

Diabetes and Cardiovascular Disease: Endothelial Dysfunction Mechanisms

Pedro Henrique Silva*

Department of Endocrinology and Metabolic Diseases, Federal University Hospital, Rio de Janeiro, Brazil

Introduction

Diabetes mellitus stands as a prominent risk factor for cardiovascular disease, with endothelial dysfunction playing a pivotal role in its pathogenesis. This dysfunction, characterized by an imbalance between vasodilation and vasoconstriction, significantly contributes to the development of vascular complications in diabetes, including atherosclerosis, hypertension, and microvascular damage. The intricate mechanisms driving this endothelial impairment are multifaceted, involving hyperglycemia, oxidative stress, inflammation, and dysregulated lipid profiles, all of which converge to compromise vascular health.

Oxidative stress is a pervasive hallmark of diabetes, profoundly impacting endothelial function. Elevated glucose levels fuel the excessive generation of reactive oxygen species (ROS), which directly damage endothelial cells, diminish the bioavailability of nitric oxide (NO), and amplify inflammatory responses within the vasculature. Consequently, interventions aimed at mitigating ROS production or bolstering antioxidant defenses are considered promising therapeutic avenues.

Inflammation is inextricably linked to the progression of endothelial dysfunction in the diabetic state. A state of chronic low-grade inflammation, instigated by hyperglycemia and broader metabolic dysregulation, activates endothelial cells. This activation promotes the expression of adhesion molecules, facilitating the recruitment of inflammatory cells to the vascular wall, thereby exacerbating vascular damage and accelerating the development of atherosclerosis.

A critical feature of diabetes-induced endothelial dysfunction is the impaired bioavailability of nitric oxide (NO). Hyperglycemia not only reduces the synthesis of NO but also accelerates its degradation by superoxide radicals. Strategies designed to restore NO levels, whether through pharmacological agents or lifestyle modifications, hold significant potential for improving endothelial function and slowing the progression of vascular disease.

Advanced glycation end products (AGEs) accumulate in the diabetic milieu and critically contribute to endothelial dysfunction. Upon binding to their receptors (RAGE) on endothelial cells, AGEs trigger a cascade of detrimental effects, including heightened oxidative stress, increased inflammation, and reduced NO production, all of which promote vascular complications.

Endothelial-to-mesenchymal transition (EndoMT) emerges as a significant process implicated in the vascular remodeling observed in diabetic complications. Hyperglycemia and other metabolic derangements associated with diabetes can induce EndoMT, leading to increased vascular stiffness, fibrosis, and a heightened pro-thrombotic state, collectively contributing to adverse vascular outcomes.

Dyslipidemia, a common comorbidity in diabetes, further exacerbates endothelial

dysfunction. This occurs through mechanisms such as the oxidative modification of lipoproteins and the amplification of inflammatory processes. Oxidized low-density lipoprotein (LDL), in particular, plays a crucial role in endothelial activation and the subsequent formation of atherosclerotic plaques.

The regulatory role of microRNAs (miRNAs) in endothelial function within the context of diabetes is gaining substantial recognition. Specific miRNAs are capable of modulating the expression of genes central to NO synthesis, oxidative stress pathways, and inflammatory responses, thereby exerting a significant influence on the development of endothelial dysfunction.

Impaired endothelial barrier function represents a critical consequence of diabetes, leading to increased vascular permeability and the infiltration of leukocytes into the vessel wall. This compromised barrier integrity fuels the inflammatory processes and tissue damage that characterize diabetic vascular complications.

Emerging therapeutic strategies are increasingly focused on directly addressing endothelial dysfunction in diabetes. These approaches encompass agents designed to enhance NO bioavailability, reduce oxidative stress and inflammation, and counteract the detrimental effects of AGEs, offering a promising outlook for improved management of diabetes-related vascular diseases.

Description

Diabetes mellitus is intrinsically linked to cardiovascular disease, with endothelial dysfunction serving as a cornerstone in its pathogenesis. This dysfunction, characterized by an imbalance between vasodilatory and vasoconstrictive forces, underpins the development of vascular complications such as atherosclerosis, hypertension, and microvascular damage, driven by hyperglycemia, oxidative stress, inflammation, and altered lipid profiles.

Oxidative stress, a salient feature of diabetes, profoundly contributes to endothelial dysfunction. Elevated glucose levels foster the overproduction of reactive oxygen species (ROS), which inflict damage on endothelial cells, impair nitric oxide (NO) bioavailability, and promote inflammation, making the modulation of ROS production or enhancement of antioxidant defenses a critical therapeutic strategy.

Inflammation is intrinsically interwoven with endothelial dysfunction in diabetes. Chronic low-grade inflammation, stemming from hyperglycemia and metabolic dysregulation, activates endothelial cells. This activation leads to increased expression of adhesion molecules and recruits inflammatory cells, thereby amplifying vascular damage and accelerating atherogenesis.

Impaired nitric oxide (NO) bioavailability is a key mechanistic feature of diabetes-induced endothelial dysfunction. Hyperglycemia directly impacts NO metabolism

by reducing its production and promoting its degradation by superoxide. Restoring NO levels through pharmacological interventions or lifestyle modifications is crucial for improving endothelial function and mitigating vascular disease progression.

Advanced glycation end products (AGEs) accumulate in diabetes and significantly contribute to endothelial dysfunction. AGEs interact with their receptors (RAGE) on endothelial cells, initiating pathways that increase oxidative stress, inflammation, and diminish NO production, thus promoting vascular complications.

Endothelial-to-mesenchymal transition (EndoMT) is increasingly recognized as a process involved in the vascular remodeling characteristic of diabetes. Hyperglycemia and associated factors can induce EndoMT, resulting in augmented vascular stiffness, fibrosis, and a pro-thrombotic milieu, all contributing to adverse vascular outcomes.

Dyslipidemia, a frequent comorbidity in diabetes, exacerbates endothelial dysfunction by promoting the oxidative modification of lipoproteins and fostering inflammation. Oxidized LDL, in particular, plays a significant role in endothelial activation and the development of atherosclerotic plaques.

The influence of microRNAs (miRNAs) on endothelial function in diabetes is a growing area of research. Specific miRNAs can regulate gene expression involved in NO synthesis, oxidative stress, and inflammation, thereby contributing to the overall profile of diabetic endothelial dysfunction.

Compromised endothelial barrier function is a significant consequence of diabetes, leading to increased vascular permeability and leukocyte infiltration. This breakdown of the endothelial barrier contributes to the inflammatory environment and subsequent tissue damage observed in diabetic complications.

Novel therapeutic strategies are being developed to directly target endothelial dysfunction in diabetes. These approaches aim to enhance NO bioavailability, reduce oxidative stress and inflammation, and prevent AGE formation, offering potential for improved management of diabetes-related vascular pathology.

Conclusion

Diabetes mellitus significantly increases the risk of cardiovascular disease, primarily through endothelial dysfunction. This dysfunction is driven by hyperglycemia, oxidative stress, inflammation, dyslipidemia, and advanced glycation end products (AGEs). Key mechanisms include impaired nitric oxide (NO) bioavailability, increased oxidative stress, inflammatory cell recruitment, and endothelial-to-mesenchymal transition (EndoMT). MicroRNAs also play a regulatory role in these processes, and impaired endothelial barrier function contributes to vascular damage. Current and emerging therapeutic strategies focus on mitigating these underlying factors to improve vascular health in diabetic patients.

Acknowledgement

None.

Conflict of Interest

None.

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***Address for Correspondence:** Pedro, Henrique Silva, Department of Endocrinology and Metabolic Diseases, Federal University Hospital, Rio de Janeiro, Brazil, E-mail: pedro.silva@fuh.edu

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