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THE ROLE OF CYSTATIN C IN ASSESSING THE FUNCTIONAL STATE OF THE KIDNEYS IN PATIENTS WITH CORONARY HEART DISEASE

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Abstract

Diagnosis and treatment of chronic coronary heart disease (CHD) is well developed, but there are often difficulties in managing patients with comorbid diseases. A very common chronic kidney disease (CKD) occupies a special place among comorbidities. The cause of death in patients with kidney dysfunction is significantly more often CHD than end-stage renal disease (ESRD). In recent years, cystatin C has been considered as an early marker for assessing the functional state of the kidneys and cardiovascular risk, the level of which, unlike creatinine, does not depend on gender, age, race, and muscle mass.

Key words: coronary heart disease, cystatin C, functional state of the kidneys.

Cardiovascular diseases (CVD) are one of the main causes of death and disability among the population of all countries without exception. According to the report of experts from the World Health Organization (WHO), confirmed by statistical analysis, for many years the main cause of morbidity and mortality in the population around the world (accounting for 55% of the total population) are atherosclerotic CVD, of which more than 2/3 are ischemic heart disease (CHD). In 2012, 17.5 million people died of CVD, accounting for 31% of all deaths worldwide. Of this number, 7.4 million people died from coronary artery disease and 6.7 million people as a result of a stroke [11,12].

Population aging and lifestyle changes are causing CVD to increasingly take hold in developing countries (up to 75% of CVD deaths occur in low- and middle-income countries), and according to WHO, an ominous upward trend in its mortality is noted: it is assumed that in 2025 22–25 million people may die from it, almost half of them will be deaths from coronary artery disease. It is concluded that humanity is on

the verge of a new non-infectious pandemic of the third millennium [12].

The prevalence of coronary artery disease among the adult population of developed countries is approximately 10%, among the elderly and the elderly - about 20%. Only 40–50% of patients are aware of their disease; in the remaining 50–60%, it remains unrecognized [3].

Based on numerous clinical, laboratory and epidemiological studies, it has been proven that the development of atherosclerosis, including coronary arteries, is associated with lifestyle, the presence of certain metabolic features and diseases or pathological conditions, which together are defined as risk factors (RF) for coronary artery disease. The most significant of which are: smoking, diabetes mellitus (DM), arterial hypertension (AH), obesity, the presence of IHD in close relatives, low physical activity. The likelihood of developing coronary artery disease increases with a combination of two, three or more of the listed risk factors, especially with a sedentary lifestyle [11]. In addition to the traditional risk factors for CAD (DM, AH), impaired renal function is associated with greater inflammation, sympathetic activity, endothelial dysfunction, atherosclerosis, plaque vulnerability, vascular calcification, and anemia. Increased activity of the sympathoadrenal system is often identified in kidney dysfunction (RD) and is associated with an increased risk of CVD and progression of kidney disease. In patients with hypertension, coronary artery disease, especially in combination with diabetes and chronic heart failure (CHF), renal dysfunction occurs quite often. At the same time, impaired renal function is an important independent risk factor for the development of such cardiovascular complications as myocardial infarction (MI), heart failure, and fatal arrhythmias [4].

The kidneys and their glomeruli are part of the microcirculatory system of the body, they influence the formation of cardiovascular pathology, at the same time they themselves are involved in the pathological process in various CVDs. In recent decades, the number of patients with DP has been growing all over the world. According to various population-based registries and studies (NHFNES III, Okinawa Study, PREVEND, Swiss SAPALDIA study, etc.), the prevalence of renal pathology in the USA, Europe and Japan is 10-13%, reaching even higher values in high-risk groups. At the same time, the increase in the number of patients with renal pathology is associated primarily with the steady increase in the prevalence of CVD, type 2 diabetes, and obesity [7].

The association of impaired renal function in the general population with

a higher incidence of CVD and its complications was first studied in The Framingham Heart Study. The study included 6223 participants (mean age 54 years, 54% women) who were followed up for 15 years. Serum creatinine was chosen as an indicator of the decline in kidney function: from 1.5 to 3.0 mg/dL in men and from 1.4 to 3.0 mg/dL in women. The upper limit of creatinine concentration was indicated in order to exclude cases of severe renal failure. Since the beginning of the observation period, 8.7% of men and 8.0% of women had a decrease in kidney function. By the end of the 15-year follow-up period, in neither men nor women, decreased renal function was associated with an increased risk of cardiovascular complications, however, in men, hypercreatininemia was associated with an increased risk of all-cause mortality. The authors of this study were forced to state a negative result and conclude that an increase in the risk of cardiovascular complications is more likely determined not by a decrease in kidney function, but by concomitant CV risk factors [3].

In a Japanese study (The Hisagama Study), which included 2634 participants aged 40 years and older and lasted 12 years, a clear relationship was established between a decrease in GFR and the incidence of coronary artery disease in men and with the incidence of ischemic stroke in women [3].

Diagnosis and treatment of coronary artery disease is well developed, but the management of patients with comorbid diseases is often difficult. A very common chronic kidney disease (CKD) occupies a special place among comorbidities, which is considered a major risk factor for cardiovascular disease. The cause of death in patients with DP is significantly more often CHD than end-stage renal disease [1].

Data from the EUROPA study indicate a high incidence of PD in patients with coronary artery disease. Since with stable coronary artery disease in 52% of cases, GFR was below 75 ml / min / 1.73 m2. On the other hand, according to the American registry USRDS, elderly patients over 65 years of age with non-terminal kidney dysfunction were more likely to have atherosclerotic heart disease (42.5 vs. 16.5%) and myocardial infarction (10 vs. 2%) compared with individuals with normal kidney function. According to the results of coronary angiography, three-vessel coronary artery disease (>50%) was determined in 53% of patients with moderate and severe DP, and in 28% with mild dysfunction or normal renal function [5].

Numerous large-scale international studies have confirmed the high prevalence of CKD, comparable to the prevalence of coronary artery disease and diabetes. The results of the study of the prognosis of CKD (Chronic Kidney

Disease Prognosis Consortium) demonstrated a significant and independent association of GFR and albuminuria with total and cardiovascular mortality, progression of CKD, and the risk of developing acute kidney injury [2].

The relationship between impaired renal function and coronary atherosclerosis was confirmed at autopsy: with GFR ≥60, 45-59, 30-44 and <30 ml / min / 1.73 m2, severe atherosclerosis of the coronary arteries was found, respectively, in 34, 42, 52 and 53 % of cases. In the COURAGE study among patients with stable coronary artery disease, the presence of CKD increased the risk of MI, death, and new cases of heart failure by 1.5 times. Two-year survival after acute MI was 57% for stages 1-2 and 30% for stages 4-5 of CKD. The risk of MI within 2 years was higher in patients with CKD than in patients with diabetes mellitus. Thus, bidirectional relationships between CAD and DP are determined with an increase in the incidence of diseases and a worsening of the prognosis of CAD in more severe CKD [1].

Decreased GFR as a risk factor for adverse outcomes in individuals with underlying cardiovascular pathology. One of the largest of the randomized and prospective Heart Outcome and Prevention Evaluation (HOPE) trials initially examined the effect of therapy with the angiotensin-converting enzyme (ACE) inhibitor ramipril and the antioxidant vitamin E on the incidence of MI, stroke and cardiovascular mortality in 9297 patients. All people included in the study belonged to a high-risk group for developing cardiovascular events. Additionally, the frequency of primary cardiovascular outcomes (cardiovascular mortality, acute MI, stroke) was studied in the group of patients with serum creatinine levels from 1.4 to 2.3 mg/dL (n=980) and in those examined with normal functional indicators. kidneys (n=8307). The same analysis was carried out after calculating GFR in groups of individuals with the level of this parameter less than 65 ml/min (n=3394) and more than 65 ml/min (n=5888). Already a simple comparison of patients in terms of creatinine or GFR showed that more than a third of patients had an initial degree of renal insufficiency, which had a significant impact (regardless of other risk factors and microalbuminuria) on primary cardiovascular outcomes. Thus, cardiovascular mortality in the group of patients with slightly elevated serum creatinine was 22.2% versus 15.1% [3].

Hillege H.Z. et al. when evaluating various hemodynamic and serological factors as prognostic factors in patients with severe but stable heart failure, it was unexpectedly found that the greatest predictive value for overall mortality in this category of patients is the degree

of decrease in GFR: the lower it is, the higher the risk of death. These authors found that lower GFR values in patients with AMI are a predictor of the development of heart failure (including patients with cardiogenic shock and acute renal failure) [3].

In recent years, cystatin C has been considered as an alternative marker for assessing the functional state of the kidneys and cardiovascular risk, the level of which, unlike creatinine, does not depend on muscle mass, which makes it possible to more accurately determine GFR in people with a non-standard physique, deficiency or excessive development of muscle mass. weight, in children, the elderly, patients with diabetes, obesity, pregnant women. When the kidneys are involved in the pathological process, the filtration of cystatin C in the kidneys worsens, which leads to an increase in its content in the blood. [13]. Estimates of GFR using the CKD-EPI formula based on cystatin C or cystatin/creatinine better predict the severity of CAD (Syntax≥23) than other formulas [26]. The GFR estimate using the CKD-EPI formula predicted outcomes of coronary intervention better than the Cockcroft-Gault and MDRD formulas [19].

The accumulated experience of large observers has shown that the method of evaluating GFR based on the determination of cystatin C in the blood has a higher sensitivity and specificity compared to the determination of serum creatinine in persons over 16 years of age [16,17,20].

Initially high levels of cystatin C at birth decrease in the first year of life and remain stable up to 50 years of age, and then increase [14].

Afshinnia F. and co-authors in their studies considered cystatin C as the most sensitive marker of early damage to kidney function and a prognostic factor of renovascular disease in patients with essential hypertension, preeclapsia, atherosclerotic changes, while the severity of kidney dysfunction was associated with diastolic dysfunction of the LV myocardium and changes in geometry LV in different groups. [5].

In patients with coronary artery disease, serum cystatin C levels were linearly related to systolic blood pressure (SBP) even with normal renal function [23].

The authors also point out that the determination of cystatin C in the blood is not only more accurate, but also an earlier indicator, reflecting a decrease in the filtration function of the kidneys. This feature of blood cystatin C as a marker of a decrease in GFR is due to the fact that its concentration does not depend on sex and age (except for children under 1 year of age), on metabolism in skeletal muscles, the enzyme is not reabsorbed and is not secreted in the

tubules of the kidneys. In addition, an increase in cystatin C in the blood is a predictor of not only adverse events in terms of kidney damage, but also the risk of cardiovascular complications, for example, in patients with CHF [6,8,21,24].

Numerous studies have shown that elevated levels of cystatin C are associated with an increased risk of mortality and cardiovascular events such as myocardial infarction, ischemic stroke, heart failure, as well as peripheral arterial disease and metabolic syndrome. Moreover, in most studies, it was found that cystatin C in these cases as a marker surpasses creatinine in accuracy [9,10,15,18].

The increase in cardiovascular risk associated with an increase in serum cystatin C is especially characteristic of the elderly [25], who, as a rule, experience an annual decrease in GFR. Moreover, such a decrease in GFR is an independent risk factor for increased mortality [22]. Since the association of serum cystatin C levels with long-term CVD outcomes is stronger than the association with such outcomes with a decrease in GFR, it has been suggested that elevated levels of cystatin C may be associated with increased cardiovascular mortality, regardless of worsening renal function [11].

In general, elevated levels of circulating cystatin C are associated with an increased risk of CVD, hypertension, dyslipidemia, and mortality. Cystatin C levels are much less affected by gender, age, race, and muscle mass and obesity than are creatinine levels. Numerous prospective studies have shown that individuals with elevated levels of cystatin C have a high risk of developing CVD and CKD under various clinical scenarios. Cystatin C measurements are of particular value in identifying patients at high risk of cardiovascular events among individuals with normal GFR and creatinine values and, therefore, inappropriately included in the low-risk category for CVD and CKD.

Thus, elevated concentrations of cystatin C are an indicator of preclinical kidney diseases associated with CVD risk and a predictor of their adverse complications. In general, cystatin C may be a reliable predictor of preclinical structural changes in the cardiovascular system, as it serves as a more accurate measure of kidney function than serum creatinine and GFR. In addition, the study of cystatin C levels provides more complete prognostic information than other markers of kidney function. Measurement of cystatin C, alone or in combination with creatinine, may allow more accurate determination of GFR and assessment of the risk of mortality and renal events in patients with coronary artery disease.

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