and the composition of muscle fibers. The bulk of fat in the body is oxidized in the muscle tissue, in its slow and fast oxidative fibers, while the fast glycolytic fibers in the muscles lack the ability to oxidize fat. With the predominance of this type of fibers in the muscles, the ability to oxidize lipids will be reduced. It is shown that women have fewer fast-twitch fibers on average than men.

Hypodynamia also contributes to the development of obesity and IR. During hypodynamism, lipolysis and utilization of triglycerides in muscle and adipose tissues slows down and the translocation of glucose transporters in muscles decreases, which leads to the development of IR. In some cases, hypertension can be the primary link in the pathogenesis of MS. Long-term, untreated or poorly treated hypertension causes deterioration of peripheral blood circulation, which leads to a decrease in tissue sensitivity to insulin and, as a result, to relative hyperinsulinemia and IR. Thus, the pathogenesis of hypertension in MS is based on IR and compensatory hyperinsulinemia.

The main metabolic pathways of carbohydrates, fats and proteins are closely interconnected at the level of nodal metabolites and key enzymes. Disruption of metabolism is the primary basis of all changes and is based on the existence of certain limitations in the mutual transformations of carbohydrates, fats and proteins. These limitations are deepened with insulin deficiency due to changes in the activity of a number of key metabolic enzymes that catalyze the phosphorylation of glucose and fructose-6-phosphate, synthesis of glycogen from UDP-1-glucose, phosphorolysis of glycogen to glucose-1-phosphate, dephosphorylation of glucose-6-phosphate by hydrolysis to free glucose, conversion of amino acids into α-keto acids by means of peramination and oxidative deamination reactions, reverse conversion of pyruvic acid into phosphoenol-pyruvate, lipolysis of triglycerides, formation of acetone bodies from acetyl-CoA. In addition to regulators that intervene in metabolic processes at the level of enzyme reactions, there is an influence of hormones associated with their release into the bloodstream. Thus, adrenaline and norepinephrine increase the rate of lipolysis in adipose tissue due to stimulation of adipocyte adenylate cyclase and cAMP synthesis. The action of glucagon is similar to the action of catecholamines. Insulin has the opposite effect of adrenaline and glucagon on lipolysis and mobilization of fatty acids. Somatotropic hormone, adrenocorticotropic hormone also have a stimulating effect on lipolysis, increasing the content of fatty acids in blood plasma. Adipose tissue has an auto-, para- and endocrine function and secretes "adipocytokines", which are characterized by various biological actions that can cause the development of obesity-related complications, including IR: leptin, tumor necrosis factor-α (TNF-α), inhibitor-1 plasminogen activator (PAI), protein that stimulates acylation (ASK), interleukin-6, interleukin-8, angiotensin-II, resistin, adiponectin, adipsin, agouti protein, transforming growth factor-β, adipophilin. Many researchers consider TNF-α as a mediator of IR in obesity. TNF-α reduces the activity of insulin receptor tyrosine kinase, inhibits the expression of intracellular glucose transporters GLUT-4 in muscle and adipose tissue. As shown in vivo, TNF-a can act synergistically with interleukins-1 and 6 and also stimulate leptin secretion. The hormone leptin is the "voice" of adipose tissue that regulates eating behavior by influencing the satiety center in the hypothalamus. The physiological effects of leptin include: increasing the tone of the sympathetic nervous system, increasing thermogenesis in adipocytes, reducing insulin synthesis, reducing glucose transport, affecting the insulin receptor of the cell. The stimulating effect of

leptin on the secretion of gonadotropins was revealed. In the prepubertal period, the level of leptin increases in parallel with the increase in weight to the maximum values with the onset of puberty. In the pubertal period, sensitivity to leptin increases. Obesity may be associated with leptin deficiency and leptin resistance. The amount of insulin and leptin in the circulatory system is directly proportional to the mass of fat deposits, and they are called "obesity signals". An elevated level of leptin in leptin resistance and MS causes the development of hormonal dysfunction and visceral obesity. Glucocorticoid instability (intracellular hypercorticism) in MS and IR also leads to the development of visceral obesity.

The most frequent variant of dyslipidemia in MS is the lipid triad: a combination of hypertriglyceridemia, a low level of HDL-C and an increase in the fraction of small dense particles of LDL-C, carriers of triglycerides, which is the result of their increased hepatic production. Hyperinsulinemia contributes to an increase in the proliferation of smooth muscle cells and fibroblasts, an increase in the activity of LDL-C receptors and the synthesis of endogenous cholesterol in the cells of the vascular wall, collagen, and stimulation of the production of IPF. The main mechanisms that lead to an increase in blood pressure (BP) in MS are hypervolemia, due to increased reabsorption of sodium in the proximal tubules of the kidneys and which causes an increase in cardiac output; activation of the sympathetic nervous system, which also causes an increase in cardiac output and leads to spasm of peripheral vessels and an increase in total peripheral vascular resistance. Under the influence of insulin, there is an increase in the endothelium's production of vasoconstrictor biologically active substances - endothelin, thromboxane A2 and a decrease in the secretion of such powerful vasodilators as prostacyclin and nitric oxide. In addition, the increase in blood pressure is due to an increase in the level of leptin, which regulates the feeling of satiety at the level of the arcuate nucleus of the hypothalamus, which is closely connected with the paraventricular nucleus, the stimulation of which leads to the activation of the sympathetic nervous system. The main mechanisms of the effect of chronic hyperinsulinemia on blood pressure: - blocks transmembrane ion exchange mechanisms (Na+, K+ and Ca2+-dependent ATPase), thus increasing the content of intracellular Na+ and Ca2+, reducing the content of K+, which leads to an increase in the sensitivity of the vascular wall to pressor influences; - increases the reabsorption of Na+ in the proximal and distal tubules of the nephron, contributing to fluid retention and the development of hypervolemia, as well as increasing the content of Na+ and Ca2+ in the vessel walls; - stimulates the proliferation of smooth muscle cells of the vascular wall, which leads to the narrowing of arterioles and an increase in vascular resistance; - stimulates the activity of the sympathetic nervous system, which leads to an increase in vascular tone; - stimulates the activity of the renin-angiotensin system. All these effects collectively contribute to an increase in blood pressure. An increase in the activity of the sympathetic nervous system, which occurs in hypertension, causes a decrease in the volumetric blood flow in the capillaries of the skeletal muscles as a result of their vasoconstriction, which increases the diffusion path of glucose to the cells and leads to IR.

Vascular endothelium has metabolic and secretory activity and plays a key role in regulating vascular tone and permeability. The unique position of endothelial cells at the border between circulating blood and tissues makes them the most vulnerable to various pathogenic factors found in systemic and tissue circulation. Currently, there are two main points of view regarding the formation of endotheliopathy. The first is that with IR syndrome, the dysfunction of the vascular endothelium develops and, in particular, the synthesis of nitric oxide in the vascular wall is disturbed (nitric oxide is a powerful vasodilator). It has a restraining effect on the proliferation of smooth muscle cells, inhibits the adhesion of monocytes to the endothelium of the vascular wall, reduces lipid peroxidation, i.e. protects the vascular walls from damage. There is also an opinion that endothelial dysfunction is not a consequence, but a cause in the development of IR, one of the primary defects underlying its development. In case of a primary defect of endothelial cells, the transendothelial transport of insulin is disturbed, which can contribute to the development of IR. However, until now, not enough data have been obtained in favor of a primary or secondary role of endotheliopathy in the genesis of insulin resistance. IR and hyperinsulinemia are among the main factors leading to the development of diabetes mellitus (DM) type 2, especially in individuals with a hereditary predisposition. It is known that one of the most important consequences of IR is an increase in the level of insulin in the blood and hyperglycemia. In the conditions of IR, the utilization of glucose by peripheral tissues decreases, the production of glucose by the liver increases, which contributes to the development of hyperglycemia. With an adequate ability of b-cells to respond to an increase in blood glucose, compensatory hyperinsulinemia maintains a normal level of glucose in the peripheral blood. However, constant stimulation of b-cells in combination with probable genetic disorders affecting their functionality and the effect of increased concentration of free fatty acids on b-cells (the phenomenon of lipotoxicity) contribute to the development of secretory dysfunction of b-cells, progressive impairment of insulin secretion. Over time, impaired glucose tolerance develops and type 2 diabetes develops. With the development of type 2 diabetes, hyperglycemia occurs, which contributes to the further progression of impaired insulin secretion by b-cells (the phenomenon of glucose toxicity) and an increase in peripheral IR. With IR syndrome, the function of the vascular endothelium is also disturbed and, in particular, the synthesis of nitric oxide in the vascular wall decreases, which restrains the proliferation of smooth muscle cells, inhibits the adhesion of monocytes to the endothelium of the vascular wall, reduces lipid peroxidation, i.e. protects the vascular walls from damage. Therefore, dysfunction of the endothelium develops, which contributes to the acceleration of the development of atherosclerotic vascular damage. Thus, according to the literature, among patients with MS, mortality from coronary heart

disease is 2-3 times higher than in the general population.

Conclusions. Therefore, insulin resistance and hyperinsulinemia in metabolic syndrome independently or indirectly (due to concomitant metabolic disorders) have an additional pathological effect on the cardiovascular system, which ultimately accelerates the development of atherosclerotic vascular diseases.

References:

1.Alexandersen P., Karsdal M.A., Christiansen C. Long-term prevention with hormonereplacement therapy after e menopause: which women should be targeted? //Womens Health. − 2019. − V.5. − №6. − P.637-647.

2. Burrows R., Burgue T.M., Leiva L., Ceballos X., Guillier I., Gattas V., Lera L., Albala C. Cardiovascular risk and metabolic profle in obese children andadolescents wi low insulin sensitivity// Rev. Med. Chil. − 2015. − Vol. 133(7). − P. 795-804.

3. Curston R., MaryFran R. Sowers, Kim Sutton-Tyrrell Abdominal adiposity and hot fashes among midlife women // Menopause. − 2009. − V.15. − №.3. − P. 429-434.

4. Fam A.G. Gout, diet and the insulin resistance syndrome // J. Rheumatol. – 2012. – Vol. 29, № 7. – P. 1350–1355.

5. Frederick I.O., Rudra C.B., Miller R.S. et al. // Epidemiology. − 2016. − Vol. 17. − P. 428-434.

6. Konturec S.J., Konturec J.W., Pawlic T., Brozozowki T. Brain-Gut axis and its role in the control of food intake // J. of Physiology and pharmacology. – 2014. – Vol. 54, 1. – P. 137-154.

7. Konturec S.J., Konturec P.C., Konturec J.W., Czesnikiewicz-Gusik M., Brozozowki T., Sito E. Neuro-hormonal control of food intake; basic mechanisms and clinical implications // J. of Physiology and pharmacology. – 2015. – Vol. 56, Supp. 6. – P. 5-25.

8. Rahmouni K., Correia M.L., Haynes W.G., Mark A.L. Obesity-associated hypertension: new insights into mechanisms // Hypertension. − 2015. − Vol. 45 (1). − P. 9-14.

9. Rutter M.K., Meigs J.B., Wilson P.W.F. Cardiovascular risk and the metabolic syndrome // Metabolic syndrome and related disorders, 2016. – P. 252-260.

10. Tsatsanis C., Zacharioudaki V., Androulidaki A., Dermitzaki E., Charalampopoulos I., Minas V., Gravanis A., Margioris A.N. Peripheral factors in the metabolic syndrome: the pivotal role of adiponectin // Ann. N-Y. Acad. Sci. − 2006. − Vol. 1083. − P.185- 95.