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ROLE OF ENDOTHELIAL DYSFUNCTION IN TYPE 2 DIABETES MELLITUS & CARDIOVASCULAR DISEASE

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ABSTRACT
Type 2 diabetes mellitus is associated with systemic insulin resistance, which promotes hyperglycemia and dyslipidaemia. These metabolic abnormalities account for increased cardiovascular risk. Endothelial dysfunction contributes to the pathogenesis and clinical expression of atherosclerosis and is associated with Type 2 diabetes mellitus and insulin resistance in experimental and clinical studies. Cardiovascular disease is a major complication of diabetes mellitus, and improved strategies for prevention and treatment are needed. Endothelial dysfunction contributes to the pathogenesis and clinical expression of atherosclerosis in diabetes mellitus. The diabetic vascular disease develops endothelial dysfunction, which is characterized by a loss of NO and development of a pro-inflammatory vascular phenotype that promotes atherosclerosis and cardiovascular disease.

KEYWORDS: Type 2 diabetes mellitus atherosclerosis and cardiovascular disease.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a major risk factor for cardiovascular disease. This condition is associated with insulin resistance and related metabolic abnormalities, including hyperglycemia, hypertension, visceral adiposity and dyslipidemia.[1,2] Current efforts to reduce cardiovascular disease (CVD) focus on risk factor reduction, but diabetics continue to have increased risk despite aggressive interventions.[3,4] Intensive glucose control has disappointing effects on the incidence of cardiovascular events.[5,6,7,8] Thus, there is a need for new approaches to the prevention and management of cardiovascular risk in diabetes. The key mechanism of diabetic vascular disease is the development of endothelial dysfunction, which is characterized by a loss of Nitric Oxide (NO) and development of a pro-inflammatory vascular phenotype that promotes atherosclerosis and cardiovascular events. Recent research work explained the mechanisms of endothelial dysfunction, which include impaired cell signalling required for activation of eNOS, increased oxidative stress and activation of pro-inflammatory signalling mechanisms. Endothelial Dysfunction (ED) refers to an impairment of the ability of endothelium to properly maintain vascular homeostasis.[9] Although the term is often used in reference to a loss of bioavailable NO, ED also reflects increased production of vasoconstrictors and disturbed regulation of inflammation, thrombosis and cell growth in the vascular wall.[9,10] There are many studies, which linked ED and resultant atherosclerosis with insulin resistant states such as obesity and diabetes.[11,12,13,14] The endothelium plays a key role in the regulation of arterial tone and blood flow. In this regard, the endothelium orchestrates the production of vasodilator molecules such as NO, prostacyclin, and endothelium-derived hyperpolarizing factor (EDHF), and vasoconstrictors, including endothelin-1 (ET-1) and angiotensin II.[9] In this article the association of ED with T2DM and CVD is reviewed.

Type 2 Diabetes Mellitus and Cardiovascular Disease

Both IFG and IGT are characterized by insulin resistance. Previous studies demonstrated that individuals with IGT have insulin resistance, whereas individuals with IFG have β-cell defect when related to the ambient glucose levels and the degree of insulin sensitivity.[15] Pre-diabetic subjects often have a clustering of different CVD risk factors, insulin resistance, obesity, central obesity, elevated blood pressure, elevated total triglycerides and low HDL cholesterol. T2DM patients are at least as insulin resistant as pre-diabetic subjects. Therefore, insulin resistance–related risk factors in the pre-diabetes and insulin resistance–related and hyperglycemia–related risk factors in T2DM involve atherothrombosis. Metabolic changes in pre-diabetes include impaired endothelial function, subclinical inflammation[16], changes in adipokines, development of atherogenic dyslipidemia, increased levels of free fatty acids (FFAs) and changes in thrombosis and fibrinolysis.[17] Insulin resistance and diabetes cause accelerated atherosclerosis via several mechanisms affecting endothelium, vascular wall,

smooth muscle cells and platelets. Insulin resistance is associated with impaired vasodilatation, increased oxidative stress and high concentration of FFAs, vasoconstrictors, cellular adhesion molecules, plasminogen activator inhibitor-1 (PAI-1), cytokines and other mediators of low-grade inflammation and thrombosis formation. T2DM further enhances these abnormalities and induces multiple adverse changes in the function and structure of vessel wall.[18]

Clustered metabolic disorders (hyperglycemia, dyslipidemia and hypertension) like metabolic syndrome, contribute to development and progression of CVD. Genetic susceptibility and environmental factors, including poor nutrition, obesity and lack of physical activity, also play a significant role in developing CVD. Mature adipocytes produce several adipokines (pro-inflammatory mediators) including C-reactive protein (CRP), IL-6, TNF-α, leptin, resistin, angiotensinogen and PAI-1 which are associated with developing CVD.[19]

Dyslipidemia

As T2DM patients have a high risk of developing CVD, the cause risk is partly due to dyslipidaemia, which is characterized by elevated serum triglycerides, reduced high-density lipoprotein cholesterol (HDL-c) and low or normal low-density lipoprotein cholesterol (LDL-c). Reduced HDL-c levels and increased triglyceride concentrations are the important characteristics of dyslipidemia in T2DM patients.[20,21] Even slight elevations of LDL-c in T2DM patients are associated with a substantial increase in CVD. When glycaemic control is poor in T2DM, postprandial triacylglycerol-rich lipoproteins (chylomicrons and very low-density lipoprotein (VLDL) particles) are increased, which enhance oxidative stress and impair endothelial function directly and indirectly by increasing the production of LDL-c particles and by reducing HDL-c.[22] Measuring LDL-c provides no information on other lipoprotein molecules or the atherogenicity of the LDL-c particles. As each pro-atherogenic VLDL, intermediate-density lipoprotein (IDL) and LDL-c particle has one apolipoprotein B (apo B) attached to the surface, the serum apo B concentration yields the number of atherogenic particles. Further, LDL-c particles are considered to be at least as atherogenic as larger LDL-c particles.[23] Serum apolipoprotein A-I (apo A-I), which is a protein attached to the HDL-c particle, is an overall index of the concentration of HDL-c in plasma. HDL particles transport cholesterol from peripheral tissue and vessels to the liver. Thus, the balance between pro-atherogenic apo B and anti-atherogenic apo A-I has been suggested to be more predictive compared with conventional lipids in the estimation of cardiovascular risk.[24]

Intimal Medial Thickening in Type 2 Diabetes Mellitus

Arteries are vessels that carry blood away from the heart. Carotid arteries are blood vessels that supply blood to the head, neck and brain. One carotid artery is position on each side of the neck. The right common carotid artery branches from the brachiocephalic artery and the left common carotid artery branches from the aorta. The basic constituents of blood vessel walls are endothelial cells, smooth muscle cells (SMCs) and extracellular matrix (ECM) including elastin, collagen and glycosaminglycans. Normal arteries have well-developed trilaminar structure, includes three concentric layers, i.e., intima, media and adventitia and are most clearly defined in larger vessels, particularly arteries. The innermost layer, the tunica intima is thin at birth and contains nonfibrillar collagen (type IV), laminin, fibronectin and other ECM molecules. With ageing, the arteries develop a more complex intima containing arterial SMCs and fibrillar forms of interstitial collagen (type I and type III). The internal elastic membrane bounds the tunica intima and continues with tunica media which contains well developed concentric layers of SMCs, interleaved with layers of elastin-rich ECM. The external elastic lamina bounds the tunica media forming the border with the adventitial layer. The adventitia contains collagen fibrils in a loose array and the cells present are fibroblasts and mast cells.

The intimal medial thickening (IMT) was defined as the distance from the leading edge of lumen-intima interface to the leading edge of media-adventitia interface of the far wall.[24] IMT is a complex process, depending on a variety of factors, including local hemodynamics, shear stress and blood pressure. Changes in shear stress may adversely affect endothelial function and particle residence time, affecting the delivery and transport of potentially atherogenic particles into the arterial wall and consequent plaque formation. The IMT greater than 0.9-1.0 mm is almost an indicative of atherosclerosis and increased risk for CVD.[25] The National Institutes of Health defines atherosclerosis as “an arteriosclerosis characterized by atheromatous deposits in and fibrosis of the inner layer of the arteries”. The major locus for the formation of atherosclerotic plaques is in the carotid arteries. The problem starts at the point where the common carotid artery bifurcates into the internal and external branches. Progression occurs mainly along the proximal part of the common carotid artery and into the proximal section of the internal carotid artery. Atherosclerosis is often asymptomatic, unless in a severe form. However, the examination of the vessel wall is necessary to detect the early stages of affected individuals. IMT can be measured by radiographic methods using X-rays, computed tomography (CT) scanners and ultrasound methods. IMT is generally measured using common carotid artery and measuring carotid intimal medial thickness (CIMT) by B-mode ultrasound was found to be a suitable non-invasive method to visualize the arterial walls and to monitor the early stages of the atherosclerotic process.[26] Dysfunction of the vascular endothelium and chronic low-grade inflammation are key features of the initiation of atherosclerosis.[27]

CIMT is associated with a number of factors, including age, sex, hypertension, smoking, lipid profile and BMI.[28] Few authors have referred to CIMT as "an intermediate phenotype for early atherosclerosis".[29] This marker for disease has an advantage as it can be measured easily by ultrasonography, which is non-invasive.[30] Hyperglycemia was linked to CVD by proposing that it creates oxidative and nitrosative stress, which act on the arterial wall to initiate the thickening process.[31] IGT was not associated with atherosclerosis, but it was associated with IMT.[32]

DM is accompanied by a substantial increase in the risk of CVD, which accounts for 70% of all deaths.[33] T2D is known to be associated with an excessively high rate of mortality and morbidity for macrovascular diseases.[34] Increased CIMT has been associated with an increased risk of stroke and MI.[35] IMT is highly used as a surrogate end point for vascular outcomes in many clinical trials aimed at assessing the effect of interventions that lower the risks for stroke and MI.[36] A meta-analysis demonstrated that for every 0.1 mm increase in CIMT, there was 10% increase in the risk of MI and 13-18% increase in the risk for stroke.[37] A recent systemic review found that measurement of CIMT is used to predict CVD risk in asymptomatic individuals. Risk factors associated with CIMT are age, smoking, hypertension and diabetes.[38,39]

Endothelial Function

Endothelium is the biological active inner layer of the blood vessels, which controls vascular and thus organ functions. The arterial vessel is outlined by three distinct layers; tunica intima - a single layer of endothelial cells, tunica media - which comprises the vascular smooth muscle cell (VSMC) and tunica adventitia, an elastic lamina with terminal nerve fibres and surrounding connective tissue. The endothelium plays an important role in vascular homeostasis by modulating blood flow, delivery of nutrients, VSMC proliferation and migration, fibrinolysis and coagulation, inflammation, platelet and leukocyte adherence.[40] To carry out the above functions, the endothelium produces components of the ECM such as collagen and a variety of regulatory mediators, including nitric oxide (NO), prostanoids, endothelin-1 (ET-1), angiotensin II (Ang II), tissue-type plasminogen activator (t-PA), plasminogen activator inhibitor-1 (PAI-1), von Willebrand factor (vWF), adhesion molecules and cytokines. The production of these moieties is responsible for various stimuli.[41] Normal endothelium actively decreases vascular tone, limits leukocyte adhesion and thus inflammatory activity in the vessel wall, maintains vascular permeability to nutrients, hormones, other macromolecules and leucocytes, inhibits platelet adhesion and aggregation by producing prostacyclin and NO, limits activation of the coagulation cascade by the thrombomodulin/protein C, heparan sulphate/antithrombin and tissue factor/tissue factor pathway inhibitor interactions, regulates fibrinolysis by producing t-PA and its inhibitor PAI-1.

The vasodilatory effect is mediated by the endothelium derived relaxing factor (EDRF), subsequently identified as NO. Endothelial cell constitutively express endothelial nitric oxide synthase (eNOS) that after Ca^{2+}/calmodulin binding generates NO using L-arginine as a substrate together with cofactors, e.g., NADPH and tetrahydrobiopterin. NO then rapidly diffuses into VSMC and binds to a heme group of soluble guanylate cyclase. This event results in the formation of cyclic guanosine monophosphate (cGMP), activating a cGMP dependent protein kinase, which leads to an increased extrusion of Ca^{2+} from cytosol in VSMC, inhibiting the contractile machinery and there by initiating vasodilation.[42] The production and release of NO may be further increased by circulating factors, such as acetyl choline (ACh), bradykinin and serotonin. NO is also released by physical stimuli such as shear stress and ischemia which is not Ca^{2+}/calmodulin dependent. Apart from vasodilator effect, NO inhibits expression of proinflammatory cytokines, chemokines and leukocyte adhesion molecules, thereby limiting vascular recruitment of leukocytes and platelets. It also inhibits VSMC proliferation, an early sign of atherosclerosis.[43] Therefore, the NO synthesized by endothelial cells is an important endothelium-derived mediator, because of its vasodilator, anti-platelet, anti-proliferative, permeability-decreasing and anti-inflammatory properties.[44] NO inhibits leucocyte adhesion and rolling as well as cytokine-induced expression of vascular cell adhesion molecule-1 (VCAM-1) and monocyte chemotactic protein-1 (MCP-1)[45], effects that are at least in part attributable to inhibition of the transcription factor nuclear factor κB (NF-κB).[46]

Endothelial Dysfunction

ED is an imbalance in the production of vasodilator factors, e.g., NO, prostacyclin (PGI_2), endothelial derived hyperpolarizing factor (EDHF) and vasoconstricting factors, e.g., ET-1, Ang-II and prostaglandin (PGH2). When this balance is disrupted, it predisposes the vasculature towards pro-thrombotic and pro-atherogenic effects. This results in vasoconstriction, leukocyte adherence, platelet activation, mitogenesis, pro-oxidation, impaired coagulation, vascular inflammation, atherosclerosis and thrombosis.[47]

In the presence of suboptimal concentrations of substrate or cofactors for the synthesis of NO, eNOS may become uncoupled, resulting in the production of reactive oxygen species (ROS). At high concentrations of ROS, the scavenging system is impeded and NO may rapidly react with superoxide species to form peroxynitrite, exaggerating the oxidative stress further. The molecular cause of oxidative stress may be due to hyperglycemia, dyslipidemia, cigarette smoking, inflammation and insulin resistance. Many studies demonstrate that the loss of biological activity and/or biosynthesis of NO are the molecular basis of ED.[48]

CONCLUSION

The diabetic vascular disease develops Endothelial Dysfunction, which is characterized by loss of NO and development of a pro-inflammatory vascular phenotype that promotes atherosclerosis and cardiovascular events.

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