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Prevention, Treatment Epidemiology, Etiopathogenesis and Prognosis of Heart Failure in Patients with Diabetes Mellitus

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The combination of diabetes mellitus and chronic heart failure (DM and CHF) is a dangerous cocktail that is an important risk factor and the main comorbid condition that accompanies the risk. DM is one of the most significant causes of chronic heart failure (CHF). This article discusses the issues of epidemiology, pathophysiology, basic principles of treatment strategy and prognosis of CHF outcomes in patients with DM2.

KEYWORDS: diabetes mellitus, chronic heart failure, Cardiovascular diseases, sugar-reducing drugs.

Diabetes mellitus (DM) is one of the most pressing problems of modern medicine, the prevalence of which is growing every year and the rate of growth of DM today has taken the scale of a worldwide epidemic. Over the past 10 years, the incidence rate has increased by 2 times, and according to the IDF in 2015 reached 415 million people, in 2017 425 million and according to the latest data in 2019, 463 million people in the world aged 20-79 years suffer from diabetes, and according to forecasts by 2030, their number will increase to 700 million. the majority of patients with DM are those at the age of the greatest work activity [1,2].

DM causes the development of serious micro-and microvascular complications: nephropathy, retinopathy, neuropathy, diabetic foot syndrome, myocardial infarction(MI), chronic heart failure (CHF), stroke, leading to high disability and mortality of patients [3,4].

According to Alimov A. In and co. as of 01.01.2019, there are 230,610 patients with diabetes registered in Uzbekistan: 18,349 patients with type 1 diabetes and 212,261 patients with type 2 diabetes. The prevalence of type 2 diabetes is 7.9% among people over 35 years of age and has increased 1.6 times over the past 14 years (4). According to conducted screening in rural regions of Uzbekistan for identification of diabetes and IGT among 6189 individuals revealed a high prevalence of type 2 diabetes in high risk patients (13.3%), compared with the data of the national register of 5-6%, indicating the importance of screening for active detection of people with diabetes, IGT and IFG in order to begin treatment and prevent the development of severe complications. The prevailing risk factors for diabetes among the rural population over 40 years of age in Uzbekistan were: AH-78.6%; obesity (BMI >30) - 43.3%, HD - 42%, hereditary predisposition-35.2%. (Ibragimova N. sh., et al., 2018) [5,6].

Diagnosis of these conditions is not difficult and is available at all levels of the health organization, however, in Uzbekistan, as in many other countries of the world, there is still a discrepancy between the data on registration for diabetes and the results of epidemiological studies (Akbarov Z. S. et al., 2016; Ismailov S. I., et al., 2012) [7].

Type 2 diabetes is one of the established risk factors for the development of cardiovascular diseases, which has been proven in the results of numerous studies. The high incidence of CVD in type 2 diabetes is due not only to the presence of risk factors such as hyperglycemia, hypertension, and dyslipidemia, but also to the existence of a number of factors that accelerate the development and progression of vascular complications in diabetes. These include hereditary predisposition to antipathies, bad habits, congenital or acquired disorders of lipid metabolism, blood clotting systems [3,4,9,10].

Epidemiology, etiopathogenesis of chronic heart failure in diabetic patients. The combination of diabetes mellitus and chronic heart failure (DM and CHF) is a dangerous cocktail that is an important risk factor and the main comorbid condition that accompanies the risk. DM is one of the most significant causes of chronic heart failure (CHF). Foreign epidemiological studies show that about 12% of patients with type 2 diabetes have signs of CHF, and 15-26% of people with CHF suffer from type 2 diabetes. The problem of combining CHF and DM2 has become so urgent that despite the existence and regular updating of separate Recommendations for both CHF and DM2, in 2019 special Recommendations for the combination of CHF and DM2 were published, proposed by experts from the American Heart Association and Heart Failure Society of America [3,4].

Chronic heart failure (CHF) as the final stage of all CVD takes a leading position in the structure of total mortality and permanent disability, including in people of working age. Currently, in all developed countries in the structure of the main causes of chronic heart failure (CHF) in addition to arterial hypertension (AH) and CHD, the share of type 2 diabetes mellitus (DM2) is increasing, which reaches 27% in the Pan-European sample [9,10].

At the same time, metabolic disorders, in particular hyperglycemia, as a risk factor for death, ranks third, second only to hypertension and Smoking, and obesity is among the top five risk factors for death.

The prevalence of CHF in patients with DM-2 aged <65 years, both men and women, is higher than in the General population — 4 and 8 times, respectively [13, 14]. Diastolic dysfunction, diagnosed in 50-75% of patients with DM-2 without concomitant cardiovascular pathology, is considered by researchers as a manifestation of diabetic cardiomyopathy [4,16,17]. CHF with a reduced ejection fraction in patients with DM is accompanied by a significantly higher probability of death and hospitalization compared to patients without DM [4,18]. Patients with DM-2 and CHF have the worst long-term prognosis. In patients with diabetes, there is an increased risk of heart failure progression (CHF) — HR 1.17; 95% CI 1.04-1.32 and hospitalizations for CHF — HR 1.19; 95% CI 1.04-1.36, patients with diabetes and CHF also differ in longer periods of inpatient treatment [4,19]. The basis for the development of CHF in DM are macroangiopathy of the coronary arteries, structural remodeling of the myocardium, myocardiomyopathy and neuropathy. Large-scale studies of BEST, RESOLVD, and MERIT-HF have confirmed that patients with type 2 diabetes have a higher rate of hospitalization and duration of hospital stay than those without carbohydrate metabolism disorders [20,21].

In the Framingham study, the relative risk of developing CHF in patients with type 2 diabetes aged 45-74 years was 2 times higher in men and 6 times higher in women compared to patients without diabetes [15]. The high incidence of CHF in patients with type 2 diabetes was also demonstrated in the well-known epidemiological study NHANESI (The National Health and Nutrition Examination Survey) [22].

As the etiopathogenesis of this combined pathology, it should be noted that the etiological relationship of CHF and DM is mutually directed. So, a long course of DM can lead to the development of myocardial dysfunction and CHF, the cause of development can be endothelial dysfunction, dyslipidemia, disorders of the clotting system, hyperglycemia, which affects the function and morphology of the myocardium. On the other hand, CHF can lead to the development of type 2 diabetes, as a result of hyper perfusion of organs and hyper activation of neurohumoral systems, pathogenic shifts develop that contribute to an increase in the concentration of glucose in the blood. These include reducing the consumption of glucose by muscle tissue, increased gluconeogenesis in the liver, kontrinsulfarin effects of catecholamine. The second mechanism for the development of CHF in patients with type 2 diabetes can be the direct effect of prolonged hyperglycemia on the heart muscles and its damage. Myocardial damage on the background of hyperglycemia is mediated by microangiopathy, impaired calcium transport and fatty acid metabolism. An example of a glucose-toxic effect on the myocardium can be considered the development of diabetic cardiomyopathy, which can be considered as a combination of violations of the properties of the myocardium, electrophysiological processes and hyper cate cholanemia [4,20,23].

Choice of hypoglycemic drugs in people with DM2 at risk of developing CHF and those who already have CHF. The degree of influence of intensive hypoglycemic therapy on the risk of macro vascular complications in DM remains

debatable [4,24]. Thus, in the UKPDS (United Kingdom Prospective Diabetes Study) [25] in the intensive care group, there was a 16% reduction in the risk of cardiovascular conditions: fatal or non-fatal MI and sudden cardiac death, but it was not statistically significant ($p=0.052$). Other major RCTS were also devoted to studying the effect of intensive antidiabetic therapy on the risk of macro vascular complications in comparison with standard therapy: ACCORD (Action to Control Cardiovascular Risk in Diabetes) [26], ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation) [27] and VADT (Veterans Affairs Diabetes Trial) [28].

In General, a meta-analysis of four major RCTS: UKPDS, ACCORD, ADVANCE, and VADT revealed a moderate and statistically insignificant reduction in the risk of major macro vascular conditions, including those associated with CHF, between groups with more intensive glycemic control (average HbA1C values of 6.4-7.0%) and its less intensive control (HbA1C levels 7.3-8.4%) [4, 26,27,28].

Biguanides (Metformin) is currently considered as the preferred initial hypoglycemic drug in individuals with DM2 in absence of contraindications. It has the same position in persons with DM2 in combination with CHF. Before 2006 it was considered contraindicated in CHF because of fears the development of such rare complications such as lactic acidosis. Now it is shown that in such patients, its use is associated with a favorable effect on the prognosis. Thus, in a meta-analysis of 9 cohort studies, which included almost 34 thousand patients, it was demonstrated that the use of Metformin in individuals with CHF and DM2 was accompanied by a distinct decrease in overall mortality (by 20%) and the frequency of decompensation of CHF [12,29]. The UKPDS RCT sub analysis provides data on a possible reduction in the risk of myocardial infarction when Metformin is prescribed [30]. Experts recommend the use of Metformin as a basic hypoglycemic agent in people with DM2 who are at risk of developing CHF, as well as in patients with pre-existing CHF. It should be canceled in cases of severe decompensation of CH [31].

In some patients with DM2 and CHF, the use of insulin therapy is required to achieve compensation of carbohydrate metabolism, but their use is associated with an increase in body weight, the risk of hypoglycemia, which requires caution and careful laboratory control. Although data from several RCTS (ORIGIN, UKPDS, BARI-2D) [34] did not show a worsening of the cardiovascular prognosis against the background of the use of insulin drugs, however, other reports show the possibility of increasing cardiovascular mortality in people with DM2 and CHF who received insulin, in comparison with other hypoglycemic drugs.

As for the use of glucagon-like peptide-1 receptor agonists in DM with CHF, several RCTS (LEADER, ELIXA, EXCEL, SUSTAIN-6) [37] have demonstrated that argpp-1 can reduce SSR in the General population of patients with DM2. With DM2 in combination with CHF, they are quite safe, although they do not have direct favorable effects on the prognosis (they do not reduce the risk of CHF decompensation). In individuals who have recently undergone CHF decompensation, their use requires caution (RCT FIGHT) [12,38].

Dipeptidyl peptidase-4 (idpp-4, dipeptidyl peptidase-4 (DPP-4) inhibitors) These oral medications are usually considered for DM2 as 2nd-line medications, in addition to Metformin. According to the RCT (SAVOR TIMI-53, EXAMINE, TECOS, VIVID) [39], the use of idpp-4 is not associated with any adverse effect on the cardiovascular prognosis. In individuals with high SSR, saxagliptin increases the risk of CHF decompensation. Given the limited and contradictory data available, experts are currently cautious about the possibility of using idpp-4 in individuals with established CHF, as well as in those who have a high risk of its development [12,39,41].

A multicenter, randomized, double-blind, placebo-controlled study, SAVOR —TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53) [4,41], focused on the effect of the DPP-4 inhibitor saxagliptin on cardiovascular outcomes, involved ~16,500 patients with DM-2 aged ≥ 40 years with a history of CVD ($n=12929$) and/or multiple FRS of their development ($n=3533$). The level of HbA1c at the screening visit was 6.5-12.0%, history of MI 38.0% and 37.6%, CHF 12.8% and 12.8%, coronary artery revascularization 43.1% and 43.3%, and was comparable in the saxagliptin and placebo groups. At the end of the follow-up period (an average of 2.1 years), both positive and negative effects of saxagliptin on cardiovascular events were noted — HR 1.00; 95% CI 0.89-1.12 ($p=0.99$), but a statistically significant increase in the frequency of hospitalization due to CHF progression in the saxagliptin group compared to the placebo group-3.5% vs 2.8%; OR 1.27; 95% CI 1.07-1.51 ($p=0.007$) [4,41].

The next group of drugs that is used in the treatment of DM and CHF is inglt-2, which is the first and so far the only class of sugar-lowering drugs for which there is strong evidence of a favorable effect on the cardiovascular prognosis,

especially in patients with DM2 and CHF with low LV FV. Against the background of their use in patients with DM2 AND CHF with low LV FV in the RCT series (CANVAS, CVD-REAL), there was a decrease in total (49%) and cardiovascular mortality, a decrease in the frequency of CHF decompensation by 33-39%, which undoubtedly makes them the hypoglycemic drugs of choice in such individuals [12,42,43]. In addition, inlt-2 can be used as a component of a preventive strategy in people with DM2 AND a high risk of developing CHF (including post-infarction patients).

The prognosis of chronic heart failure in patients with diabetes mellitus. It is known that DM2, as comorbidity, leads among other diseases that burden the clinical course of all CVD without exception, mainly due to the early development of cardiovascular complications that worsen the prognosis. For a long time, it was believed that compensation of carbohydrate metabolism in patients with DM2 is a key factor in the prevention of cardiovascular complications, however, meta-analysis data showed that even intensive control of glycaemia does not reduce the risk of developing cardiovascular complications (Parry M., 2015; Wang Y., 2015; Newman J. D., 2017).

On the other hand, heart failure leads to a significant increase in the death rate of diabetic patients. For example, in the DIABHYCAR study, the annual mortality rate of diabetics who developed heart failure was 12 times higher than in patients with diabetes without heart failure (36.4 and 3.2 %) [20,21]. In a large American cohort study that included 151,738 diabetic patients over 65 years of age, the 5-year survival rate for patients with heart failure was 12.5%, compared to 80% for diabetics without heart failure [45]. In another BEST study, the presence of DM was independently correlated with an increase in cardiovascular mortality in patients with ischemic cardiomyopathy [20,44].

LVF and DM2 risk of decompensation of heart failure (CHF) 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 hospital admissions for CHF, and a lower quality of life. SD2 it also negatively affects the course of CHF with preserved LVF, increasing the risk of decompensation and mortality. In randomized controlled trials (RCTs) CHARM I and I-PRESERVE [46,47], it is shown that these adverse effects of DM2 in this variant of CHF may be even more pronounced than in individuals with CHF with low LVF.

CONCLUSIONS

Thus, type 2 diabetes is an important risk factor for chronic heart failure, independent of coronary heart disease, hypertension, and other factors. Diabetes patients have a high incidence and mortality rate from heart failure. It is known that the close Association of heart failure and diabetes is due to the greater frequency and severity of its risk factors in diabetes mellitus, accelerated development of atherosclerosis and specific diabetic myocardial damage associated primarily with metabolic and neurohumoral disorders. However, the mechanisms of cardiac dysfunction directly related to diabetes require further study.

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