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Opinion Article

The Role of SGLT2 Inhibitors and Metformin in Modulating Immunity for Rheumatic Disease Management

Daniel Sullivan*

Department of Clinical Immunology, University of Pittsburgh, Pittsburgh, USA

ABOUT THE STUDY

Rheumatic diseases, encompassing a broad spectrum of autoimmune and inflammatory conditions such as rheumatoid arthritis, lupus, and ankylosing spondylitis, present significant challenges in terms of treatment and disease management. These disorders often require a multi-faceted approach that not only discusses inflammation and symptoms but also the underlying immune dysregulation. In recent years, the potential of certain metabolic drugs, particularly Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors and metformin, to modulate immune responses has garnered considerable attention.

Metabolic pathways and immune system interactions

Understanding how these medications interact with immune processes begins with the insight into their basic mechanisms. Metformin, a fundamental of type 2 diabetes treatment, primarily acts by reducing hepatic glucose production and improving insulin sensitivity. SGLT2 inhibitors, such as empagliflozin and dapagliflozin, work by blocking the reabsorption of glucose in the proximal convoluted tubule of the kidneys, leading to increased urinary excretion of glucose and reduced blood glucose levels.

Both classes of drugs impact cellular metabolism, which has profound implications for immune function. Recent research has shown that metabolism and immunity are interconnected processes, where metabolic state can influence inflammatory responses and immune cell activity.

SGLT2 inhibitors and immune modulation

SGLT2 inhibitors are well-known for their effects on glucose metabolism and cardiovascular health, but they are now being studied for their potential impact on immune responses. Evidence has emerged showing that these agents may have direct and indirect anti-inflammatory effects that could benefit rheumatic disease management.

Anti-inflammatory mechanisms

Studies have revealed that SGLT2 inhibitors can modulate cytokine profiles and decrease systemic inflammation. For example, SGLT2 inhibitors have been shown to reduce levels of pro-inflammatory cytokines such as IL-6 and TNF-α. This modulation may help alleviate systemic inflammation in patients with autoimmune conditions, where these cytokines are often elevated.

Additionally, these drugs promote ketogenesis, leading to the production of ketone bodies such as β-hydroxybutyrate, which has anti-inflammatory properties. β-hydroxybutyrate is known to inhibit the NLRP3 inflammasome, an important component in the activation of inflammatory pathways. By suppressing inflammasome activity, SGLT2 inhibitors can contribute to a reduction in chronic inflammation, a significant contributor to the pathophysiology of rheumatic diseases.

Impact on immune cell function

SGLT2 inhibitors also influence the function of immune cells, particularly T cells and macrophages. Research has shown that these medications may promote the polarization of T cells toward anti-inflammatory phenotypes and reduce the activity of macrophages in producing pro-inflammatory mediators.

Metformin's immunomodulatory role

Metformin's potential for modulating immune responses is linked to its action on cellular energy metabolism. By activating AMP-activated Protein Kinase (AMPK), a central regulator of cellular energy homeostasis, metformin influences pathways that are important for immune cell function.

AMPK activation and immune modulation

AMPK activation has been shown to inhibit the mechanistic Target Of Rapamycin (e mTOR) pathway, which is often upregulated in inflammatory conditions. The mTOR pathway plays a critical role in T cell activation and differentiation. By suppressing mTOR activity, metformin can limit the proliferation

Correspondence to: Daniel Sullivan, Department of Clinical Immunology, University of Pittsburgh, Pittsburgh, USA, E-mail: sullivan96@pitt.edu

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and function of pro-inflammatory T cells, promoting a more balanced immune response.

Additionally, metformin has been shown to reduce oxidative stress and improve the function of regulatory T cells (Tregs). Tregs are vital for maintaining immune tolerance and preventing autoimmune reactions.

Effects on macrophages and cytokine production

Macrophages are key players in the immune response and are involved in both the initiation and resolution of inflammation. Metformin can alter macrophage polarization from a pro-inflammatory M1 phenotype to an anti-inflammatory M2 phenotype, which is beneficial in controlling chronic inflammation. This shift is associated with a decrease in the production of pro-inflammatory cytokines and an increase in anti-inflammatory cytokines, aiding in the regulation of immune responses.

SGLT2 inhibitors in rheumatic disease

Clinical trials and observational studies have hinted at the potential benefits of SGLT2 inhibitors in conditions such as rheumatoid arthritis and Systemic Lupus Erythematosus (SLE). For instance, a study involving patients with rheumatoid arthritis found that those on SGLT2 inhibitors experienced improved clinical outcomes, including reduced levels of inflammatory markers and better overall disease activity scores.

Metformin and autoimmune diseases

Research into metformin's impact on autoimmune diseases like rheumatoid arthritis has shown promising results. A study focusing on type 2 diabetic patients with coexisting rheumatoid arthritis reported that metformin use was associated with reduced disease activity and improved quality of life. These benefits were attributed to the drug's ability to modulate immune responses and decrease systemic inflammation.

Energy metabolism and immune signaling

AMPK activation by metformin and the ketosis induced by SGLT2 inhibitors both shift cellular metabolism from a state of energy abundance to one of energy conservation and utilization. This metabolic shift can lead to decreased production of Reactive Oxygen Species (ROS) and reduced activation of pro-inflammatory pathways. Moreover, AMPK activation can inhibit the activity of Nuclear Factor-kappa B (NF-κB), a transcription factor that drives the expression of numerous pro-inflammatory cytokines.

The role of SGLT2 inhibitors and metformin extends beyond their well-established use in metabolic disorders to potentially significant roles in the modulation of immune responses. Their capacity to alter inflammatory pathways, promote anti-inflammatory cell types, and improve metabolic regulation makes them potential candidates for rheumatic disease management.