CARDIOVASCULAR CONSEQUENCES OF INSULIN RESISTANCE: AN OVERVIEW OF CURRENT EVIDENCE

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Annotation. However, the literature on the role of NTG as RF CHD differs significantly. Meanwhile, in some cases, NTG can precede the development of DM and, in a certain sense, it can be considered as a state of "pre-disease" in relation to DM. Hyperglycemia, including latent hyperglycemia, often proceeds with hyperinsulinemia, which is considered one of the components of the "metabolic" syndrome. which plays an important role in the formation of cardiovascular diseases, including coronary artery disease.

Key words: Blood pressure, hyperlipidemia, obesity, diabetes mellitus.

Topicality. The epidemiological situation with regard to coronary heart disease (CHD) in different regions of the world and in individual populations is very ambiguous. More than 1 million Americans had new cases of CHD or exacerbations of this disease (qualified as myocardial infarction or fatal CHD). Moreover, 650,000 of them had newly diagnosed CHD, and 350,000 had an exacerbation of chronic CHD. About 250,000 patients died before the hospital stage. ventricular fibrillation was observed. The value of the standardized indicator of CHD prevalence in different cities differed significantly. Thus, the highest value of this indicator was noted in Baku, Kiev and Moscow (19.5%, 16.4% and 14.5%), and the lowest it was in Nalchik (6.9%). In Tashkent, the prevalence of CHD was 9.3%. Exertional angina pectoris is most common among the examined contingents (4.5%), somewhat less often (3.8%) there are "possible" ischemic changes on the ECG. Past myocardial infarction and painless forms of CHD are even less common (in 1.3% and 1.5%, respectively), and a possible history of myocardial infarction (not confirmed by ECG changes) was determined in 1.0%. Factors contributing to an increase in sudden death, along with such generally recognized risk factors as high blood pressure, hyperlipidemia, obesity, diabetes mellitus, etc., also include non-painful myocardial ischemia [9] and untimely establishment (or non-establishment) of diagnosis [16]. In France, a 20-year study of the causes of death of the population was carried out, which showed a decrease in mortality from cardiovascular diseases (CVD) by more than 30% [8]. In this regard, the issue of determining the range of risk factors for mortality from CHD and the development of adequate methods for the prevention of this disease is of particular importance. Summary data from studies conducted in three regions of France, two regions of Italy, two regions of Sweden, Barcelona, Belfast and Glasgow covered the population aged 35-64 years [10]. The authors concluded that the mortality rate of the population is influenced by both geographical location and lifestyle, diet and other factors. At the same time, it has been shown that one of the most important factors in the increase in mortality from CHD is a very low coverage of treatment of both patients suffering from CHD and those with high blood pressure.

Objective: To study the relationship between insulin resistance and increased cardiovascular risk.

Introduction: Large population-based studies conducted by the Center of Cardiology of the Ministry of Health of the Republic of Uzbekistan indicate the importance and fairly high effectiveness of preventive measures against cardiovascular diseases [3,2,15]. Preventive programs implemented in production teams made it possible to increase the effectiveness of drug control of hypertension by 7 times, reduce the incidence of hypertension by 10%, and quit smoking up to 25% of men [2]. Multifactorial prevention in general was effective in both men and women [3]. However, it should be noted that the effectiveness of AH and smoking prevention was more pronounced among men than among women. Among men aged 30-59 years in Samarkand, the incidence of coronary artery disease was 3.4% in normal BP, 7.5% in borderline hypertension, and 16.7% in hypertension, respectively [3,4]. Studies in Tomsk were conducted among 647 patients with CHD, whose average age was 53.1 ± and 2.36 years, and it was shown that HDL-C has a stabilizing effect on atherosclerotic plaque and has a positive effect on the course of CHD, as well as to a certain extent prevents the development of MI [9]. Dyslipoproteinemia in some cases can be a manifestation of a general hereditary syndrome. In patients with a hereditary burden of cardiovascular diseases, hypertension was significantly more common among patients with dyslipoproteinemia than in patients with normolipidemia (20.2% and 12.5%, respectively). At the same time, the authors support the opinion that excess fat consumption contributes to an increase in blood cholesterol, and this, in turn, leads to an increase in the risk of developing CHD.

A certain importance in the development of CHD is given to excess body weight (BMI). Most researchers note that the frequency of BMI among people engaged in mental work is higher than among people engaged in physical labor. According to an epidemiological study in Finland [6], BMI is more common among people with low physical activity than with normal physical activity. At the same time, the risk of death from CHD among people with BMI and low physical activity is much higher than the risk of death from CHD among people with normal body weight and sufficient physical activity. Patients with CHD suffering from BMI are significantly more likely to have increased anxiety, psychosocial maladaptation, a higher frequency of cardialgias, and less tolerance to isometric load. Among people with BMI suffering from CHD, the correlation coefficient between body fat mass and anxiety level is 0.53±0.09 (p <0.001). 60.6% of angina patients have a BMI [4]. CHD patients with BMI have a low tolerance to physical activity and less efficiency of the cardiovascular system [6]. It should be noted that impaired central and peripheral hemodynamics is considered one of the important risk factors for death from cardiovascular diseases [1]. The importance of tobacco smoking in the development of CHD is so great that many researchers attach great influence to passive smoking. Although the relationship between secondhand smoke and CHD has not yet been fully understood, there are reports that secondhand smoke contributes to the development of CHD [8]. It should be noted that it is possible to objectively assess the importance of alcohol in the formation of CHD only on the basis of a multivariate analysis. However, alcohol plays an important role in mortality from other, non-cardiovascular diseases. Studies conducted in various scientific centers indicate that the same RF, as well as their combinations, have different prognostic significance in relation to the development of CHD and the prognosis in this disease. Therefore, the need for further, in-depth research in the field of RF studies becomes obvious.

The high importance of DM in the formation of CHD and mortality from it is indicated by the results of many population studies [13, 15]. A 20-year prospective study conducted in the UK included 2779 people [2]. Overall, 31.1% of those under observation developed coronary artery disease. Among patients with diabetes, the frequency of new cases of CHD was significantly higher and amounted to 57%. In Finland, the prevalence of CHD among patients with newly diagnosed type II diabetes was studied [2]. It turned out that among patients in whom DM was detected for the first time, the incidence of CHD was 3 times higher than in the control group, i.e. among patients without DM. The Oxford study was conducted over a period of 10 years and included 3055 men suffering from type II diabetes, whose average age was 52 years [13]. During this period, 335 people developed coronary artery disease. The significance of such indicators as high- and low-density lipoprotein cholesterol, triglycerides, SBP, smoking and fasting glucose levels was analyzed. A pronounced relationship between RF CHD and DM has been established. The greatest association was established with SBP and low-density lipoprotein cholesterol, i.e. with those RFs that play an important role in the development of CHD. At the same time, it should be noted that there are indications in the literature that there is no direct relationship between DM and CHD [15]. Such a view of this problem is explained by the fact that the etiopathogenetic aspects of DM and CHD have much in common. The authors believe that in some cases patients with CHD develop DM, and in other cases, patients with DM develop CHD. A 9-year prospective follow-up of DM patients showed that DM is a very important RF of death from CHD [9]. This study found that the mortality rate from CHD per 1000 person-years of observation was 28.4 among patients with DM, and 10.2 among people without DM. At the same time, the total mortality from cardiovascular diseases in patients with DM was 39.6 per 1000 person-years of follow-up, and among people without DM – 15.5. It should be noted that mortality from other, non-cardiovascular diseases was 16.6 and 13.5, respectively. The course of MI in patients with diabetes is characterized by a large number of complications and high mortality. The severity of MI is to a certain extent related to the severity of DM, and the mortality rate in MI patients in DM patients reaches 54% [9]. In patients with DM, the risk of recurrent MI is significantly higher, and the survival rate is significantly lower than in patients without DM [3]. The presence of DM increases the likelihood of rupture of the left ventricular wall in MI [2]. Along with a higher incidence of chronic pain-free CHD in patients with diabetes, pain-free cases of MI are also more often observed [13]. It should be noted that not all authors share the opinion about a higher incidence of CHD without pain forms among patients with diabetes. As a result of a study based on a retrospective analysis of the prognostic significance of the appearance of pain-free myocardial ischemia during exercise on treadmills, the authors concluded that the incidence of pain-free myocardial ischaemia does not depend on the presence of diabetes [15]. Higher mortality from CHD in patients with diabetes is to a certain extent associated with such a factor as ethnicity [14]. A comparative analysis of mortality from acute MI in South Asia showed that out of 149 Asians and 313 whites admitted to the clinic with acute MI, there were significantly more whites alive than Asians [13]. It should be noted that among Asians admitted to the hospital, the incidence of diabetes was 38%, and among whites - 11%. At the same time, a study conducted among 150 Europeans and 77 Africans suffering from insulin-independent diabetes showed that Africans have a lower risk of developing cardiovascular diseases than whites [7]. Various RF CHDs are significantly more common among patients with diabetes than among people without diabetes [5]. Patients with CHD [6] with DM have a higher concentration of blood triglycerides and lower high-density lipoprotein cholesterol than CHD patients without DM (2.51 and 2.07

mmol/L, 0.93 and 1.19 mmol/L, respectively). At the same time, the atherogenicity coefficient in CHD patients with DM was 1.4 times higher than among patients without DM (6.43 and 4.60, respectively). A prospective follow-up of 1342 men in Trinidad revealed 178 deaths, of which 38% were CVD, with 12% having cerebrovascular disease. With an increase in the level of systolic BP, the risk of all-cause mortality from CVD and cerebral stroke increased. With a SBP level above 180 mmHg. mortality from CVD increased by 4 times [16]. A 7-year study of mortality among men aged 50-59 years in Moscow revealed that hypertension is an important risk factor for death from CHD [10]. When comparing RFs such as hypertension, overweight, smoking, and impaired carbohydrate tolerance, it turned out that hypertension was the most unfavorable factor, since mortality from coronary artery disease among people with elevated blood pressure was 7 times higher than in normal blood pressure, which was significantly higher than in other RFs.

In the presence of hypertension caused by SBP, the risk of death from CVD increases by 5 times, and in the presence of DBP due to DBP, the risk of death increases by 3 times. This study showed that the risk of myocardial infarction and cerebral stroke increases with an increase in blood pressure levels, and the risk of cerebral stroke increases more intensively [104]. It should be noted that it is growing not only among the urban, but also among the rural population. A study of the mortality structure in Tashkent showed that CVD is the cause of death in men aged 20-59 years in 33.1% of cases (CHD - 23.87%, HA - 7.16%, other CVD - 2.06%) [11].

The increase in total mortality rates from 9.6 to 24.1 cases per 1000 people/year as diastolic BP increases is shown by the data of B.Kh. Makhmudov [8]. According to his data, mortality from CVD in the group of examined hypertensions was 5 times higher, in the group of borderline hypertensions - 1.8 times higher than in the group with normal BP. Prospective observations of the male population of Bishkek have shown that the overall mortality from CVD and other causes increases significantly with SBP [11].

In 1995, for the first time since 1986, a decrease in mortality was registered in Russia, and its decrease was noted in 70 regions of the country [9], which was the result of a significant reduction in mortality from diseases of the circulatory system and unnatural causes of death - accidents, poisoning and injuries. However, it is noted that the maternal mortality rate remains high and is not decreasing. The maternal mortality rate in Russia is 5-10 times higher than in developed Western European countries.

According to the data, cardiovascular diseases are one of the main causes of mortality in the population of Moscow, accounting for 57% of the total mortality, which exceeds the same indicators in Russia as a whole. A study of the mortality structure in Tashkent revealed that CVDs are the cause of death in 37.5% of cases [9,10]. According to data [11], the female population has an increase in mortality from CVD in all age groups starting from 30-39 years old. Cardiovascular diseases also occupy the first place in the structure of extragenital pathology, which is one of the main causes of death in pregnant women [10].

Based on the data presented in this section, it can be concluded that hypertension is of great importance in the formation of coronary artery disease, cerebral stroke and mortality from them. Timely detection, treatment and prevention of hypertension significantly reduces the risk of death from CVD. At present, a lot of work is being done in Uzbekistan to improve

the health of women of childbearing age, which is crucial in the formation of a healthy generation.

From the information given in the previous chapter, it follows that according to the data of most studies, the importance of DM as a risk factor for CHD can be considered proven. At the same time, there is no consensus in the literature regarding the importance of NTG as a RF for the development of CHD and mortality from it.

According to a number of studies, the risk of developing arterial sclerosis significantly increases in NTG [15, 16]. A long-term prospective follow-up of 26 years in Framingham (USA) included 1672 men and 2264 women [16]. After 26 years, 210 men and 199 women developed coronary artery disease. Among individuals with NTG, along with coronary vessel involvement, peripheral vascular lesions (primarily the femoral artery) were also affected. The authors concluded that in conditions of hyperglycemia among persons with peripheral vascular lesions, there is a high risk of developing coronary artery disease. Apparently, the combination of lesions of the coronary and peripheral arteries causes hemodynamic disorders and the formation of a hypokinetic type of blood circulation [11].

There are reports in the literature that NTG significantly affects the severity and clinical course of CHD [12]. Among people with NTG suffering from CHD, repeated, frequent hospitalizations, tachycardias, and ischemic changes in the ECG are much more common [15]. Over time, the glycemia level can change both in the direction of increasing the glycemic curve and decreasing, and in other cases, the glycemia level stabilizes. prevalence of coronary artery disease and basal insulinemia levels among individuals with different dynamics of NTG [14]. It turned out that the development and severity of CHD are closely related not only to the presence of NTG, but also to the dynamics of hyperglycemic states. Thus, among individuals with initial IGT, with normalization of glycemia level, the incidence of CHD is 25%, and with stabilization of NTG, the incidence of CHD reaches 76.5%. At the same time, the level of basal insulinemia increases in accordance with the progression of hyperglycemia. Among patients in whom hyperglycemia normalized, the level of basal insulinemia was 18.27 ± 0.92 µU/ml, when NTG turned into overt DM, the insulin content was more than 2 times higher (39.08 ± 2.1 µU/ml), and when NTG stabilized, basal insulinemia was the highest – 44.56 ± 3.32 µU/ml. During the entire follow-up period, 864 people developed CHD and 384 people died from this disease.

Along with the works showing the important role of NTG in the formation of CHD and mortality from it, there is evidence in the literature that denies the role of NTG as RF CHD. A multivariate analysis that takes into account age, sex, education, hypertension, height-weight index, and smoking allowed the authors to conclude that, in contrast to DM, NTG is not CHD RF. One of the largest works devoted to the study of the importance of NTG in the formation of CHD and deaths in this disease is a cooperative study conducted by The International Collaborative Group in 14 scientific centers in 11 countries [15]. Studies were conducted in Australia, England, Denmark (2 populations: males 40 and 50 years old), Ireland, the USA (2 populations: employees of the gas company and the Western Electric Company), Italy, Switzerland, Scotland, Finland (2 populations: policemen and unorganized population), France, and Japan [16]. Such indicators as the prevalence of CHD, the presence of ischemic changes in the ECG, MI cases and mortality from CHD among individuals with NTG and different blood glucose levels were taken into account. The results were very

mixed. Studies among policemen in Finland, employees in Italy, and workers in Japan have shown that CHD is significantly more common among people with NTG than among people with normal glucose tolerance. A positive relationship between ischemic changes on ECG and the presence of NTG in the populations of Australia, Italy, and the unorganized population of Finland and France was revealed. A higher mortality from CHD was found among people with NTG in the population of the Gas Company of the USA, France and policemen in Finland. At the same time, among those surveyed in England, Denmark, Switzerland and Scotland, no relationship was found between the presence of NTG and the prevalence of CHD. As follows from these data, the results of studies of different centers differ significantly. These discrepancies can be explained by the fact that different methods of population selection were used in the studies, age groups and follow-up periods differed significantly, not in all studies the study of glucose tolerance covered the state of glycemia at 1 and 2 hours after glucose loading. For example, in Denmark, the population of policemen is represented by people aged 40 years, and in Italy, the population aged 35-59 years was surveyed. A prospective study in Finland among an unorganized population lasted 4 years, in the same country the study of mortality among policemen was carried out for 10 years, and in the United States among employees of the Western Electric Company the duration of observation was 15 years. The significance of hyperglycemia for the formation of CHD was judged by the level of glucose: in Italy - on an empty stomach, in Australia - 1 hour after glucose loading, in the USA - 2 hours after glucose loading. Thus, the discrepancies in the results of the cooperative study conducted by The International Collaborative Group in 14 scientific centers in 11 countries and in a number of other population-based studies on the relationship between the prevalence of CHD and mortality from it with NTG, are largely due to differences in methodological approaches to both sampling and methods for detecting NTG, as well as different follow-up periods. At the same time, the results of studies on the significance of NTG as RF CHD can also be influenced by other factors, as well as their combinations [14, 15, 16]. The results of a number of population studies indicate that when several RFs are combined, the prevalence of CHD increases. At the same time, it has been shown that some RFs can contribute to the formation of other risk factors. In this regard, the question of the relationship between NTG and other RF CHDs is of some interest. A prospective study conducted in Italy and followed for 11.5 years involved 1376 people aged 40-59 years. During this follow-up period, systolic BP increased by 7.6 mmHg among people with NTG. higher than among people with normoglycemia, and diastolic blood pressure is 3.3 mm Hg. The existence of a relationship between the frequency of hypertension and the presence of NTG is also indicated by a study in Philadelphia conducted among black Americans [15]. A study of 437 people over 15 years of age in Central Australia found a direct correlation between glucose levels on the one hand and the prevalence of hypercholesterolemia, hypertriglyceridemia, hypertension, and BMI on the other [16]. Another study conducted in Western Australia among men and women aged 25-64 years examined the association between the presence of NTG and RF levels of CHD. It is shown that individual RFs are related to NTG in different ways. For example, hyperglycemia was associated with BMI in both men and women. Systolic BP was significantly higher in NTG than in normoglycemia in both men and women. Elevated triglyceride levels were observed in NTG only among women. However, there were no differences between the concentrations of total cholesterol and high-density lipoproteins among men and women depending on the presence of NTG. In general, it was found that in both men and women with hyperglycemia, RF CHD was more pronounced than in normoglycemia. Studies in the United States have shown that among obese individuals,

there is an increased release of insulin in response to glucose load [12]. However, the authors do not specify what comes first in this regard: whether the presence of obesity leads to an increased release of insulin or hyperinsulinemia contributes to the development of obesity. According to the Fremmingham study, the role of DM and NTG as RF CHD increases significantly when they are combined with other RFs [14]. Observation of the population of 3595 people for 16 years allowed the authors to establish that DM and NTG lead to a significant increase in fibrinogen and triglycerides in the blood, as well as an increase in blood pressure and body weight. The combination of these factors contributes to an increase in the risk of CHD formation.

In Uzbekistan, as early as 1985-1990, a study of the prevalence of DM in the regions of the republic was carried out [6]. At the same time, 5000 people were examined in each region. The prevalence of DM was 1.9% and NTG was 3.6% to 4.0%. This study shows that the true incidence of DM significantly exceeds the official statistics. The results of another population study conducted in Tashkent [4] indicate a significant increase in the incidence of DM and NTG. Between 1980 and 1988, the prevalence of DM among men aged 40-59 increased from 3.9% to 6.92%, and NTG from 29.3% to 38.93%. According to the American Heart Association, more than 10 million Americans suffer from diagnosed diabetes [5]. The number of new cases of DM is 798,000 per year. The prevalence of DM among black men is higher than among white men.

Thus, summarizing the literature data, it can be concluded that CHD is one of the most significant problems of modern medicine. This is determined by the wide prevalence of CHD and the high mortality associated with this disease. In most countries of the world, including Uzbekistan, the number of patients with CHD continues to grow. The formation of CHD, its course and outcomes are influenced by various risk factors for this disease.

The role of a number of RFs in the development of CHD (such as hypertension, obesity, age, etc.) is beyond doubt. One of the most significant RFs of CHD is DM. However, the literature on the role of NTG as RF CHD differs significantly. Meanwhile, in some cases, NTG can precede the development of DM and, in a certain sense, it can be considered as a state of "pre-disease" in relation to DM. Hyperglycemia, including latent hyperglycemia, often proceeds with hyperinsulinemia, which is considered one of the components of the "metabolic" syndrome that plays an important role in the formation of cardiovascular diseases, including coronary artery disease. Differences in the literature, often contradictory, on the role of NTG in the formation of CHD may be associated with rather significant differences in the methodology of research. Along with a fairly large number of one-time and long-term prospective studies, there is a lack of work on the dynamics of CHD development among patients with NTG in "end-to-end" populations. Based on the above, further study of the role of NTG in the formation of CHD and the outcomes in this disease is of particular interest.

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