

METABOLIC SYNDROME IS A CURRENT PROBLEM OF MODERN MEDICINE

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Abstract

Metabolic syndrome is not a disease, but a condition that unites a group of risk factors that lead to the development of heart disease, diabetes and stroke. This syndrome is a complex of metabolic, hormonal and clinical disorders. The problem has been attracting the attention of clinicians for more than half a century, since the conditions associated with MS. This paper summarizes modern aspects of the metabolic syndrome, its causes, pathogenesis and clinical presentation and treatment options according to the conditions of the patients.

Key words: metabolic syndrome, insulin resistance, hypertension, abdominal obesity.

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INTRODUCTION

Metabolic syndrome (MS) is a complex of interrelated and modifiable risk factors for the development of cardiovascular diseases (CVD) and type 2 diabetes mellitus (diabetes) (as defined by the World Health Organization (WHO, 1999) and NCEP ATP III (2001) - National Cholesterol Education Program Adult Treatment Panel III - US National Cholesterol Reduction Program, III revision of therapy for adults) [1]. The main components of MS are disorders of carbohydrate metabolism, abdominal obesity, dyslipidemia, and arterial hypertension [2].

In developed countries, metabolic syndrome is a serious problem [3,4]. Very often, in the USA, it can be observed in more than 40% of people over 50 years old. Metabolic syndrome can develop in children and adolescents, but the definition is not established in these age groups [5,6,7].

Initially, a complex of interconnected symptoms was called metabolic syndrome, including insulin resistance, hyperinsulinemia, hypertriglyceridemia, impaired glucose tolerance, arterial hypertension and low levels of "good" cholesterol (HDL) [8]. As this phenomenon has been studied, MS has acquired new "details" and today this complex, in addition to the above components, includes abdominal-visceral obesity (when fat accumulates in the abdominal cavity), increased blood cholesterol (dyslipidemia), microalbuminuria and early atherosclerosis [9,10].

Depending on the amount of "ingredients" present that make up the metabolic syndrome, and there may be 4 or 5, the risk of developing diabetes and ischemic heart disease is increasing [11,12]. Some mistakenly equate MS with obesity. Yes, they correlate in many respects, but nevertheless, the concept of MS is much broader. Obesity can exist by itself, in isolation, without being included in the list of manifestations of any disease [13,14]. MS is a more global thing, incorporating the notorious obesity, but as already mentioned, it is abdominal-visceral when fat deposits are localized in the abdomen and upper shoulder girdle (an apple-like figure, not a pear).

According to D.L. Alyavi et al., In patients with MS and coronary heart disease (CHD) mortality from CVD increases 5 times for women and 2 times for men [2], and myocardial infarction and stroke are 3.5 times more common [15]. From the point of view of public health and clinical practice, the obesity epidemic, the pathogenetic basis of which is insulin resistance (IR), is becoming the main socio-economic problem of mankind, for which early diagnosis and timely effective treatment of the main components of MS are extremely important [16].

For justice, it should be noted that MS is possible without obesity. It is enough to have at least 3 of its above components, each of which in itself is a significant risk factor for the development of CVD [17,18].

FACTORS CONTRIBUTING TO MS AND ITS CLINICAL MANIFESTATIONS

Let's start with external factors: the nature of nutrition (high-calorie, atherogenic); lack of physical activity; stress; bad habits (alcohol, smoking). The key link in the development of the metabolic syndrome, for which all its other components "cling", is insulin resistance, i.e. decreased tissue sensitivity to insulin. Insulin resistance, in turn, is affected by visceral (intracavitary, not subcutaneous) adipose tissue. How? The fact is that the cells of this tissue have a low density and sensitivity of insulin receptors, therefore, low sensitivity to the antilipolytic effect of insulin [19,20,21,22]. Lipolysis is intensified, the concentration of free fatty acids in the blood rises, through the portal system they migrate to the liver, where they are used as a substrate for the synthesis of triglycerides. Here is another sign of MS - hypertriglyceridemia.

Insulin resistance leads to an increase in blood glucose - hyperglycemia, which in turn provokes the release of insulin (hyperinsulinemia) [23,24]. All these phenomena with the prefix "hyper" lead to vascular endothelial dysfunction, increased vascular tone and arterial hypertension. Insulin resistance and hyperglycemia create fertile ground for dyslipidemia, characterized by high blood levels of "bad" cholesterol (LDL) [25]. Moreover, LDL particles in this case are less than usual and more dense. They easily migrate to the subendothelial space, forming an atherosclerotic plaque.

Even in ancient times, Hippocrates, who lived in the 5th century BC, noted that people who are very obese by nature die more often than thin people. However, the first scientific publications on the problem of MS appeared in the XX century. So, in 1923, the Swedish doctor E. Kylin described a syndrome that included gout, arterial hypertension and hyperglycemia.

In 1940, J. Vague introduced the concept of central obesity. In subsequent years, there has been a progressive increase in the number of scientific studies confirming the close relationship of obesity with CVD and type 2 diabetes. Various terms have been proposed to describe this condition.

The founder of the modern concept of MS is considered the American scientist Gerald Riven (Jerald Reaven), who proposed in 1988 an elegant pathophysiological model of the

development of MS, in which the IR phenomenon was called a key factor in the occurrence of this condition.

The term "insulin resistance" is understood to mean a decrease in the reaction of insulin-sensitive tissues to insulin at its sufficient concentration, leading to chronic compensatory hyperinsulinemia [26,27,28]. IR is based on various genetic defects responsible for signal transmission after the connection of insulin with its receptor (postreceptor defects). Normally, receptor autophosphorylation occurs with the participation of tyrosine kinase and its subsequent connection with the substrate of the insulin receptor (IRS-1 and -2). IRS molecules activate phosphatidylinositol-3-kinase (PI3K), which stimulates translocation of the glucose transporter GLUT-4 through the cell membrane, which activates the metabolic and mitogenic effects of insulin [29,30]. In patients with type 2 IR and type 2 diabetes, translocation of the glucose transporter is impaired, and the expression of other genes that provide glucose and lipid metabolism is disrupted, including mutations in the genes for glycogen synthetase, hormone-sensitive lipase, tumor necrosis factor (TNF) alpha, uncoupling protein, etc.

The reasons for the wide spread of the above mutations are not entirely clear, but most researchers support the theory of "economical genotype", put forward by professor James Neel (James Neel) in 1962. According to this hypothesis, during evolution, the most appropriate "thrifty" genes were fixed in the genotype, which provided IR for the purpose of storing energy in the form of fat "in reserve" [31]. Under the primitive communal system, this process was of adaptive importance for survival in conditions when the human nutrition abilities were irregular and periods of abundance alternated with periods of prolonged fasting [32,33,34]. However, for a very short (on the scale of evolution) period of time in countries with a high standard of living, mankind has switched to high-calorie nutrition in combination with a decrease in the consumption of muscle energy. The result of the IR mechanism fixed in the genetic memory is the development of an MS pandemic, including its main components: obesity, dyslipidemia, arterial hypertension, and type 2 diabetes.

Since the publication of one of the most cited papers by G. Reaven "The Role of Insulin Resistance in Human Diseases", all subsequent scientific studies should either confirm or refute the pathogenetic theory about the fundamental role of IR in the development of MS. However, this did not happen [35,36]. Countless publications that appeared after 1988 only confirmed the positive relationship between the individual components of the MS and its outcomes, or described all the new components of the MS.

After 10 years, G. Reaven publishes an updated version of the concept of pathogenesis of MS (X-Syndrome: 10 years later), in which the author calls abdominal obesity the second key link in the development of MS, in addition to IR [37]. The scientist also increases the number of main components of this syndrome.

PATHOPHYSIOLOGY OF THE DEVELOPMENT OF METABOLIC SYNDROME

In scientific studies, it was shown that excess adipose tissue with auto-, para- and endocrine function serves as the basis for the development and progression of IR and is itself capable of secreting a large number of cytokines and vasoactive substances. To date, the most studied are leptin and adiponectin. TNF-alpha, C-reactive protein, interleukins (IL) 1, 6 and 8 also belong to mediators of chronic subacute inflammation [38,39,40].

To date, the etiology and pathogenesis of MS have not been fully disclosed [41]. Publications containing the results of scientific research describe various hormonal disorders that contribute to the development of abdominal obesity, including activation of the hypothalamic-pituitary-adrenal axis, increased levels of testosterone and androstenedione, and decreased progesterone production in women. As a clinical manifestation of MS, one cannot but mention arterial hypertension [42]. The cornerstone of its development is

hyperinsulinemia, which blocks the transmembrane mechanisms of ion exchange, making the vascular wall sensitive to pressure, retains water by increasing sodium reabsorption in the distal and proximal tubules of the nephron, increases vascular tone, and narrows the lumen of arterioles [43,44].

To date, there is no single treatment strategy for MS. The presence in patients of a wide variety of non-modifiable risk factors (gender, heredity, age, ethnicity) in combination with modifiable factors (overweight or abdominal obesity, a sedentary lifestyle, arterial hypertension, dyslipidemia, impaired glucose tolerance and / or impaired fasting glucose) determines the existence of a huge number of phenotypic variants of MS, requiring a personalized approach to the selection of therapy of its individual components. In this regard, the use of the concept of MS, according to WHO experts, is limited as a diagnostic and therapeutic tool [45].

The main therapeutic measures for MS include lifestyle changes, as the main way to correct metabolic risk factors, and drug treatment of the combined components of MS [46]. When treating MS, they are repelled by the main threat that emanates from it: the risk of CVD. First of all, you must make adjustments to the lifestyle, diet (to limit animal fats, give preference to foods high in polyunsaturated fatty acids), forget about alcohol forever. All efforts should be directed at getting rid of excess weight [47,48]. Many patients are condescending to such recommendations. In this case, it is not forbidden, but even welcomed to put the subject before the fact: if you do not want to die in 8-10 years, fundamentally change your usual way of life.

"In the beginning there was insulin resistance" - this is how you can rephrase the lines of the New Testament in the refraction to the MS. Therefore, with its medical correction, drugs are used that increase tissue sensitivity to insulin: rosiglitazone, avandia. This is achieved by reducing the level of triglycerides and free fatty acids in the blood, inhibiting the breakdown of glycogen in the liver and increasing the number of glucose transporters in the cells [49,50,51].

Arterial hypertension in MS is stopped by angiotensin converting enzyme inhibitors or angiotensin receptor blockers. To reduce the risk of vascular complications, aspirin is prescribed [52,53].

Atherogenic dyslipidemia is one of the main components of MS described by G. Reaven in 1988. In the process of studying the concept, it became clear that another common disease associated with MS is non-alcoholic fatty liver disease (NAFLD), which proceeds in two forms, or successive stages: liver steatosis and non-alcoholic steatohepatitis (NASH). According to Uzbek authors, in patients with MS and abdominal type of obesity, NAFLD occurs in 100% of cases, and NASH in 41.7% [54]. It is proved that the leading mechanisms of the development of this disease are pathological activation of lipolysis processes with the release of a large amount of free fatty acids in individuals with abdominal obesity, concomitant IR and oxidative stress, which provokes an inflammatory reaction in hepatocytes and leads to the formation of steatohepatitis.

In those cases when a hypocaloric and hypocholesterol diet and a change in physical activity do not allow you to adjust the lipid spectrum and the activity of liver enzymes, it is necessary to consider the possibility of using drug therapy [55,56].

Metformin (biguanide) has proven activity against NAFLD due to its ability to directly inhibit glucose production by the liver, improve insulin sensitivity, and reduce the concentration of free fatty acids in the blood, inhibiting the expression of lipogenic enzymes. In a number of studies, it was shown that the use of metformin in NAFLD reduces the level of alanine aminotransferase by 30% [57].

TREATMENT OF DYSLIPIDEMIA

The main drugs for the treatment of atherogenic dyslipidemia are hydroxymethylglutaryl-CoA reductase inhibitors (HMG-

CoA reductase) (statins) and fibroic acid derivatives (fibrates) [58,59,60].

Statins represent the first line of lipid-lowering therapy due to its proven effectiveness in reducing LDL [61] and due to a significant reduction in the number of end-cardiovascular outcomes, including cardiovascular mortality and all-cause mortality in most patients. According to data from a meta-analysis of independent studies (4S, HPS, ASCOT-LLA, CARDS, 4D) published in 2005, the risk of coronary heart disease while taking statins was 23% (11 to 51%) on average.

The main mechanism of the effective effect of statins on dyslipidemia and NAFLD is the blocking of the isoprenoid pathway, which inhibits the synthesis of total cholesterol, LDL and triglycerides against the background of increased production of HDL [62]. In addition to a direct effect on lipogenesis, drugs have an antioxidant effect, reduce angiogenesis by affecting ED, have antitumor activity, including the ability to prevent the development of hepatocellular cancer.

Fibrates lower triglycerides from 20 to 50%, increase HDL from 1 to 34%, and can lower LDL to 20%.

Over the past 10–15 years, several large prospective studies have been conducted, among which the most extensive was the FIELD study (The Fenofibrate Intervention and Event Lowering in Diabetes trial) with the participation of 9795 patients with impaired carbohydrate metabolism. The effectiveness of fibrates in patients with type 2 diabetes and / or signs of MS was shown - the relative risk of cardiovascular complications was significantly reduced. The reason for this positive effect is the proven pleiotropic effect of fibrates: they inhibit the migration of vascular endothelial cells and the activity of oxidative stress, as a result of which they have an anti-inflammatory effect.

PHARMACOTHERAPY OF HYPERTENSION

The frequent development of arterial hypertension in MS is due to a whole complex of the previously described pathogenetic mechanisms of the development of the syndrome, against the background of the polygenic nature of the inheritance of concomitant diseases - obesity, type 2 diabetes and dyslipidemia, as well as hyperactivation of the renin-angiotensin-aldosterone system [62,63,64,65].

Antihypertensive therapy for MS should be carried out until the target blood pressure level of less than 130 and 80 mm RT. Art., especially in the presence of type 2 diabetes [66]. Numerous studies using a wide range of antihypertensive agents have proven that effective blood pressure control significantly reduces the risk of CVD and mortality [67]. Moreover, strict control of blood pressure in patients with type 2 diabetes leads to a more significant decrease in the frequency of macrovascular complications of diabetes than the achievement of target glycemic levels.

The general principles of the medical treatment of arterial hypertension are: continuous, long-term therapy, starting treatment with the minimum doses of one drug, switching to drugs of another class with insufficient treatment effect (at the maximum dosage) or poor tolerance, the use of drugs mainly of long duration, the use of optimal combinations of drugs to achieve maximum hypotensive effect and minimize side effects.

According to the latest domestic and international recommendations, first-line drugs in the treatment of arterial hypertension in patients with MS are angiotensin-converting enzyme inhibitors, type I angiotensin receptor blockers and calcium antagonists [68].

PHARMACOTHERAPY OF INSULIN RESISTANCE AND DISORDERS OF CARBOHYDRATE METABOLISM

One of the main dramatic outcomes of MS is the development of type 2 diabetes. This disease is characterized by a gradual onset - it begins with mild or moderate disorders of carbohydrate metabolism due to IR and functional

hyperinsulinemia, which over time cause beta-cell dysfunction and impaired insulin production, which leads to prediabetes [69, 70]. Then, already for a much shorter period, the manifestation of type 2 diabetes occurs.

In 2007, ADA and IDF experts adopted the Conciliation Consensus on the treatment of prediabetes in people with impaired glucose tolerance and / or impaired fasting glucose, in which metformin therapy is indicated along with lifestyle changes [62]. Acceptance of these recommendations was based on the results of a prospective randomized clinical trial DPP (Diabetes Prevention Program), in which evidence was obtained that during the 3.2-year observation period, lifestyle changes and treatment with metformin (the original drug Glucophage® metformin was used) were 58% 31%, respectively, reduced the risk of type 2 diabetes in patients with prediabetes compared with the control group of patients [70]. This trend also continued in the subsequent observation period - for 10 years (34% and 18%, respectively) [64]. The greatest positive effect on the prevention of type 2 diabetes was observed in young patients with more pronounced disorders of carbohydrate metabolism and obesity.

Consensus calls for early diagnosis and prophylactic treatment of prediabetes with metformin in combination with lifestyle changes in people at high risk for type 2 diabetes [65]. These should include persons with impaired fasting glucose and impaired fasting glycemia combined with another additional risk factor (age <60 years or BMI ≥ 35 kg / m², in the presence of diabetes in relatives of the first degree of kinship, with an increased level of triglycerides, low HDL, hypertension, or HbA1c ≥ 6%).

In addition to the above recommendations of the joint consensus of ADA and IDF, the American College of Endocrinology (ACE) in its paper recommends an early diagnosis of carbohydrate metabolism disorders and lifestyle modifications, along with the simultaneous identification of concomitant risk factors such as arterial hypertension, obesity and dyslipidemia [47]. Experts recommend the appointment of acarbose and metformin for people at high risk of developing type 2 diabetes who have impaired fasting glucose, impaired glucose and / or MS tolerance, increased glycemia, CVD, a history of gestational diabetes, NAFLD, or polycystic ovary syndrome.

Metformin is an antihyperglycemic drug from the biguanide group that does not have a hypoglycemic effect and has been used to treat type 2 diabetes since 1953. The drug improves the sensitivity of adipose and muscle tissue to insulin, reduces glucose production by the liver through its effect on gluconeogenesis, reduces glycogenolysis, and inhibits glucose absorption in the intestine, has an anorexigenic effect, which helps many patients to comply with recommendations for hypocaloric nutrition [58].

Bioequivalence studies have shown that the efficacy and safety profile of the drug can extend to the innovative form of sustained release metformin.

In addition, a retrospective study revealed a significant decrease in the incidence of diarrhea from 18.05% on rapid release metformin to 8.29% on sustained release metformin. The frequency of occurrence of any adverse events was 26.34% among patients with fast-release metformin and decreased to 11.7% when taking a prolonged form of metformin when transferring patients to this form [69, 70].

An additional advantage of the drug Glucofage Long is the possibility of taking it once a day in the presence of two doses - 500 mg and 750 mg in one capsule, which allows for gradual titration of the drug to achieve the optimal daily dose [71].

CONCLUSION.

We note that, despite the exclusion of MS from the ICD-10 as a condition that does not meet the definition of the concept of "disease", this concept still causes great scientific interest. The early detection of metabolic risk predictors is of great clinical importance in order to start the timely prevention of CVD and

type 2 diabetes, the main causes of death among the world's population.

REFERENCES

1. O'Neill S, O'Driscoll L. Metabolic syndrome: a closer look at the growing epidemic and its associated pathologies. *Obes Rev* 2015; 16: 1-12.
2. Uzokov J. Optimization antihypertensive therapy in patients with metabolic syndrome // *European journal of cardiovascular nursing*. – 1 Oliver's yard, 55 city road, london ec1y 1sp, england : sage publications ltd, 2015. – T. 14. – C. S106-S107.
3. Alyavi A. L., Alyavi B. A., Uzokov J. K. Metabolic syndrome is associated with obstructive sleep apnea syndrome // *European journal of cardiovascular nursing*. – 1 olivers yard, 55 city road, london ec1y 1sp, england : sage publications LTD, 2017. – T. 16. – C. S48-S48.
4. Uzokov J. Optimization antihypertensive therapy in patients with metabolic syndrome // *European journal of cardiovascular nursing*. – 1 Oliver's yard, 55 city road, london ec1y 1sp, england : sage publications ltd, 2015. – T. 14. – C. S106-S107.
5. Kaur J. A comprehensive review on metabolic syndrome. *Cardiol Res Pract* 2014; 2014: 943162.
6. Uzokov J., Alyavi A., Alyavi B. Influence of combination therapy of rosuvastatin and telmisartan on vascular and metabolic profile in hypercholesterolemic patients with metabolic syndrome // *Atherosclerosis*. – 2017. – T. 263. – C. e241.
7. Alyavi A. L. et al. Features of Inflammatory Markers in Patients With Coronary Heart Disease // *International Journal of Healthcare and Medical Sciences*. – 2018. – T. 4. – №. 10. – C. 188-192.
8. Beltrán-Sánchez H, Harhay MO, Harhay MM, McElligott S. Prevalence and trends of metabolic syndrome in the adult U.S. population, 1999-2010. *J Am Coll Cardiol* 2013; 62: 697-703.
9. Babaev M. et al. P2533 Influence of l-arginine aspartate on vascular markers in hypertensive patients with metabolic syndrome // *European Heart Journal*. – 2018. – T. 39. – №. suppl_1. – C. ehy565. P2533.
10. Uzokov, Jamol. "Influence of abnormal lipid components in statin-naive young adults: Is there any gap?." (2019): 2047487319894693.
11. Alyavi A., Alyavi B., Uzokov J. Efficiency and safety of rosuvastatin in patients with metabolic syndrome // *Atherosclerosis*. – 2017. – T. 263. – C. e245.
12. Абдуллаев А. Х. и др. Оценка эффективности колмстрес у больных коронарной болезнью сердца // *Кардиоваскулярная терапия и профилактика*. – 2019. – T. 18. – №. S1. – C. 5-6.
13. Lutfullayevich A. A. et al. GW28-e0698 Telmisartan with amlodipine versus lisinopril with amlodipine on home blood pressure variability in patients with metabolic syndrome // *Journal of the American College of Cardiology*. – 2017. – T. 70. – №. 16 Supplement. – C. C138.
14. Saydaliyev R. S. i dr. β -adrenoblokatory i ostyrovyy infarkt miyokardda // *Vestnik eksternoy meditsiny*. – 2015. – №. 2.
15. Usarov M. et al. Ps 11-56 Efficacy Of Combination Therapy Using Nebivolol And Trimetazidine In Hypertensive Patients With Metabolic Syndrome And Stable Angina // *Journal of Hypertension*. – 2016. – T. 34. – C. e349.
16. Alyavi A., Uzokov J. Treatment of stable angina pectoris: focus on the role of calcium antagonists and ACE inhibitors // *Ont Health Technol Assess Ser*. – 2017. – T. 15. – №. 9. – C. 1-12.
17. Aydin S, Aksoy A, Aydin S, Kalayci M, Yilmaz M, Kuloglu T, et al. Today's and yesterday's of pathophysiology: biochemistry of metabolic syndrome and animal models. *Nutrition* 2014; 30: 1-9.
18. Larqué C, Velasco M, Navarro-Tableros V, Duhne M, Aguirre J, Gutiérrez-Reyes G, et al. Early endocrine and molecular changes in metabolic syndrome models. *IUBMB Life* 2011; 63: 831-9.
19. Alyavi A.L., Alyavi B.A., Abdullaev A.X., Tulyaganova D.K., Uzokov J.K., Radjabova D.I., Shodiev J.D., Nuritdinova S.K., and Yunusova L.I., –Interleukins in coronary heart disease, // *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 1, Issue 5, pp. 38-42, 2018.
20. Radjabova DI, et al. The Features of Cytokine Status in Patients with Coronary Heart Disease. *Hypertension & Vasc Biol Int J* 2018, 1(1): 000101.
21. Mamatkulov, X. A., Usarov, M. X., Uzokov, J. K., va Arzieva, Yu. B. Vliynie interventsion revaskulyarizatsii miokardada u bolnyx ostym in-farktom miokardada bez zubtsa «q». O 'zbekiston terapiya axborotnomasi, 18.
22. Baxrom Alyavi, Jamol Uzokov. Peripheral artery disease in the lower extremities: indications for treatment // *E-Journal of Cardiology Practice*. Vol. 16, № 9 - 02 May 2018. <https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-16/Peripheral-artery-disease-in-the-lower-extremities-indications-for-treatment>
23. Lyutfullayevich A. A. et al. Relationship between hemodynamic parameters and NPPA, NPPB, NPR3 genes polymorphism in patients with ischemic heart disease // *International scientific review*. – 2017. – №. 7 (38).
24. Park J. B. The Pulse of Asia 2016 Seoul, September 24-26, 2016, Seoul, Republic of Korea: Abstracts // *Pulse*. – 2016. – T. 4. – №. 2-3. – C. 93.
25. Iskhakov S., Uzokov J., Kamilova S. Comparative Analysis Of The Inflammatory Biomarkers In Patients With Stable Coronary Artery Disease And Metabolic Syndrome // *Atherosclerosis*. – 2019. – T. 287. – C. e171.
26. Zhang P, Tian B. Metabolic syndrome: an important risk factor for Parkinson's disease. *Oxid Med Cell Longev* 2014; 2014: 729194.
27. Mukhamedova M. et al. P120 Relationship between left ventricular global function index and cardiac systolic functions in patients with chronic ischemic disease of the heart and diabetes mellitus // *European Heart Journal-Cardiovascular Imaging*. – 2019. – T. 20. – №. Supplement_3. – C. jez147. 008.
28. Ahmedov I. et al. Features of hyperreninemic aldosteronism in hypertension patients with metabolic syndrome: 87 // *European Journal of Preventive Cardiology*. – 2016. – T. 23. – №. 1.
29. Habib G. et al. The ESC-EORP EURO-ENDO (European Infective Endocarditis) registry // *European Heart Journal-Quality of Care and Clinical Outcomes*. – 2019. – T. 5. – №. 3. – C. 202-207.
30. Alyavi B., Alyavi A., Uzokov J. Role of pro-inflammatory cytokines in metabolic syndrome // *ALLERGY*. – 111 RIVER ST, HOBOKEN 07030-5774, NJ USA : WILEY, 2018. – T. 73. – C. 562-562.
31. Lutfullayevich A. A. et al. GW28-e0698 Telmisartan with amlodipine versus lisinopril with amlodipine on home blood pressure variability in patients with metabolic syndrome // *Journal of the American College of Cardiology*. – 2017. – T. 70. – №. 16 Supplement. – C. C138.
32. Usarov M. et al. Ps 11-56 Efficacy Of Combination Therapy Using Nebivolol And Trimetazidine In Hypertensive Patients With Metabolic Syndrome And Stable Angina // *Journal of Hypertension*. – 2016. – T. 34. – C. e349.
33. Alyavi A. et al. GW29-e0869 Features Of Cytokine Status In Patients With Coronary Heart Disease. – 2018.
34. Lutfullayevich A. A. et al. GW28-e0699 Cardiovascular risk stratification and gender differences in hypertensive patients with metabolic syndrome // *Journal of the American College of Cardiology*. – 2017. – T. 70. – №. 16 Supplement. – C. C138-C139.
35. Larue C, Le Magnen J. Effect of the removal of olfactory bulbs upon hyperphagia and obesity induced in rats by V.M.H. lesion. *Physiol Behav* 1970; 5: 509-13.
36. Uzokov J., Alyavi B. Combination lipid lowering therapy with rosuvastatin and ezetimibe in dyslipidemic patients with stable coronary artery disease and metabolic syndrome // *Atherosclerosis*. – 2018. – T. 275. – C. e231.

37. Alyavi B. et al. GW29-e0942 Contrast induced nephropathy in coronary patients. – 2018.
38. Uzokov, J., Alyavi, A., Karimov, B., Ahmedov, I., Rakhmonkulov, E., Sultanova, G., & Vakhidova, I. (2016). Comparison of perindopril-amlodipine and losartan-amlodipine combinations in the management of hypertension in patients with metabolic syndrome: P1635. *European Journal of Heart Failure*, 18, 384-385.
39. Xu J, Koni PA, Wang P, Li G, Kaczmarek LK, Wu Y, et al. The voltage-gated potassium channel Kv1.3 regulates energy homeostasis and body weight. *Hum Mol Genet* 2003; 12: 551-9.
40. Uzokov, Jamol, Anis Alyavi, and Bekzod Karimov. "Prevalence of metabolic syndrome in patients with chronic obstructive pulmonary disease." (2016): PA3776.
41. Alyavi A., Uzokov J. Depressive impairments in patients with metabolic syndrome // *clinical cardiology*. – 111 river st, hoboken 07030-5774, nj usa : wiley-blackwell, 2016. – T. 39. – C. 14-14.
42. Uzokov J. et al. Ps 14-47 Combined Antihypertensive Therapy With Angiotensin Ii Receptor Antagonist And Calcium Channel Blocker In Patients With Metabolic Syndrome // *Journal of Hypertension*. – 2016. – T. 34. – C. e447.
43. Alyavi A., Alyavi B., Uzokov J. Efficiency and safety of rosuvastatin in patients with metabolic syndrome // *Atherosclerosis*. – 2017. – T. 263. – C. e245.
44. Cook KK, Fadool DA. Two adaptor proteins differentially modulate the phosphorylation and biophysics of Kv1.3 ion channel by SRC kinase. *J Biol Chem* 2002; 277: 13268-80.
45. Uzokov J. et al. Ps 14-54 Efficacy And Safety Of Combined Antihypertensive Therapy With Lisinopril And Moxonidine In Patients With Metabolic Syndrome // *Journal of Hypertension*. – 2016. – T. 34. – C. e448-e449.
46. Alyavi A. L. et al. Predictors of contrast induced nephropathy in patients with metabolic syndrome // *European heart journal*. – Great clarendon st, oxford ox2 6dp, england : oxford univ press, 2017. – T. 38. – C. 1283-1283.
47. Alyavi B., Uzokov J., Payziev D. TCTAP A-081 Influence of Low Glycemic Diet on Lipid Profile in Patients with Ischemic Disease of the Heart After Percutaneous Intervention // *Journal of the American College of Cardiology*. – 2018. – T. 71. – №. 16 Supplement. – C. S45.
48. Uzokov J. et al. Influence of metabolic syndrome on renal function in patients with hypertension // *Journal of Hypertension*. – 2018. – T. 36. – C. e84.
49. Zaghoul H, Pallayova M, Al-Nuaimi O, Hovis KR, Taheri S. Association between diabetes mellitus and olfactory dysfunction: current perspectives and future directions. *Diabet Med* 2018; 35: 41-52.
50. Uzokov J., Alyavi A., Alyavi B. TCTAP A-158 Short Term Outcomes After Coronary Artery Stenting in Patients with Metabolic Syndrome // *Journal of the American College of Cardiology*. – 2017. – T. 69. – №. 16 Supplement. – C. S84.
51. Абдуллаев А. Х. и др. Некоторые подходы к повышению эффективности лечения ишемической болезни сердца // VI Евразийский конгресс кардиологов. – 2018. – С. 75-76.
52. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications: part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998;15:539-53.
53. Alyavi B., Uzokov J. TCTAP C-156 Successful Percutaneous Coronary Intervention of a Left Circumflex Artery Departing from the Right Coronary Sinus // *Journal of the American College of Cardiology*. – 2018. – T. 71. – №. 16 Supplement. – C. S225-S226.
54. Jung JG, Kim JS, Yoon SJ, Oh MK. Relationships among alcohol consumption, facial flushing response, and metabolic syndrome in healthy men. *Ann Epidemiol* 2012;22:480-6.
55. Oh EC, Vasanth S, Katsanis N. Metabolic regulation and energy homeostasis through the primary cilium. *Cell Metab* 2015; 21: 21-31.
56. Alyavi A. et al. Influence of Diet with Low Glycemic Index on Lipid Spectrum in Patients with Ischemic Disease of the Heart // *Atherosclerosis Supplements*. – 2018. – T. 32. – C. 158.
57. Radjabova, D. I., Alyavi, A. L., Alyavi, B. A., Tulyaganova, D. K., Uzokov, J. K., Shodiev, J. D., ... & Nuritdinova, S. K. The Features of Cytokine Status in Patients with Coronary Heart. 2018.
58. Rees DA, Alcolado JC. Animal models of diabetes mellitus. *Diabet Med* 2005; 22: 359-70.
59. Uzokov J. et al. PS 14-53 Comparison of two combined antihypertensive therapy in hypertensive patients with metabolic syndrome // *Journal of Hypertension*. – 2016. – T. 34. – C. e448.
60. Baik I, Shin C. Prospective study of alcohol consumption and metabolic syndrome. *Am J Clin Nutr* 2008;87:1455-63.
61. JU Anis Alyavi, Baxrom Alyavi. Antihypertensive therapy using two free dosed combination of drugs with calcium channel blocker and angiotensin receptor blocker in patients with metabolic syndrome // 2nd Prague European Days of Internal Medicine. 2016/12.
62. Alyavi, A. L., Alyavi, B. A., Uzokov, J. K., Payziev, J. J., Ishakov, S. A., & Azizov, S. I. (2017). P6088 Predictors of contrast induced nephropathy in patients with metabolic syndrome. *European Heart Journal*, 38(suppl_1).
63. Patel ZM, Del Gaudio JM, Wise SK. Higher body mass index is associated with subjective olfactory dysfunction. *Behav Neurol* 2015; 2015: 675635.
64. Alyavi B., Uzokov J. TCTAP C-078 Left Main Coronary Artery Departs from the Right Sinus of the Ascending Aorta // *Journal of the American College of Cardiology*. – 2017. – T. 69. – №. 16 Supplement. – C. S168.
65. Crabb DW. Ethanol oxidizing enzymes: roles in alcohol metabolism and alcoholic liver disease. *Prog Liver Dis* 1995;13:151-72.
66. Uzokov j. K., Alyavi b. A., Abdullaev a. X. Assessment of the clopidogrel action with regard to cyp2c19 gene polymorphisms in patients with coronary artery disease after implantation of des stents // Евразийский кардиологический журнал. – 2019. – №. S2. – С. 309-309.
67. Kim MY, Kim SS, Kim JS, Jung JG, Kwon BR, Ryou YI. Relationship between alcohol consumption and metabolic syndrome according to facial flushing in Korean males. *Korean J Fam Med* 2012;33:211-8.
68. Alyavi A. L., Uzokov J. K. Optimization antihypertensive therapy in patients with metabolic syndrome using two free dosed combinations of drugs // Противоречия современной кардиологии: спорные и нерешенные вопросы. – 2016. – С. 45-46.
69. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005;112:2735-52.
70. Jamol U., Aniskhon A. GW27-e0518 Effects of telmisartan/amlodipine combination compared to single monotherapies in hypertensive patients with metabolic syndrome // *Journal of the American College of Cardiology*. – 2016. – T. 68. – №. 16 Supplement. – C. C137.
71. Simchen U, Koebnick C, Hoyer S, Issanchou S, Zunft HJ. Odour and taste sensitivity is associated with body weight and extent of misreporting of body weight. *Eur J Clin Nutr* 2006; 60: 698-705.