Pharmacological Treatment Strategies In Metabolic Syndrome

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***Abstract*— Metabolic syndrome (MS) is considered the risk for the development of the cardiovascular disease (CVD) and type II diabetes mellitus (T2DM) and consisted of several components such as abdominal obesity, hypertension, dyslipidemia, impairment of the glucose tolerance and insulin resistance. This article summarizes the treatment strategies of the metabolic syndrome from the lifestyle modification to the medication therapy. Early detection and start of the interventions will allow reduction of the development of the T2DM and CVD.**

Keywords—metabolic syndrome; abdominal obesity; insulin resistance; dyslipidemia; hypertension;

I. INTRODUCTION

The term “metabolic syndrome” (MS) refers to a combination of glucose impairments, dyslipidemia, high blood pressure and obesity [1]. To date, there is no single treatment strategy for the treatment of the metabolic syndrome. Patients who have a large variety of unmodifiable risk factors (gender, heredity, age, ethnicity) in combination with modifiable factors (overweight or abdominal obesity, 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 for its individual components [2]. In this regard, the use of the concept of MS, according to WHO experts, is limited as a diagnostic and therapeutic tool. The main therapeutic measures in MS include lifestyle changes, as the main method of correcting metabolic risk factors, and drug treatment of combined MS components.

LIFESTYLE MODIFICATION - THE BASIS OF TREATMENT OF PATIENTS WITH MS.

Despite the fact that views on the beginning and tactics of drug therapy may differ, most researchers are unanimous that the basis of successful treatment and therapy of the first choice is a lifestyle change. First of all, we are talking about the reduction of body weight against the background of a low-calorie diet and an adequate mode of physical activity, since approximately 85% of all patients with MS are overweight. In addition, it is important to reduce alcohol consumption, stop smoking, reduce food intake with a high content of saturated fatty acids, and include foods rich in unsaturated fatty acids and fish oil in the diet. The increase in physical activity has a positive effect on all parameters of MS [3]. The effect is achieved by increasing energy consumption and the associated weight loss. Physical training also leads to an increase in insulin sensitivity, even without a decrease in body weight [4]. The high efficacy of non-pharmacological interventions is beyond doubt and has been proven by the results of a number of randomized clinical trials. The average life expectancy of full people is 8-10 years less than in the population as a whole, and over 2.5 million people die every year from diseases associated with obesity [5]. A decrease in body weight of 9–10 kg contributes to an increase in the life expectancy of patients: a reduction in total mortality by 25%, mortality from cancer by 30–40%, and from type 2 diabetes - by 30–40% [6]. The above data demonstrate that in case of successful implementation of the task of reducing body weight, a constant non-drug therapeutic effect on the whole complex of pathogenetic disorders in patients with MS is carried out. For many people, lifestyle modification activities cannot completely correct the existing disorders, and the severity of risk factors increases with age, so the need for drug therapy increases. Today there are no drugs that can significantly reduce all metabolic risk factors for a long time. For this reason, drug treatment may include the correction of each risk factor separately, for example, a combination of lipid-lowering drugs, antihypertensive drugs and hypoglycemic therapy. Unfortunately, as the disease progresses, a single drug is no longer effective in controlling the corresponding risk factor, so several medications are required. The problem is compounded when a multitude of drugs are required to control several risk factors. For example, when a patient develops type 2 diabetes against MS, 10 or more medications are often required, most of which are aimed at correcting risk factors, but others may be required to treat complications, aggravating the problem of polyphragmas [7]. All this indicates the relevance of a comprehensive study of MS and the search for the most rational, patient-friendly and highly effective methods of pharmacotherapy.

PHARMACOTHERAPY OF OBESITY IN PATIENTS WITH MS

The prescription of drug therapy for abdominal obesity can be thought of if the lifestyle change did not reduce body weight by 5% within three to six months. In addition, drug therapy is indicated if the patient has obesity (body mass index (BMI)> 30 kg / m², or if there are other, in addition to increased body weight (BMI> 27 kg / m²), components of MS. Currently, for the treatment of obesity and overweight recommended the

appointment of two drugs: orlistat and sibutramine. But both drugs are effective only in combination with lifestyle changes. This therapy, together with a change in lifestyle, leads to a decrease in body weight of approximately 10 kg. In addition to having a positive effect on the risk factors for CVD development during pharmacotherapy, it is possible to improve the quality of life of patients [8]. Orlistat is a specific, long-acting inhibitor of gastrointestinal lipases. The drug covalently binds to the active center of the enzyme, inactivating it. This prevents the splitting and subsequent absorption of about 30% of the fat from food, thereby creating an energy deficit, which contributes to a decrease in body weight. At the same time, orlistat reduces the amount of free fatty acids and monoglycerides in the intestinal lumen, which reduces the solubility and subsequent absorption of cholesterol, helping to reduce hypercholesterolemia. The study XENDOS (XENical in the Prevention of Diabetes in Obese Subjects) included 3305 patients aged 30 to 60 years with obesity, with normal (79%) or impaired (21%) glucose tolerance, 40% of whom had MS . It was shown that in the active treatment group, the combination of orlistat with a change in lifestyle significantly reduced the incidence of type 2 diabetes for 4 years and allowed for a more pronounced decrease in body weight compared with the control group. In addition, there was an improvement in lipid metabolism and blood pressure and a more stable retention of the achieved results than in the control group. With orlistat, a decrease in body weight of more than 5% from baseline was observed in 69.6% of patients, over 10% in 42.1%, while in the placebo group, in 51.9% and 22.7% patients respectively. More intensive weight loss during treatment with orlistat was accompanied by a decrease in CVD risk factors such as hyperinsulinemia, hypercholesterolemia, as well as a decrease in the mass of visceral adipose tissue.

PHARMACOTHERAPY OF DYSLIPIDEMIA AND NON-ALCOHOLIC FATTY LIVER DISEASE

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 occurs in two forms, or successive stages: liver steatosis and nonalcoholic steatohepatitis (NASH). According to uzbek authors, in patients with MS and abdominal obesity, NAFLD occurs in 100% of cases, and NASH in 51% [9]. It has been proven that the leading mechanisms for the development of this disease are the pathological activation of lipolysis processes with the release of large amounts of free fatty acids in people with abdominal obesity, concomitant IL and oxidative stress, which provokes an inflammatory reaction in hepatocytes and leads to the formation of steatohepatitis. In those cases where the hypocaloric and hypocholesterol diet and changes in physical activity do not allow for adjusting the lipid profile and the activity of liver enzymes, it is necessary to consider the possibility of using drug therapy [10]. The main drugs for the treatment of atherogenic dyslipidemia are hydroxymethylglutaryl CoA reductase inhibitors (HMG CoA reductase inhibitors) (statins) and fibroic acid derivatives (fibrates). Statins are the first line of hypolipidemic therapy due to their proven efficacy in reducing LDL and due to a significant reduction in the outcome of cardiovascular outcomes, including cardiovascular mortality and all-cause mortality in most patients [10,11]. According to independent research meta-analysis (4S, HPS, ASCOT-LLA, CARDS, 4D), published in 2005, the reduction in the risk of CHD while taking statins averaged 23% (from 11 to 51%). The main mechanism of the effective effect of statins on dyslipidemia and NAFLD is the blockade of the isoprenoid pathway, which leads to the suppression of the synthesis of total cholesterol, LDL and triglycerides against the background of increased HDL production [12]. In addition to the direct effect on lipogenesis, the drugs have an antioxidant effect, reduce angiogenesis by affecting ED, have antitumor activity, including the ability to prevent the development of hepatocellular cancer [13]. It is important to note that the conducted meta-analysis, which included 13 studies involving 91,140 patients showed a slight increase in the risk of developing type 2 diabetes (by 9%) among patients taking statin drugs compared to placebo. Another meta-analysis of 5 studies on the comparison of high-dose and standard statin therapy, including 32,753 patients, showed an increase in the risk of type 2 diabetes by 12% over the observation period of 2–5 years. However, when recalculating the risk of type 2 diabetes for 10 years in the first case, the additional risk of type 2 diabetes is 1%, in the second - 2%, which is incomparable with those benefits for treatment of CVD, which are proven during the treatment with statins. Fibrates reduce triglycerides from 20% to 50%, increase HDL levels from 1% to 34%, and can reduce LDL levels by up to 20%.

PHARMACOTHERAPY OF ARTERIAL HYPERTENSION

Frequent development of arterial hypertension in MS is caused by a whole complex of the previously described pathogenetic mechanisms of syndrome development, against the background of the polygenic nature of inheritance of associated diseases - obesity, type 2 diabetes and dyslipidemia, as well as hyperactivation of the renin-angiotensin-aldosterone system [14]. Antihypertensive therapy for MS should be carried out to achieve the target level of blood pressure less than 130 and 80 mm Hg. Art., especially in the presence of type 2 diabetes. Numerous studies using a wide range of antihypertensive drugs have proven that effective control of blood pressure significantly reduces the risk of CVD and mortality. Moreover, strict control of blood pressure in patients with type 2 diabetes leads to a more significant reduction in the frequency of macrovascular complications of diabetes than the achievement of the target glycemic level [15]. The general principles of drug treatment of hypertension are: constant, long-

term therapy, the start of treatment from the minimum dose of one drug, the transition to drugs of another class with insufficient treatment effect (maximum dosage) or poor portability, the use of drugs mainly long-acting, the use of optimal combinations of drugs for achievement of the maximum hypotensive effect and minimization of side effects [17]. According to the latest domestic and international recommendations, first-line drugs for treating arterial hypertension in patients with MS are angiotensin-converting enzyme inhibitors, type I angiotensin receptor blockers and calcium antagonists [18].

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 debut - it starts with mild or moderate carbohydrate metabolic disturbances caused by IR and functional hyperinsulinemia, which over time causes beta cell dysfunction and insulin production, which leads to prediabetes [19]. Then, in a much shorter period, manifestation of type 2 diabetes occurs. In 2007, ADA and IDF experts accepted the Consensus Consensus on the treatment of prediabetes in people with impaired glucose tolerance and / or impaired fasting glucose, which, along with lifestyle changes, showed metformin therapy [20]. The adoption of these recommendations was based on the results of a prospective randomized clinical trial (DPP (Diabetes Prevention Program)), in which evidence was obtained that over the 3.2-year observation period, lifestyle changes and treatment with metformin (the original drug Metformin Glucophage® was used) was 58% and 31%, respectively, reduced the risk of developing type 2 diabetes in patients with pre-diabetes compared with the control group of patients [21]. This trend continued also in the subsequent observation period - for 10 years (34% and 18%, respectively) [22]. The greatest positive effect on the prevention of the development of type 2 diabetes was noted in young patients with more pronounced disorders of carbohydrate metabolism and obesity. The consensus calls for early diagnosis and prophylactic treatment of pre-diabetes with metformin in combination with lifestyle changes in people at high risk of developing type 2 diabetes. These should include persons with impaired glucose tolerance and impaired fasting glucose in combination with another additional risk factor (age <60 years or BMI ≥ 35 kg / m2, in the presence of diabetes in first-degree relatives, with an increased level of triglycerides, low HDL, hypertension or HbAlc level ≥ 6%). In addition to the above recommendations of the joint consensus of the ADA and the IDF, the American Society of Endocrinology (American College of Endocrinology - ACE) in its document recommends early diagnosis of carbohydrate metabolism disorders and lifestyle modification, along with the simultaneous identification of associated risk factors such as arterial hypertension, obesity and dyslipidemia [30]. Experts recommend prescribing acarbose and metformin for people with a high risk of developing type 2 diabetes who have impaired fasting glucose, impaired glucose tolerance and / or MS, increased blood glucose levels, CVD, and a history of NAFLD or polycystic ovary syndrome. Metformin is an antihyperglycemic drug from the biguanide group that does not have a hypoglycemic effect, and is used to treat type 2 diabetes since 1953 [22]. The drug improves the sensitivity of fat and muscle tissue to insulin, reduces the production of glucose by the liver by affecting gluconeogenesis, reduces glycogenolysis, inhibits glucose absorption in the intestine, has an anorexigenic effect, which helps many patients to comply with recommendations for low-calorie nutrition [22]. Numerous experimental and clinical studies have shown that metformin has a beneficial effect on lipid metabolism (by reducing the concentration of free fatty acids, LDL, very low density lipoproteins and increasing HDL) and hemostasis (reducing levels of plasminogen activator inhibitor and Willebrand factor, increased tissue plasminogen activator, reduced platelet aggregation and adhesion, improved vascular relaxation and increased capillary blood flow) [23]. Today, metformin is the only oral glucose-lowering drug that has a proven effect on reducing the frequency of cardiovascular complications of type 2 diabetes. Thus, in the study UKPDS 34 (the original drug Metformin Glucophage® was used) in patients with type 2 diabetes and obesity, a decrease in total mortality was shown by 36%; mortality associated with diabetes, myocardial infarction and stroke — by 42, 39 and 41%, respectively, compared with patients treated with insulin or sulfonylurea drugs. One of the barriers in prescribing metformin to correct IR in individuals with MS who are at risk of developing type 2 diabetes is the relatively high incidence of side effects from the gastrointestinal tract [24]. Thus, according to different sources, the incidence of various dyspeptic phenomena in patients receiving metformin of the usual duration reaches 20–25%, and 5–10% of patients are forced to cancel taking the drug. Reducing the frequency of side effects is achieved by gradual titration of the drug to the optimally tolerated daily dose and taking the drug during or after meals. In addition to the occurrence of side effects, another barrier to achieving positive clinical results of treatment is the need for a large number of drugs to be taken by a patient with MS, which leads to a decrease in patient's adherence to treatment [25,26]. According to WHO, non-compliance with medical recommendations by patients suffering from chronic diseases is a global medical problem that leads to a decrease in the effectiveness of treatment and serious economic consequences (loss of time, money, aggravation of the disease). This patented technology is a two-phase system - a double hydrophilic polymer matrix (GelShield Diffusion System), due to which a gradual release of metformin granules occurs. In studies on bioequivalence, it was shown that the efficacy and safety profile of a drug can extend to an innovative form of metformin sustained release [27]. In addition, in a retrospective study revealed a significant decrease

in the incidence of diarrhea from 18.05% on fast-release metformin to 8.29% on prolonged-release metformin. The incidence of any adverse events was 26.34% among patients on fast-release metformin and decreased to 11.7% while receiving a prolonged form of metformin when transferring patients to this form [28]. In conclusion, we note that, early detection of predictors of metabolic risk is of critical clinical importance in order to start timely the prevention of the development of CVD and type 2 diabetes - the main causes of death among the world's population. In our country, it is necessary to actively develop effective prevention strategies based on available resources that will complement preventive strategies, focusing on controlling and reducing metabolic and behavioral factors by acting on key determinants.

[2].ACKNOWLEDGMENT

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