

Novel mechanisms of endothelial dysfunction in diabetes

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ABSTRACT

Diabetes mellitus is a major risk factor for cardiovascular morbidity and mortality. This condition increases the risk of developing coronary, cerebrovascular, and peripheral arterial disease fourfold. Endothelial dysfunction is a major contributor to the pathogenesis of vascular disease in diabetes mellitus patients and has recently received increased attention. In this review article, some recent developments that could improve the knowledge of diabetes-induced endothelial dysfunction are discussed.

Key words: Arginase, diabetes, endothelial dysfunction, protein kinase C, reactive oxygen species, tumor necrosis factor

DOI: 10.4103/0975-3583.64432

INTRODUCTION

According to the World Health Organization, diabetes mellitus now affects about 220 million people worldwide,^[1] and the growth in its prevalence represents a global health crisis already accounting for more than 10% of the total healthcare expenditure in many countries.^[2] In the USA, over 24 million children and adults (almost 8% of the entire population) have diabetes, whereas another 57 million have prediabetes and are thus likely to develop the disease unless they make lifestyle changes.^[3] Diabetes without proper treatment can cause many complications, with cardiovascular diseases accounting for up to 80% of premature mortality.^[4]

The endothelium, once considered a mere selectively permeable barrier between the bloodstream and the outer vascular wall, is now recognized to be a crucial homeostatic organ, fundamental for the regulation of the vascular tone and structure.^[5] Therefore, endothelial dysfunction during diabetes has been associated with a number of pathophysiologic processes.^[6] A considerable body of evidence in humans indicates that endothelial dysfunction is closely associated with the development of diabetic retinopathy,^[7] nephropathy, and atherosclerosis in both type 1 and type 2 diabetes.^[8] In this article, the recent

findings on the mechanisms of endothelial dysfunction in diabetes, which could contribute to the development of new treatment options are discussed.

PHYSIOLOGIC ROLE OF THE VASCULAR ENDOTHELIUM

The healthy endothelial monolayer is optimally positioned in order to respond to physical and chemical signals, by producing a wide range of factors that regulate vascular tone, cellular adhesion, thromboresistance, smooth muscle cell proliferation, and vessel wall inflammation. The importance of the endothelium was first recognized by its effect in limiting the vascular tone.^[9] The vascular endothelium also regulates blood flow and, limits leukocyte adhesion and platelet aggregation by producing nitric oxide (NO), prostacyclin, and ectonucleotidases. As such, inflammatory activity in the vessel wall is blunted. In addition, the endothelium regulates vascular permeability to nutrients, macromolecules, and leukocytes; limits activation of the coagulation cascade by the thrombomodulin/protein C, heparin sulfate/antithrombin, and tissue factor/tissue factor pathway inhibitor interactions; and regulates fibrinolysis by producing tissue activator of plasminogen (t-PA) and its inhibitor, PAI-1.^[10]

DIABETES-INDUCED ENDOTHELIAL DYSFUNCTION

The term endothelial dysfunction refers to a condition in which the endothelium loses its physiologic properties and shifts toward a vasoconstrictor, prothrombotic, and proinflammatory state.^[11] Endothelial dysfunction has been associated with a variety of processes, including hypertension, atherosclerosis, aging, heart and renal failure, coronary syndrome, obesity, vasculitis, infections, sepsis, rheumatoid arthritis, thrombosis, smoking as well as with type 1 and type 2 diabetes ^[6]

Diabetes mellitus, often simply referred to as diabetes, is a condition with elevated blood glucose levels, as a result of either the body not producing enough insulin, or because cells do not properly respond to the insulin that is produced. The latter condition is characterized by fasting hyperglycemia and by a high risk of atherothrombotic disorders affecting the coronary, cerebral, and peripheral arterial trees.^[12] Despite improvement in the management of patients with unstable coronary syndromes, diabetes is still linked to a substantial increase in mortality and morbidity among these patients.^[13] Accordingly, developing new therapies for the treatment of diabetic patients is of great clinical importance.^[14,15]

In diabetes, dysfunction of the vascular endothelium is regarded as an important factor in the pathogenesis of diabetic micro- and macroangiopathy.^[8] There are three main sources contributing to endothelial dysfunction in diabetes: (1) hyperglycemia and its immediate biochemical sequelae directly alter endothelial function; (2) high glucose (HG), which influences endothelial cell functioning indirectly by the synthesis of growth factors and vasoactive agents in other cells and alters endothelial monolayer permeability; and (3) the components of the metabolic syndrome that can affect endothelial function.^[8]

There are many signaling molecules involved in the pathogenesis of endothelial dysfunction. In the following paragraphs, recent studies on this topic, mainly focusing on the roles of arginase and reactive oxygen species (ROS), protein kinase C (PKC), and tumor necrosis factor (TNF), are addressed.

ROLE OF ARGINASE AND REACTIVE OXYGEN SPECIES IN DIABETES-ASSOCIATED ENDOTHELIAL DYSFUNCTION

Conditions contributing to diabetic vascular remodeling and dysfunction include the effects of oxidative stress

and decreased NO bioavailability.^[16-19] NO production by endothelial NOS (eNOS) is critically involved in maintaining the integrity and stability of the vascular endothelium, preventing platelet aggregation and leukocyte adhesion, and maintaining blood flow.^[20] Availability of the semi-essential amino acid L-arginine is required for eNOS activity and NO production and is therefore essential for vascular integrity and function. Arginase is a hydrolytic enzyme, which converts L-arginine into urea and ornithine and exists as 2 isoforms: arginase I and II.^[21] Whereas arginase I is a cytosolic enzyme, expressed at high levels in the liver, arginase II is a mitochondrial enzyme expressed primarily in the extrahepatic tissues, especially in the kidney. Knockdown of arginase I has been shown to restore NO signaling in the vasculature of old rats.^[22] Both arginase I and II have been found in endothelial cells, arginase I being the dominant isoform.^[23]

Arginase and eNOS compete for their common substrate, L-arginine. As such, increased arginase activity can lead to eNOS dysfunction.^[23,24] We have shown that hepatic and vascular arginase activity is increased in diabetic rats and that arginase I expression and activity are increased in aortic endothelial cells exposed to HG.^[24] TNF has also been shown to induce arginase activity.^[25] Furthermore, arginase actions causing endothelial dysfunction, as indicated by decreased NO availability, are blocked by the Rho kinase inhibitor Y-27632.^[26] Additionally, an inhibitor of arginase reversed diabetes-induced endothelial dysfunction in the coronary vessels of diabetic rats.^[24] Also, arginase was found to mediate retinal inflammation in lipopolysaccharide (LPS)-induced uveitis.^[21]

Taken together, these findings^[21-26] suggest that arginase and RhoA may be mediators of diabetes-induced inflammatory effects in vascular disease. Apart from arginase, ROS also play an important role in vascular dysfunction in diabetes, although the source of their generation remains elusive. Overproduction of superoxide can lead to scavenging of NO and to its reduced bioavailability.^[27,28] ROS have been implicated in increased arginase activity and expression. Indeed, arginase activation can cause uncoupling of eNOS by reducing the supply of L-arginine. The uncoupled eNOS uses molecular oxygen to produce superoxide, thereby further reducing NO and increasing ROS formation [Figure 1].

IMPLICATION OF PROTEIN KINASE C

An important glucose-induced alteration in cellular metabolism that may account for endothelial dysfunction

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