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Type 2 Diabetes and Chronic Heart Failure

Saidova L. B., Saidova F. I.
Bukhara State Medical Institute

Abstract: The article presents a literature review of the epidemiology, pathogenesis and significance of increased risk of cardiovascular disease in patients with diabetes and prediabetes . The hyperglycemia and insulin resistance seen in diabetes and pre-diabetes results in an increase in reactive oxygen species, which triggers intracellular molecular signaling. The resulting prothrombotic the state and increase in inflammatory mediators accelerate atherosclerotic changes and the development of macrovascular complications. Individuals with diabetes or pre-diabetes have a higher risk of developing myocardial infarction, stroke, and peripheral arterial disease.

Key words: diabetes mellitus; macrovascular complications; hyperglycemia; insulin resistance; prediabetes.

Introduction. Diabetes mellitus is the most common human endocrine disease, which is characterized by a complex of disorders in the secretion and functions of insulin, glucose productivity. This disease is a major cause of kidney failure, blindness, amputation of the lower extremities, and a major factor in the development of cardiovascular disease (CVD). Therefore, many patients suffer complications at diagnosis or shortly thereafter. A strong association between diabetes and CVD has been observed in many studies independently of other traditional CV risk factors [4]. Being the most common cause of death in patients with diabetes mellitus, CVD mortality accounts for 52% of deaths in T2DM and 44% in type 1 diabetes mellitus (T1DM) [6].

The main cause of type 2 diabetes mellitus (DM2) is insulin resistance , that is, a significant decrease in the sensitivity of body cells to the effects of insulin. Violations occur in the early stages of the development of the disease. At the molecular level, numerous defects in insulin signaling affect insulin resistance, reduce the number of insulin receptors, reduce the activity of receptor kinases , phosphorylate intracellular substrates, and affect translocation and activation of the glucose transporter. It has recently been shown that pre-diabetic conditions characterized by impaired fasting glycemia or impaired glucose tolerance (IGT) are also associated with cardiovascular morbidity and mortality [17]. Therefore, it is important to better understand the pathophysiology in order to define a new approach to the treatment or prevention of macrovascular disease . complications at an early stage. This article attempts to review the current understanding of the epidemiology, pathogenesis, and significance of the increased risk of cardiovascular disease in patients with diabetes and prediabetes .

Insulin resistance in the pathogenesis of CVD

It is believed that hyperglycemia and insulin resistance, along with other factors, contribute significantly to atherosclerotic changes and the pathogenesis of macrovascular complications in diabetes. Although both are commonly seen in diabetic patients, insulin resistance usually develops years before hyperglycemia becomes clinically significant.

Obesity plays an important role in the pathogenesis of insulin resistance , which is commonly observed in patients with type 2 diabetes [2]. By releasing free fatty acids and inflammatory mediators, adipose tissue alters lipid metabolism, increases the production of reactive oxygen species (ROS) and enhances systemic inflammation [3]. Insulin resistance is associated with abnormal function of glucose transporter type 4 (GLUT-4), an insulin-mediated glucose transporter primarily found in fat and muscle cells. When free fatty acids bind to the Toll -like receptor (TLR), PI3 kinase (PI3K) and Akt activity is suppressed, which reduces GLUT-4 expression [1], resulting in a reduced insulin binding response.

Meanwhile, decreased PI3K and Akt activity also leads to inactivation of endothelial nitric oxide synthase (eNOS), which decreases nitric oxide (NO) production. NO activity is further reduced by increased ROS formation caused directly by obesity and insulin resistance due to the NO inactivating effect of ROS. NO is a key molecule in the maintenance of normal endothelial cell function. Obesity and insulin resistance caused a decrease in NO activity, thus contributing to endothelial dysfunction and subsequent atherosclerotic changes.

In addition to downregulating PI3-kinase and Akt , free fatty acid binding to TLR also activates the nuclear factor NF- kB , which triggers the transcription of inflammatory molecules, contributing to insulin resistance and atherosclerosis. Blockade of NF- κB in a mouse model led to a decrease in systemic oxidative markers, expression of adhesion molecule genes, and macrophage infiltration, processes that contribute to the development of atherosclerosis [10], which indicates an important role of NF- κB in the development of CVD.

In parallel with atherosclerotic changes, thrombosis plays an important role in the development of macrovascular complications in diabetes mellitus. Under physiological conditions, insulin inhibits thrombosis and increases fibrinolysis , and insulin resistance creates a prothrombotic state [1]. Lack of insulin also leads to calcium accumulation in platelets, which increases platelet aggregation, further contributing to the development of cardiovascular disease.

Hyperglycemia is also involved in the pathogenesis of cardiovascular complications of diabetes mellitus. It increases the production of ROS, which inactivate NO [14], which subsequently leads to endothelial dysfunction. On the other hand, increased ROS production contributes to cardiovascular disease by causing activation of protein kinase C (PKC). It has been shown that PCC acts as a group of enzymes that can affect the function of other cellular proteins, vascular cell growth and apoptosis , permeability, extracellular matrix synthesis, and cytokine production [8]. Activation of the PCC leads to changes in vascular homeostasis and predisposition to vascular complications. PCC, in turn, induces ROS production in vascular cells, perpetuating the vicious cycle. PKC also affects endothelial cells in various molecular ways, including NO inactivation and overproduction of vasoconstrictors. As mentioned above, PCC increases ROS production, which decreases NO availability. At the same time, PKC directly reduces eNOS activity by inhibiting eNOS gene expression and induces the synthesis of vasoconstrictors: production of endothelin-1, a molecule involved in platelet aggregation and vasoconstriction ; increases cyclooxygenase-2 expression activity, which increases thromboxane A2 and reduces prostacyclin production . The combination of reduced NO availability and increased production of vasoconstrictors contributes to the development of vascular atherosclerotic changes.

Hyperglycemia and PKC-induced ROS production cause inflammatory changes in the vascular endothelium. With an increased level of ROS, the expression of the p65 subunit of the nuclear factor NF- κB and nuclear translocation are enhanced, which leads to an increase in the transcription of genes encoding inflammatory factors [9]. Increased production of inflammatory mediators leads to adhesion of monocytes, extravasation and formation of foam cells, which further contributes to the development of atherosclerosis. Chronic hyperglycemia is also responsible for cardiovascular injury through activation of other major biochemical pathways, including polyol pathway flux, increased formation of advanced glycation end products , increased expression of the glycation receptor and its activating ligands , and increased activity of the hexosamine pathway [3].

Risk of coronary heart disease in patients with diabetes mellitus

Diabetes is associated with an increased risk of coronary heart disease (CHD). In patients without prior myocardial infarction (MI), the 7-year risk of MI is 20.2% and 3.5% for diabetics compared with non-diabetics , respectively. Similarly, in patients with a history of MI, the 7-year risk of MI is 45.0% and 18.8% for diabetics and nondiabetics, respectively [7]. The 7-year risk of MI in diabetic patients was comparable to the risk of MI in non-diabetic patients with a history of MI, suggesting that diabetes is a significant contributor to MI and may perhaps be considered equivalent to CAD risk. However, a population-based study that included Danish adults aged 30 years and older found that diabetes increased the risk of CHD, but not to a degree equivalent to risk, over a 5-year follow-up. In this study, diabetic men had a relative risk (RR) of MI of 2.30, which was lower than that of non-diabetic men with prior MI (who had a RR of 3.97) [15]. Similar results were observed for CHD mortality, all CVD incidence, and CVD mortality. In a meta-analysis of 13 studies, diabetic patients without a history of MI had a 43% lower risk of developing CAD than non-diabetics with a history of MI [7].

Diabetes mellitus also has a negative impact on the treatment of coronary artery disease. When evaluating percutaneous coronary intervention performed in patients with ST-segment elevation MI, patients with diabetes had a higher 3-year risk of target lesion revascularization , recurrent MI, and all-cause mortality compared with patients without diabetes [12]. An analysis of patients treated with a drug-eluting stent after MI found that diabetes was more common in patients who developed stent thrombosis than in those who did not. Patients with diabetes are 1.8 times more likely to develop stent thrombosis than patients without diabetes 1 year after stenting [13]. Regarding coronary bypass surgery, patients with diabetes had a significantly higher operative mortality with a relative risk of 1.67 compared to patients without diabetes. Interestingly, due to the intense antiplatelet effect of prasugrel in patients with DM, there is a more significant reduction in the incidence of MI compared with individuals without DM [18]. This discovery may indicate a significant role for platelet activation and aggregation in the development of coronary artery disease in diabetes.

The association of cardiovascular disease with prediabetes

Violation of glucose metabolism plays an important role in the development of atherosclerosis and cardiovascular diseases. The aggregate evidence suggests that elevated plasma glucose is a risk factor for cardiovascular disease, independent of the presence of diabetes. Pre-diabetic status can be defined by fasting glucose (5.6–6.9 mmol /l), IGT (2-hour post-charge glucose 7.8–11.0 mmol /l), and/or a level of 5.7–6. 4% [16].

Compared to those with fasting glucose levels of 3.90 to 5.59 mmol /l, those with levels above 5.60 mmol /l (i.e., prediabetics or diabetics) have an increased risk of developing coronary artery disease. In the Heart study Outcomes Prevention _ Evaluation (HOPE) the risk of cardiovascular events (MI, stroke and death from cardiovascular diseases) in the next 4.5 years increases by almost 9% for each 1 mmol / l increase in fasting glucose . Each 1% increase also correlated with a higher risk of CV events, with a relative risk of 1.07. These relationships were independent of other cardiovascular risk factors (age, gender, blood pressure, and hyperlipidemia) and remained significant after adjusting for diabetic status [7]. Similarly, the Epidemiology of Diabetes: A Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study showed a correlation between fasting plasma glucose levels and CVD-related mortality, independent of diabetic status. The relationship between fasting plasma glucose and CV-related mortality was a “J-shaped” curve, with no threshold effect observed at high glucose levels.

IGT and appear to be more correlated with CVD risk than fasting glucose levels. In a separate analysis, the incidence of CVD during 4 years of follow-up correlated with fasting glucose, glucose tolerance, and HbA1c levels with a relative risk of 1.13 for every 0.7 mmol /L increase in fasting glucose, 1.26 for every 2.1 mmol / l increase. postprandial glucose and 1.24 for every 0.7% increase in HbA1c. When analyzed in the same model, fasting glucose had a much weaker

effect, while postprandial glucose still significantly increases CVD risk. In a meta-analysis of 53 cohort studies, patients with pre-diabetic conditions were found to be at increased risk for cardiovascular disease, coronary artery disease, and stroke. Patients with IGT had a higher risk compared with patients with IGT [11].

Conclusion. Thus, both diabetes and pre-diabetes predispose patients to the development of macrovascular complications of diabetes through complex molecular pathways, including hyperglycemia and insulin resistance. While intensive glycemic control alone may not reduce mortality and major CV events, a global approach consisting of lifestyle modification, reduction of hyperglycemia, and treatment of diabetes-related CV risk factors is useful for the risk profile of CVD. -vascular disease in these patients; therefore, the goal of blood glucose control must be tailored to individual patients.

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