The immunometabolic interface: anti-inflammatory effects of innovative antidiabetic medications - the need for a more comprehensive understanding

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The immunometabolic interface represents a crucial link between metabolic dysfunction and chronic inflammation. Chronic low-grade inflammation is increasingly recognized as a key driver of metabolic, cardiovascular, and renal disorders. In the pathophysiology of diabetes mellitus and its complications—including cardiovascular disease and nephropathy—activation of the nuclear factor kappa B (NF-κB) signaling pathway plays a central role. Triggered by pro-inflammatory cytokines and damage-associated molecular patterns, this pathway promotes sustained inflammatory responses, β-cell dysfunction, and the development of insulin resistance. Furthermore, activation of the NLRP3 inflammasome, mediated by mitochondrial dysfunction and impaired autophagy, amplifies the inflammatory cascade through the release of interleukin (IL)-1 and IL-18. These processes together establish a chronic pro-inflammatory state that contributes to metabolic deterioration and vascular injury[1,2]. Recent advances in antidiabetic therapy have highlighted that several novel drug classes, initially developed for glycemic control, possess significant immunomodulatory and anti-inflammatory properties. Sodium-glucose cotransporter-2 (SGLT2) inhibitors improve vascular health by attenuating oxidative stress and inflammation, enhancing endothelial function, modulating microRNA expression, and delaying vascular aging and atherosclerosis[1]. Dipeptidyl peptidase-4 (DPP-4) inhibitors exert anti-inflammatory effects by suppressing NF-κB activation, reducing pro-inflammatory cytokines, and limiting macrophage and T-cell infiltration, thereby improving endothelial function and stabilizing atherosclerotic plaques. Similarly, glucagon-like peptide-1 (GLP-1) receptor agonists reduce systemic inflammation through downregulation of CRP, TNF-α, IL-1, and IL-6, while also inhibiting NF-κB signaling. By mitigating vascular inflammation and oxidative stress, these agents improve cardiovascular outcomes and reduce heart failure–related hospitalizations[2]. These findings highlight the therapeutic significance of targeting immunometabolic and inflammatory pathways to preserve vascular and renal integrity. By attenuating chronic low-grade inflammation and oxidative stress, such interventions may not only prevent cardiovascular events and slow chronic kidney disease progression but also provide a framework for developing future therapies targeting inflammation-driven complications in type 2 diabetes.

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LITERATURE

1. Schönberger E, Mihaljević V, Steiner K, Šarić S, Kurevija T, Majnarić LT, et al. Immunomodulatory Effects of SGLT2 Inhibitors-Targeting Inflammation and Oxidative Stress in Aging. Int J Environ Res Public Health. 2023 Aug 29;20(17):6671. https://doi.org/10.3390/ijerph20176671
2. Theofilis P, Sagris M, Oikonomou E, Antonopoulos AS, Siasos G, Tsioufis K, et al. The Anti-Inflammatory Effect of Novel Antidiabetic Agents. Life (Basel). 2022 Nov 9;12(11):1829. https://doi.org/10.3390/life12111829