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MUTUAL INFLUENCE OF HEART FAILURE ON THE COURSE OF TYPE 2 DIABETES MELLITUS

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Abstract: Chronic heart failure (CHF) is one of the most significant medical and social pathologies characterized by a high prevalence and mortality. According to experts, CHF in Western countries occurs in 1-2% of the general population, reaching 10% in people over 70 years of age. In the Russian Federation, CHF is diagnosed in 7-10% of cases, while more than 65% of Russian patients are people over 60 years old. In the structure of mortality from diseases of the circulatory system, CHF occupies one of the leading positions 19, 13, 15, 16].Among the reasons leading to the development of CHF, arterial is traditionally considered - hypertension (AH) and coronary heart disease (CHD), which occupy the largest share in the structure of nosologies that cause the formation of heart failure (95.5% and 69.7%, respectively). The classical causes of CHF (heart defects, cardiomyopathies, myocarditis, etc.) are less common. At the same time, one of the frequent and significant diseases characterized by the early development of heart failure is type 2 diabetes mellitus (DM), which has been shown in a number of studies. In the Russian Federation, DM ranks third (15.9%) among the causes of CHF [9, 13, 14]. In addition, the occurrence and progression of heart failure in patients with DM is one of the main causes of death in this cohort of patients.

Key words: diabetes mellitus, pharmacotherapy, ischemic cardiomyopathy, hypoglycemia, multidisciplinary approach.

Pathogenetic relationships between CHF and type 2 diabetes

The above relationships between CHF and DM, in terms of increasing severity and accelerating the progression of pathological manifestations, are explained by pathophysiological relationships that have recently been intensively studied, supplemented by new facts and theories. Previously The negative impact. Of DM on the development of CHF was considered from the standpoint of the atherosclerotic concept, according to which heart failure develops as a result of a multifactorial pathological process associated with changes in lipid metabolism, hyperglycemia, insulin resistance, hypertension, which create conditions for the formation of coronary artery disease, and later CHF. An undoubted contribution to the formation of CHF Is made by developing diabetic cardiomyopathy. In recent years, the above concept has been supplemented by a cardioreno-metabolic approach that considers the pathogenetic links between DM and CHF from the point of view of mechanisms not related to the atherosclerotic process. These include: impaired renal function, systemic inflammation, endothelial dysfunction, activation of the sympathetic nervous system, renin-angiotensin-aldosterone system, etc.. leading to an increase in myocardial stiffness, its hypertrophy, interstitial fibrosis, and ultimately to heart failure [4]. The variety of pathogenetic bases for the development of CHF in patients with DM determines the importance of adequate and justified, from the standpoint of evidence-based medicine, pharmacotherapy. The latter should be considered differentiated depending on the form of heart failure, namely the presence of systolic or diastolic dysfunction of the left ventricle (LV), which are characterized by reduced or preserved (respectively) ejection fraction (EF). In patients with DM, the development of the diastolic form of CHF Predominates [4, 23).

Influence of type 2 diabetes on prognosis in CHF

DM 2 has a significant adverse effect on the prognosis in individuals with various types of CHF. According to major meta-analyses, it is considered in CHF with low LV ejection fraction (EF) as a significant independent risk factor for death. Among in persons with CHF with low LV EF and DM 2, the risk of decompensated heart failure (HF) is approximately 2 times higher than in patients with CHF without diabetes. Individuals with a combination of these two conditions also show a higher rate of repeated admissions to the hospital for CHF, and a lower quality life. SD 2 negatively also affects course of CHF with preserved LV EF, increasing risk development decompensation and mortality. Randomized controlled trials (RCTs) CHARM I and I-PRESERVE [9, 10] have shown that these adverse effects of DM 2 in this variant of CHF may be even more pronounced than in individuals with CHF with low LV EF.

Pathophysiological aspects of the development of CHF in patients with type 2 diabetes

In the development of CHF in type 2 diabetes, a key stimulating role is assigned to the changes inherent in diabetes, including insulin resistance, hyperinsulinemia, hyperglycemia, and accumulation of glycosylation end products (AGES) - advanced glycation end - products - AGES [2, 11]. The impact of these factors determines the formation of three main pathophysiological mechanisms: (1) accelerated atherosclerotic lesions of the coronary arteries (due to increased proliferation of smooth muscle cells of the vascular wall, stimulation of inflammation processes, thrombosis, endothelial dysfunction, creation of a highly atherogenic variant of dyslipidemia) with an increased risk of myocardial ischemia (due to increased vulnerability of atherosclerotic plaques), development of a heart attack, post- infarction LV remodeling followed by a cascade of disorders leading to systolic and diastolic LV dysfunction (the complex of these disorders is the so-called "ischemic cardiomyopathy"); (2) an increased predisposition to the development of LV hypertrophy and increased fibrosis of its myocardium, which leads to an increase in myocardial stiffness, impaired relaxation processes and an increase in LV diastolic disorders; in the development of LV diastolic dysfunction, an important role is played by disturbances in calcium homeostasis and dysfunction of the sarcoplasmic reticulum inside myocardiocytes (MCC), as well as activation under the action of hyperglycemia of the local renin- angiotensin-aldosterone system (RAAS) with hyperproduction angiotensin II and aldosterone, which in turn further stimulates the development of myocardial hypertrophy and fibrosis; (3) creation of conditions for an imbalance in the energy balance of the MCC due to defects in the utilization of glucose and free fatty acids, with the accumulation of lipids in the MCC, the formation of lipotoxicity, increased apoptosis of the MCC and, ultimately, the development of impaired LV systolic function. Among the important factors contributing to the formation of LV systolic disorders in DM 2 are also an increase in the formation of active oxygen radicals in the mitochondria of the MCC (mitochondrial dysfunction), a violation of the intracellular calcium balance, an increase in the processes of inflammation and apoptosis of the MCC. Note that the complex of changes listed above in paragraphs 2 and 3 constitutes the processes united by the general term " diabetic cardiomyopathy." This designation was proposed back in 1972 [12]; it now means the presence in a patient with type 2 diabetes diastolic and/or systolic LV dysfunction in the absence of other than diabetes, clear reasons for the development of these disorders, including coronary heart disease, arterial hypertension and valvular defects. The terms "ischemic cardiomyopathy" and "diabetic cardiomyopathy" in the literature are more often used as pathophysiological rather than clinical concepts; they are recognized as useful for a clearer understanding of the mechanisms of CHF development in type 2 diabetes [13]. It is quite clear that in practice it is difficult to distinguish between them; in each individual patient with DM 2 and CHF, they are more likely to coexist, while the relative importance of each of them varies widely.

Target levels of glycemia in people with DM 2 and CHF

The question of the optimal levels of HbAIC in individuals both with DM 2 in general and when it is combined with CHF continues to be discussed. Although a more intense decrease in glycemia with the achievement of relatively low (6.5-7.0%) levels of HhAIC is associated with a decrease in the risk of microvascular complications of type 2 diabetes (retinopathy. nephropathy, peripheral neuropathy), and possibly the risk of developing myocardial infarction, there is no decrease in the overall mortality. cardiovascular mortality and the frequency of cerebral strokes while maintaining the indicated values of HbA1C. The largest RCTS UKPDS, ADVANCE, ACCORD, VADT [14] showed no significant differences in the incidence of cardiovascular complications, including those associated with CHF, between groups. with more intensive glycemic control (mean HbA1C values 6.4-7.0%) and its less intensive control (HbA1C levels 7.3-8.4%). Epidemiological studies and registries also indicate that the relationship between HbAIC levels and mortality in individuals with type 2 diabetes and CHF is U-shaped, with the lowest mortality rates correspond to HbA1C values in the range of 7.0-8.0%. These data are reflected in the modern recommendations of the world's leading endocrinological and cardiological associations [2], which indicate that: (1) HbA1C levels of 6.5-7.0% are suitable as targets mainly for those patients with DM 2 who have a sufficiently long life expectancy and do not have significant comorbidities, complications of diabetes and severe episodes of hypoglycemia; T2DM, who have a moderate and life expectancy, with the presence of micro- and macro-vascular complications of diabetes, episodes of severe hypoglycemia, significant comorbidities; it is these HbAIC values that experts recommend using as targets for most patients with DM2 and CHF: (3) levels can be recognized as targets for a limited category of the most severe patients with DM 2 with limited life expectancy, pronounced micro and macrovascular complications of diabetes, severe concomitant diseases (final stages of renal, respiratory failure or CHF, severe dementia, uncurable oncological lesions).

The complexity of the treatment regimen

Persons with a combination of CHF and DM 2 usually require the appointment of a treatment program consisting of many components, the implementation of which in many cases is difficult for the patient. So, in order to achieve adequate glycemic control, the patient receives recommendations from the doctor, including the choice of diet, level of physical activity, control of body weight and emotional stress, monitoring the level of glycemia, taking hypoglycemic drugs; particular attention will be drawn to the need to remain committed to all these advice. In addition, the presence of CHF will entail recommendations to limit salt and fluid intake, as well as the use of several necessary drugs. The complexity of prescriptions often leads even motivated and careful patients to emphasize some of them as leaders at the expense of others (for example, carefully control glycemic levels, ignoring body weight, etc.), which reduces the effectiveness of treatment. As the severity of CHF increases, it is the approaches to its treatment that gain dominance in the eyes of the patient, and the diabetic component of the treatment regimen goes to the second plan. This requires the attending physicians to competently create an individual feasible treatment program that takes into account all the necessary priorities; constant benevolent explanation and control [1-3].

Prospects:

The problem of the combination of CHF and DM 2 is extensive and requires further study. Unresolved issues include (1) the reversibility of diabetic cardiomyopathy: (2) the optimal

HbA1C target for individuals with different stages CHF: (3) the safety of hypoglycemic agents in individuals with type 2 diabetes and high cardiovascular risk, including sulfonylurea drugs (an ongoing RCT CAROLINA [20]) and DPP-4 (RCT MEASUREHF); (4) the possibility of improving the prognosis against the background of the use of hypoglycemic drugs in CHF with low and intact LV EF (RCT EMPEROR, DAPA HF, SOLOIST WHF); (5) the choice of hypoglycemic agents for individuals with CHF and severe DNP (RCT DAPA-CKD, EMPA-KIDNEY]); (6) choice of preferred B-AB and AMP in CHF and T2DM; (7) features of treatment tactics for decompensated heart failure in patients with diabetes. Since both CHF and DM 2 are chronic progressive diseases, their optimal control requires the combined efforts of not only doctors of various specialties (a multidisciplinary approach - endocrinologists, cardiologists, nephrologists, etc.), but also, which is especially important, of the patients and their family members (which is referred to as an integrative approach).

Conclusion: At the present stage of development of diabetology, the priorities in planning and conducting large- scale randomized trials have changed. The results of historical studies of UKPDS, ACCORD, ADVANCE. VADT, etc. have shown the important role of achieving glycemic control in preventing the development and progression of chronic complications of type 2 diabetes. At the same time, hypoglycemia and weight gain, as well as complex pathophysiological mechanisms for the development and progression of DM 2, which limit the possibility of optimal long-term treatment, have led to the creation of new pathogenetic antidiabetic drugs. The question arose about the safety, and above all cardiovascular safety, of new antidiabetic drugs. The American Agency for the Safety of Medicines and Foods FDA defined requirements for pharmaceutical manufacturers, according to which an anti-diabetic drug can be registered for use in real clinical practice based on data not only on sufficient hypoglycemic potential (HbA1c dynamics of at least 0.6%) but also subject to cardiovascular and general safety. The main endpoints associated with cardiovascular outcomes, the so-called MACE (major cardiovascular events); is the frequency of deaths associated with cardiovascular events, non-fatal MI, and non-fatal stroke. Unfortunately, HF endpoints were not included in the MACE list, which led most large randomized clinical trials to include HF as a secondary endpoint or combined secondary endpoint. Thus, on the basis of the data obtained in the course of these studies, it is not possible to obtain complete information, and therefore, there are no grounds for formulating unambiguous conclusions. The data obtained only indicate the high relevance of research in the field of studying the relationship between the course of DM 2 and HF, as well as a differentiated approach in the choice of antidiabetic therapy, taking into account the presence of a high risk of developing HF in patients with DM2.

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