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ENDOTHELIAL GLYCOCALYX DAMAGE AS A KEY MECHANISM LINKING TYPE 2 DIABETES AND ARTERIAL HYPERTENSION

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Abstract: This report examines the critical role of endothelial glycocalyx damage as a central mechanism linking type 2 diabetes and arterial hypertension, with a focus on its structural and functional significance, the pathological consequences of its degradation, and potential therapeutic approaches. The endothelial glycocalyx, a dynamic layer composed of proteoglycans, glycosaminoglycans, and associated plasma proteins, is essential for maintaining vascular homeostasis. It regulates endothelial barrier function, mechanotransduction, blood flow, and selective permeability while preventing leukocyte adhesion and vascular inflammation. Disruption of the glycocalyx leads to impaired endothelial function, characterized by increased vascular permeability, inflammation, and oxidative stress, which are pivotal contributors to the pathogenesis of both type 2 diabetes and hypertension.

In type 2 diabetes, chronic hyperglycemia induces glycocalyx damage through oxidative stress, inflammation, and the accumulation of advanced glycation end products (AGEs), resulting in compromised vascular integrity and heightened susceptibility to diabetic complications. Uraemic toxins, often elevated in diabetic patients with renal impairment, further exacerbate glycocalyx degradation, linking kidney dysfunction with vascular inflammation and cardiovascular risks. The report underscores the correlation between glycocalyx damage and the progression of microvascular and macrovascular complications, such as retinopathy, nephropathy, and cardiovascular disease, in diabetic populations.

Similarly, the report highlights the involvement of glycocalyx disruption in arterial hypertension. Damage to the glycocalyx contributes to vascular stiffness and impaired endothelial function, key factors in the pathophysiology of elevated blood pressure. The interplay between hyperglycemia-induced glycocalyx degradation and hypertension is explored, with emphasis on the biochemical pathways linking elevated blood glucose levels, increased vascular resistance, and hypertensive states. This intersection underscores the shared mechanisms driving vascular dysfunction in both conditions.

Emerging research has also identified molecular pathways involved in glycocalyx damage in hypertensive and diabetic states. The upregulation of matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, has been implicated in the proteolytic degradation of glycocalyx components. Additionally, the activation of the renin-angiotensin-aldosterone system (RAAS), a hallmark of hypertension, contributes to glycocalyx disruption through angiotensin II-mediated oxidative stress and inflammation. These molecular insights provide potential therapeutic targets for protecting the glycocalyx and mitigating its role in hypertension and T2DM.

Therapeutic strategies aimed at preserving glycocalyx integrity or restoring its function hold promise in addressing the vascular complications associated with T2DM and hypertension. Interventions such as the use of heparan sulfate mimetics, antioxidants, and anti-inflammatory agents have shown potential in preclinical studies. For instance, supplementation with

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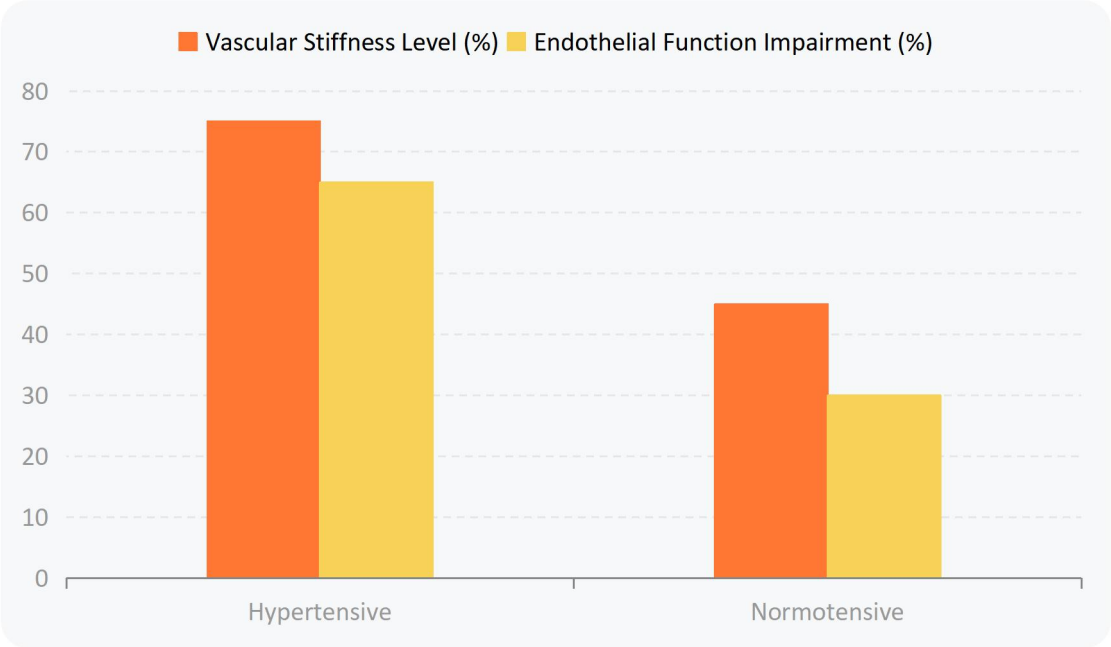
glycocalyx-protecting compounds has been associated with improved endothelial function and reduced vascular stiffness in experimental models. Furthermore, lifestyle interventions, including glycemic control and blood pressure management, play a crucial role in mitigating glycocalyx damage and its downstream effects on vascular health.

In conclusion, the endothelial glycocalyx serves as a critical link between T2DM and arterial hypertension, with its degradation playing a central role in the pathophysiology of both conditions. The loss of glycocalyx integrity leads to vascular stiffness, endothelial dysfunction, and impaired mechanotransduction, all of which contribute to elevated blood pressure. The bidirectional relationship between glycocalyx damage and the pathophysiological mechanisms of T2DM and hypertension underscores the importance of this structure in vascular health. Ongoing research into glycocalyx-targeted therapies offers a promising avenue for mitigating the vascular complications associated with these conditions and improving patient outcomes[13][14].



Interplay Between Hyperglycemia, Glycocalyx Damage, and Hypertension

The endothelial glycocalyx, a complex layer of glycoproteins and proteoglycans lining the luminal surface of blood vessels, plays a pivotal role in vascular homeostasis. Its structural integrity is essential for regulating vascular permeability, mechanotransduction, and maintaining anti-inflammatory and antithrombotic properties. The degradation of the glycocalyx has emerged as a critical mechanism linking hyperglycemia and arterial hypertension, particularly in individuals with type 2 diabetes. This chapter explores the interplay between hyperglycemia-induced glycocalyx damage and arterial hypertension, emphasizing the biochemical pathways that connect elevated glucose levels, glycocalyx degradation, and heightened vascular resistance.

Hyperglycemia, a hallmark of type 2 diabetes, exerts deleterious effects on the endothelial glycocalyx. Sustained high blood glucose levels lead to oxidative stress and inflammatory responses that compromise the structural integrity of the glycocalyx. Research has demonstrated that hyperglycemia induces the formation of neutrophil extracellular traps (NETs), which are

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networks of DNA, histones, and proteolytic enzymes released by neutrophils during inflammation. NETs have been implicated in glycocalyx degradation, as their proteolytic enzymes can disrupt the glycan-rich layer, exposing the endothelial cells to further oxidative and inflammatory damage[15]. The study by Hirota et al. (2020) highlighted this process in a mouse model of type 2 diabetes, providing experimental evidence of the link between hyperglycemia and glycocalyx damage[15].

The biochemical pathways underlying glycocalyx damage in hyperglycemic conditions involve several mechanisms. Excess glucose leads to the generation of advanced glycation end-products (AGEs), which interact with their receptors (RAGEs) on endothelial cells, triggering oxidative stress and inflammatory cascades. These processes diminish the synthesis and structural integrity of glycocalyx components such as syndecan-1 and heparan sulfate. Furthermore, hyperglycemia increases the activity of matrix metalloproteinases (MMPs), enzymes capable of degrading the glycocalyx. The combined effect of these mechanisms results in a thinner, less functional glycocalyx layer[16]. Tarbell and Cancel (2016) emphasized the significance of the glycocalyx in vascular health, noting its role in mitigating shear stress and preventing the adhesion of inflammatory cells and platelets[16]. Its degradation, therefore, represents a critical step in the pathogenesis of vascular complications such as arterial hypertension.

Arterial hypertension, characterized by elevated systemic blood pressure, is closely linked to glycocalyx damage. The glycocalyx serves as a mechanosensor, translating shear stress from blood flow into biochemical signals that regulate vascular tone. A compromised glycocalyx impairs this mechanotransduction, leading to dysregulated endothelial function and increased vascular resistance. Evidence suggests that glycocalyx degradation contributes to the stiffening of blood vessels, impairing their ability to adapt to changes in blood flow and pressure. Additionally, a damaged glycocalyx allows greater exposure of endothelial cells to circulating inflammatory mediators and AGEs, amplifying vascular dysfunction and promoting hypertension.

In conclusion, therapeutic opportunities targeting endothelial glycocalyx restoration represent a promising frontier in the management of arterial hypertension, particularly in patients with type 2 diabetes. Pharmacological agents such as A2AR agonists and sulodexide, along with lifestyle modifications and biotechnological innovations, provide diverse strategies for enhancing glycocalyx integrity and mitigating vascular dysfunction. However, the complexity of glycocalyx dynamics and the challenges of clinical implementation necessitate ongoing research and multidisciplinary collaboration. By prioritizing glycocalyx restoration as a therapeutic target, the medical community can pave the way for more effective and holistic approaches to cardiovascular health.

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