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Review Article

Contemporary Problems of Cardiovascular Disorders at Diabetes Mellitus

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Abstract: At the present time, the number of patients with comorbid cardiometabolic dysfunctions, which cause more early onsets of cardiovascular diseases (CVD) and their quick progressions, has increased. Results of studies permit to suggest that such high comorbidity of cardiovascular diseases and diabetes mellitus (DM) are caused by commonness of pathogenic mechanisms. Special attention should be given to predictors of cardiac dysfunctions occurrence in cases of diabetes mellitus, which will allow to improve prognosis for a patient and to decrease risk of death. In the article, there are outlined contemporary problems of important cardiovascular dysfunctions in cases of progression of diabetes mellitus; that will allow to draw attention of doctors to the most complicated problems of comorbid cardiometabolic disorders.

Keywords: Diabetes Mellitus, Cardiovascular Disease, Chronic Heart Disease, Arterial Hypertension

1. Epidemiology and Factors Provoking the Prevalence of Diabetes Mellitus in Individual Regions

A progressive increase in the incidence of diabetes worldwide has become one of the most important global health problems of the 21st century [1-3]. Thus, in 2015, approximately 415 million people had newly diagnosed diabetes, that is equal to 8.8% of population aged 20–79 years. The annual increase in the incidence of diabetes accompanied by a significant increase in the number of related complications.

Although the pathogenesis of diabetes is well understood and the modern strategy of treatment is developed, many experts suggest that the number of patients with this disorder will increase further [4, 5]. Mainly this is because the governments of many countries have still not fully realized the severity of the social and economic consequences of diabetes and do not take the appropriate preventive measures [6].

About 75% of diabetic patients live in the countries with low and middle income. According to experts, if these trends continue, the number of patients will increase to 642 million people by 2040 [1, 2, 7]. In this case, every tenth person will be diagnosed with diabetes. The greatest growth will occur in regions with underdeveloped economies and low income levels. This is primarily because the high cost of treatment of diabetic patients that requires large amounts of insulin and specialized equipment, is a significant economic burden on poor countries and their national health system. Low economic opportunities in these countries are one of the factors for the increase in the incidence of diabetes. Most countries diabetes spends makes from 5 to 20% of total health care costs [1, 8]. These high costs confirm the importance and seriousness of the problems associated with the high prevalence of diabetes.

However, it should be noted that in regions with a high quality of life there is also a high incidence of diabetes. Thus, despite the fact that in North America and the Caribbean Region is the highest income per person, one in eight people is diagnosed with diabetes [2, 8]. One of the reasons is that DM doesn't always present a clear clinical pattern. Therefore, the diagnosis of diabetes in some patients is often established with a long delay, and in some patients, the diagnosis is not even recognized. According to the researches in 2015, diabetes is not diagnosed in every second patient [7]. According to the estimation of the international diabetes Association, 193

million people with diabetes (46.5% of all diabetic patients) have not been diagnosed, and the patients did not receive the necessary treatment. The earlier diabetes is diagnosed and treatment is started, the less likely the progression of the disease and its complications is. Therefore, at present, the timely diagnosis of diabetes and provision of care to such patients is the most relevant problem.

According to some authors [7-9], there is the greatest number of children (about 140 000) diagnosed with type 1 diabetes in Europe. Moreover, the annual increase in patients is 21 600, and in 2015 the number of children with diabetes for the first time exceeded half a million children.

Currently, there are the following types of diabetes: 1) type 1 diabetes; 2) type 2 diabetes; 3) gestational diabetes mellitus; 4) other specific types of diabetes.

According to the literature, countries with high income have 87 to 91% of patients have type 2 diabetes, 7 to 12%—type 1 diabetes and 1–3%—other types of diabetes [10, 11]. Unfortunately, in countries with poor quality of life there were no researches of the correlation between type 1 and type 2 diabetes. The incidence of type 1 diabetes is increasing by 3% worldwide every year. In most countries with high income type 1 diabetes is more common in children and adolescents [12-14]. Approximately 86 000 children each year are firstly diagnosed with type 1 diabetes. If the insulin therapy time is not performed promptly, the life expectancy of patients is significantly reduced.

The high prevalence of type 2 diabetes is due to social changes: ageing of the population, urbanization increasing, low physical activity, high sugar consumption, low intake of fruit and vegetables, etc. [2, 5, 15, 16]. With increasing age, the number of people of both sexes with DM is increasing [1, 2, 7]. Thus, in 2015, the diabetes was diagnosed in 320.5 million people of working age (20 to 64 years) and in 94.2 million patients aged from 65 to 79 years. The number of men suffering from diabetes is 15.6 million higher than women (215.2 million men and women 199.5 million) [7]. In the future, from 2015 to 2040, a slight gender difference is predicted. The authors believe that by 2040 this difference will decrease to 15.1 million, but the vast number of patients will remain male (328.4 million men against 313.3 million women).

Most diabetic patients are city dwellers. According 2015, the city is home to 269.7 million patients with diabetes, and in rural areas there are 145.1 million patients [1, 7, 17]. In countries with low and middle income the number of people with diabetes in urban areas is 186.2 million, and in rural areas 126.7 million. By 2040, the number of diabetic patients living in the city will grow to 477.9 million, and in rural areas to 163.9 million.

It is known that complications of diabetes are a major cause of disability, deterioration in quality of life and premature death. More than 50% of patients with diabetes suffer from complications of varying severity [2, 7, 18, 19]. Cardiovascular diseases are the main cause of death among patients with diabetes. More than 50% of all deaths in diabetes are caused by cardiovascular diseases. In most cases, a high mortality rate is due to coronary heart disease. It should be noted that the statistics of mortality in DM is not always objective and the mortality may be even greater. This is due to the fact that medical statistics often underestimates the number of deaths caused by diabetes, and more than a third of countries have no mortality statistics for diabetes [20]. The worst statistics for deaths from diabetes was recorded in 2015. This year, about 5 million people aged 20 to 79 years died from DM, which corresponds to approximately one death every six seconds [1, 2, 7]. This is the cause of 14.5% of all deaths among people in this age group.

The World Health Organization has determined that not only diabetes, but also increased glucose in blood is the third largest risk factor for early mortality after high blood pressure and smoking [4, 21, 21]. Impaired glucose tolerance and fasting glucose levels are diagnosed when the level of blood glucose is above normal but not high enough to be classified as diabetes. The people with impaired glucose tolerance have a high risk of type 2 diabetes development. Although not all people with impaired glucose tolerance develop diabetes, 318 million people worldwide (6.7% of adult population) are diagnosed with impaired glucose tolerance [7, 23, 24]. According to preliminary estimates, the number of patients with impaired glucose tolerance will increase from 2015 and 2040. The vast majority (69.2%) of these patients live in countries with low and middle income. According to preliminary estimates, by 2040 the number of people with impaired glucose tolerance will increase to 482 million (about 7.8% of the adult population). Impaired glucose tolerance significantly increases the risk of developing type 2 diabetes and cardiovascular diseases [25, 26].

The pathogenesis of DM is a progressive increase in blood glucose as the result of impaired insulin secretion by β-cells, its mechanism of action, or the development of insulin resistance of tissues. The combination of multiple pathogenic disorders is most common. In DM, there is not only a disorder of carbohydrate metabolism, but also protein and lipid metabolism. All these metabolic disorders exacerbate atherosclerotic vascular damage and significantly increase the risk of cardiovascular dysfunctions.

Clinical symptoms of diabetes are not highly specific, they can often be seen in other metabolic disorders. Thus, in DM polydipsia, polyuria, nocturia, impaired visual acuity, fatigue, weight loss, hunger, paresthesia, frequent infections etc. occur. The most common signs at DM are neuropathy, retinopathy, nephropathy, cardiovascular dysfunction, gastrointestinal and urogenital disorders.

2. Role of Insulin Resistance and Diabetes Mellitus in Pathogenesis of Coronary Heart Disease

Among the cardiological patients, diabetes is diagnosed in 50%, and among cardiac surgery patients in 15 to 40%. The

coronary artery disease (CAD) develops for 20 years earlier among the diabetic patients than those without diabetes [27-29]. CAD is the major cause of mortality in patients with diabetes. CAD is characterized by rapid progress and multivessel coronary artery damage [30, 31].

CAD occurs by 2–4 times more often in diabetic patients [32]. Diabetic patients more commonly have the distal atherosclerotic lesions of coronary arteries, left ventricular dysfunction and other complications. CAD is the cause of death of diabetic patients in 75% of cases [33]. The risk of coronary death in women with diabetes is 2 times higher than in men [34].

The diabetes diagnostic criteria are often established more than 10 years later after the onset of metabolic disorders [17, 35, 36]. The Whitehall Study (1991) revealed the increased risk of CAD not only at overt diabetes, but at its subclinical forms [27]. Therefore, the preventive measures for cardiovascular disease are important to identify early changes in carbohydrates metabolism. MRFIT (1982) results indicate that diabetes is an independent risk factor for CAD [36]. This is also confirmed by several studies, which found that patients with clinical manifestation of CAD and patients with DM without CAD have the same risk of coronary complications [38].

The study results allow suggesting that such a high comorbidity of CAD and DM is due to the similar pathogenic mechanisms [4, 27, 29]. A number of authors believe that in DM, the process of progression of atherosclerosis is similar with such in non-diabetic patients [27]. This is evidenced by the increase of anti-inflammatory cytokines, an increase in procoagulants, fibrinolysis disorder, increased inflammatory reaction. In DM, there is an inflammatory reaction, which is accompanied by formation of immune complexes and the release of a large number of cytokines and reactive oxygen forms and increased expression of matrix metalloproteinases. Severe immunological reaction not only initiates the process of atherosclerosis, but leads to plaque rupture. In addition, there are a number of mechanisms of CAD progression that are specific for DM [39]: 1) metabolic (hyperglycemia, free fatty acids, insulin resistance, diabetic dyslipidemia); 2) oxidative stress and glycosylation; 3) endothelial dysfunction; 4) inflammation; 5) thrombotic (increase of fibrinogen level, the overexpression of plasminogen activator inhibitor-1, platelet activation).

In general, it can be concluded that the development and progression of CAD in DM is potentiated by specific pathogenetic mechanisms. Currently, numerous studies have shown that diabetes trigger different links of the pathophysiological mechanisms that cause dysfunction of the cardiovascular system. In the initial stages of type 2 diabetes, insulin resistance is accompanied by insulin hypersecretion, which also contributes to the worsening of cardiovascular dysfunctions. Increased insulin production in type 2 diabetes reduces the secretion of vasodilators and increases the adhesion of cardiomyocytes [4].

Diabetes leads to morphological and functional alterations of myocardial structure with the development of diabetic cardiomyopathy [4]. At this condition, the hypertrophy and local cytolysis of cardiomyocytes, the interstitial tissue sclerosis, the formation of a large number of elastic fibers and deposition of glycogen occur [40]. This also changes the structure of organelles in the cardiomyocyte: an extension of the sarcoplasmic reticulum, Golgi apparatus, micromechanics, lipid infiltration. The decrease in the number of glucose transporters GLUT-1 and GLUT-4 in the membrane of the cardiomyocyte in diabetes causes insulin resistance. These changes underlie disorders of adenosine triphosphate synthesis, the changes of the action potential of the cardiomyocyte and its electrical instability [41]. Insulin resistance enhances lipolysis with the formation of toxic metabolic products that increase cardiomyocyte sensitivity to adrenaline [4]. Oxidative stress on the background of hyperglycemia causes the formation of highly toxic peroxide compounds that damage the cardiomyocyte structure. The foci of necrosis and areas of fibrosis contribute to the formation of re-entry circles, which increase the risk of cardiac arrhythmias [42]. Probably, these disturbances may underlie the mechanisms of sudden cardiac death in type 2 diabetes. Many studies have confirmed that type 2 diabetes doubles the risk of sudden cardiac death [43-45]. Epidemiological studies have shown that the type 2 diabetes increases the frequency of sinus tachycardia by 1.58 times, the frequency of supraventricular extrasystole by 1, 7 times, paroxysmal atrial fibrillation almost by 8 times [46-47].

The studies have revealed increased *QT* interval in patients with diabetes, which is a predictor of sudden cardiac death occurrence [48]. The *QTc* increase for>460 ms is found to increase the risk of death by 2 times. In type 2 DM, the variance of *QTc* by more than 0.08 times increases the risk of death by 1.26 times and can serve as a predictor of sudden cardiac death.

In 1995, Stern proposed a theory that diabetes and atherosclerosis have common initial pathogenetic basis and, on this basis, it is necessary to build a common treatment strategy [27]. According to this theory, endothelial dysfunction plays an important role in the development of diabetes and atherosclerosis. This theory provides a new conceptualization of prevention and treatment strategies of comorbid diseases (CAD+DM). On the one hand, both ACE inhibitors and statins improve endothelial dysfunction and anti-inflammatory reactions [27]. This reduces the progression of atherosclerosis and the risk of developing diabetes. On the other hand, hypoglycemic drugs (Metformin, thiazolidinediones) also improve endothelial function and production of proinflammatory cytokines.

Another important predictor of cardiovascular mortality is a glycemia variability [49-50]. The increase of glycemia variability in patients in the intensive care unit increased the mortality rates by 3.12 times. The experimental and clinical studies have found that high variability of glycemia is accompanied by an increase of adhesion of monocytes to the vascular endothelium, the activity of oxidative stress increase, and inflammatory cytokines [51-53]. Variability of glycemia contributes greater to the increase in cardiovascular mortality than prolonged elevation of blood glucose.

One of the main directions of patients treatment is dyslipidemia correction. According to the US study, 69% of diabetic patients have abnormal lipid metabolism [54]. The abnormal amount of lipids and the lipid fractions relation were found. 17 randomized studies have shown that the increase in triglyceride levels in men increased the risk of CVD by 30% and in women up to 70%. Lipid disorders persist even after correction of blood glucose level, which gave reason to define this as diabetic dyslipidemia. Currently, the first-line drugs for the correction of dyslipidemia in DM are statins. This strategy is based on numerous international studies: 4S, ALLHAT-LLT, ASCOT-LLA, ASPEN, CARDS, CARE, HPS, LIPID [55]. Another effective tool that increases HDL levels are fibrates [5, 27, 29]. In studies, the fibrates have shown lower efficiency in comparison with statins because they have less effect on low-density lipoproteins. At this, numerous studies (BIP, DAIS, HHS, VAHIT) show the effectiveness of the primary and secondary prevention of CVD.

Treatment strategy of diabetic patients should be aimed at reducing the risk of CAD complications. It is comprised in the correction of hyperglycemia, insulin resistance, hypertension, and dyslipidemia [4, 56]. Besides well-known cardiovascular risk factors (hypertension, inflammation, dyslipidemia), diabetes causes specific risk factors–insulin resistance and hyperinsulinemia. At this, by the time of diagnosis the sensitivity of peripheral receptors to insulin is decreased by 70% and insulin secretion by 50%. Hyperglycemia, insulin resistance and dyslipidemia are the main specific factors that lead to changes in the vascular wall. In this regard, the normalization of a set of risk factors will reduce the incidence of CVD in DM.

Collateral blood flow is a compensatory mechanism that helps to improve blood flow to the myocardium in ischemic heart disease [28, 57]. According to the researches, the development of collateral circulation in the myocardium significantly reduces the mortality of patients [58]. However, the efficiency of the collateral circulation in CAD is often determined by individual characteristics [58, 59]. The insulin resistance and impaired glucose tolerance are the factors, which alter collateral blood flow [60].

CAD in diabetic patients is characterized by high lethality and mortality [4, 29, 61, 62]. Within 5 years, more than half of diabetic patients die from myocardial infarction, and without diabetes, one-third of patients die from myocardial infarction. Moreover, diabetes increases the risk of recurrent myocardial infarction by 60%. The clinical pattern of CAD in DM is characterized by the following features [63]: 1) high frequency of painless forms of ischemic heart disease and myocardial infarction; 2) high risk of sudden death; 3) high frequency of postinfarction complications.

According to studies, painless myocardial ischemia is one of the common forms of CAD in patients with type 2 diabetes [28, 64]. E. Cosson with co-authors (2011) showed that about 30% of heart attacks intercourse without a pain syndrome that leads to delayed emergency care and poor prognosis [65]. In DM, the frequency of painless forms of myocardial infarction increases by more than 2 times compared to patients without carbohydrate metabolism abnormalities.

3. Interdependence of Arterial Hypertension and Diabetes Mellitus, as Underlying Cause of Comorbid Disorders

Diabetic patients have high prevalence of hypertension [66]. Hypertension significantly increases not only the risk of other cardiovascular dysfunctions, but also nephropathy, retinopathy and other disorders [67].

Hypertension in diabetes is characterized by an earlier increase in systolic blood pressure and a high prevalence of isolated systolic hypertension at any age compared to people without diabetes [68]. Type 2 diabetes hypertension is more common in women than in men [69].

In 80% of cases, the reason of the hypertension development in type 1 diabetes is diabetic nephropathy, 10%–essential hypertension, 5–10%–isolated systolic hypertension, 1–3%–endocrine dysfunction. And diabetic nephropathy occurs in approximately 40% of cases in diabetic patients [68, 70]. With the progress of diabetic nephropathy the risk of developing hypertension increases. Diabetic nephropathy with the combination of hypertension and diabetes greatly increases the risk of cardiovascular dysfunctions.

One of the pathophysiological links of type 2 diabetes is insulin resistance [68, 71]. Currently, the high correlation between insulin resistance and hypertension in both obese patients and patients with normal body weight has been proven. Hyperinsulinemia leads to increased activity of the sympathetic nervous system, reabsorption of sodium, the increase in circulating blood, the increase in intracellular sodium and calcium, the proliferation of smooth muscle cells.

Several studies have shown that hyperinsulinemia causes an increase in noradrenaline in the blood for 64% [29, 72]. It is supposed that the mechanism of action of insulin on the sympathetic nervous system is due to its penetration through the hematoencephalic barrier and direct action on the central nervous system, and in the periventricular region of the hypothalamus, insulin binds to the receptor and reduces the activity of the parasympathetic nervous system, which leads to increased heart rate. The increase in sympathetic tone causes spasm of peripheral vessels and increase peripheral vascular resistance.

Patients with hypertension are also at high risk of developing diabetes mellitus type 2 [73, 74]. Hypertension is an independent risk factor for diabetes development. Patients with hypertension have by 2.5 times higher risk of diabetes development within five years [75]. Hypertension and microalbuminuria, regardless of blood pressure level [76], may lead to the diabetes development a few years earlier and reduce patient survivance [67].

Risk factors of type 2 diabetes mellitus and cardiovascular

disease are often complementary to each other and significantly increase the risk of adverse outcomes [77]. Diabetes is a disease in which there is substantial loss of micro- and macrocirculatory channel. Atherosclerotic vascular disease is found in almost 90% of patients, diabetic retinopathy occurs in 80-90% of diabetic patients, and nephropathy in 35-40% of patients [29, 68].

4. Conclusions

Analysis of results of clinical studies of diabetes mellitus convinces that treatment of this disease independently of dysfunctions encouraged by it in other organs and systems cannot be effective as interdependent disorders aggravate each other and predetermine unfavorable outcome of the disease. That is why identification of fundamental mechanisms of interdependent disorders, when one disease encourages intricate complex of associated (comorbid) dysfunctions, is one of the most urgent problems in development of new approaches of treatment of DM. By prescribing antidiabetic medication a doctor must be convinced that their administration over years and often for entire life of a patient will decrease the risk of dysfunctions of cardiovascular system.

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