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REVIEW

Narrative Review of Immunomodulatory and Anti-inflammatory Effects of Sodium-Glucose Cotransporter 2 Inhibitors: Unveiling Novel Therapeutic Frontiers

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Sodium-glucose cotransporter 2 inhibitors (SGLT2 inhibitors) have evolved from their initial role as antidiabetic drugs to garner recognition for their remarkable cardio-protective and reno-protective attributes. They have become a crucial component of therapeutic guidelines for congestive heart failure and proteinuric chronic kidney disease (CKD). These benefits extend beyond glycemic control, because improvements in cardiovascular and renal outcomes occur swiftly. Recent studies have unveiled the immunomodulatory properties of SGLT2 inhibitors; thus, shedding light on their potential to influence the immune system and inflammation. This comprehensive review explores the current state of knowledge regarding the impact of SGLT2 inhibitors on the immune system and inflammation, focusing on preclinical and clinical evidence. The review delves into their antiinflammatory and immunomodulating effects, offering insights into clinical implications, and exploring emerging research areas related to their prospective immunomodulatory impact.

Kidney Int Rep (2024) **9,** 1601–1613; https://doi.org/10.1016/j.ekir.2024.02.1435
KEYWORDS: anti-inflammation; cardiovascular disease; chronic kidney disease; immune modulation; inflammation; sodium-glucose cotransporter 2 inhibitors

SGLT2 inhibitors, originally introduced as antidiabetic drugs, have gained recognition for their remarkable cardio-protective and reno-protective attributes.[1-4] SGLT2 inhibitors have now become an integral part of the therapeutic guidelines for managing congestive heart failure and proteinuric CKD. The reduction in the incidence of adverse cardiovascular and renal events occurs relatively quickly, indicating that factors beyond enhanced glycemic control contribute significantly to these advantageous outcomes because the clinical outcomes related to improved glycemic control typically require a longer time to become measurable.

Chronic low-grade inflammation stands out as a prominent characteristic of type 2 diabetes and its complications, notably atherothrombotic cardiovascular disease (CVD).[5] In addition, inflammation plays a pivotal role in the pathogenesis of diabetic kidney disease.[6] As found in metformin and glitazones, certain antidiabetic medications demonstrate antiinflammatory effect beyond their glucose-lowering capabilities,[7-9] which holds the potential to improve clinical outcomes for patients with high-risk CVD and renal issues.[10]

In recent years, many studies have unveiled novel facets of SGLT2 inhibitors beyond glycemic control, shedding light on their potential immunomodulatory properties (Figure 1).[11-14] This comprehensive review aims to provide the current state of knowledge surrounding the influence of SGLT2 inhibitors on the immune system and inflammatory processes with a focus on both preclinical and clinical evidence. This review offers insights into the clinical implication of SGLT2 inhibitors focusing on its antiinflammatory and immunomodulating effects. Finally, we explore emerging research areas related to the prospective immunomodulatory impact of SGLT2 inhibitors.

IMMUNOMODULATORY MECHANISM OF SGLT2 INHIBITORS AND ITS IMPACT ON KIDNEY AND CARDIOVASCULAR HEALTH

Glucose Lowering Effect of SGLT2 Inhibitors

The glucose-lowering effects of SGLT2 inhibitors may contribute to the amelioration of proinflammatory

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Received 19 December 2023; revised 8 February 2024; accepted 25 February 2024; published online 1 March 2024

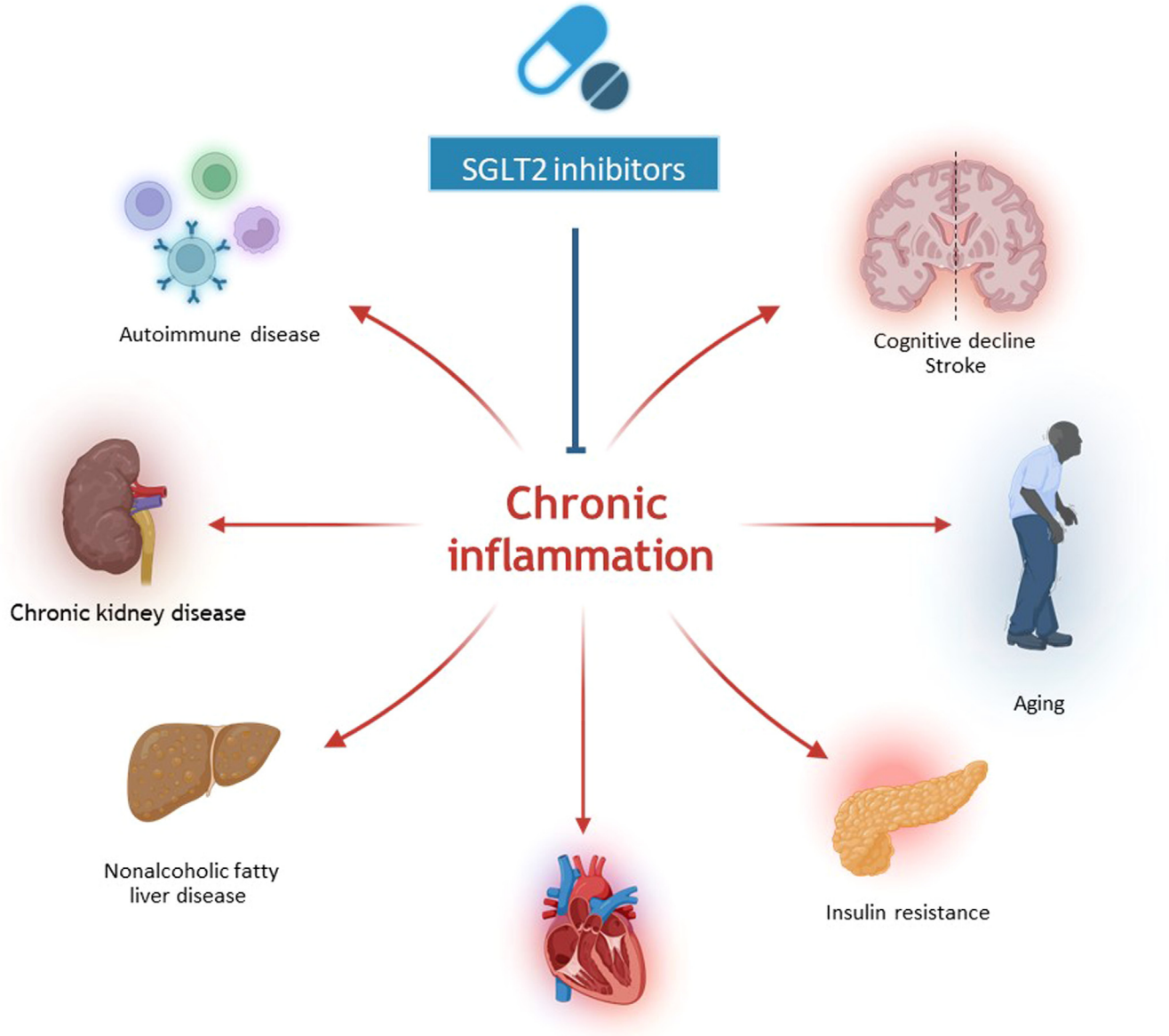

Figure 1. Immunomodulatory effects of SGLT2 inhibitors on various medical conditions. SGLT2 inhibitors, sodium-glucose cotransporter-2 inhibitors. Created with BioRender.com.

reactions by mitigating glucotoxicity.[15] Several studies have shown the direct detrimental effect of hyperglycemia on inflammation. An earlier human experimental study demonstrated that hyperglycemia could trigger an abrupt increase in circulating cytokine levels, including interleukin (IL)-6, tumor necrosis factor (TNF)-α, and IL-18 through oxidative process, implying a causal link between hyperglycemia and immune activation in diabetes.[16] A murine study by Dror *et al*. demonstrated that eating triggers IL-1ß expression in macrophages in a glucose-dependent manner compared to fasting status.[17] IL-1ß contributes to postprandial insulin secretion, reinforcing a proinflammatory state, promoting reactive oxygen species production, and activating inflammasome.[18] This study also showed that decreasing serum glucose level via inhibition of SGLT2 could decrease postprandial IL-1ß level in the circulation.[17]

However, additional subgroup analyses of data from multiple cardiovascular outcome trials involving SGLT2 inhibitors have shown that the cardiovascular benefits of SGLT2 inhibitors were not dependent on the extent of their hypoglycemia effects.[19,20] This implies the existence of potentially intricate, glucose-independent mechanism at play in the immunomodulatory impact of SGLT2 inhibitors, which we delve into in the subsequent section.

Neurohormonal Effect of SGLT2 Inhibitors

The substantial renal and cardiovascular benefits of SGLT2 inhibitors prompted further studies to investigate their potential impact on the renin-angiotensin-

aldosterone system (RAAS). However, these studies produced varying results, leaving the question unresolved.[21-23] Theoretically, enhanced sodium delivery to renal distal tubule by SGLT2 inhibitors can decrease renin secretion, whereas osmotic diuresis induced by SGLT2 inhibitors might stimulate baroreceptors, leading to increased renin secretion.[24] Filippatos *et al*. suggested that SGLT2 inhibitors may act through nonclassic RAAS pathways in the presence of RAAS blockades in the system via the angiotensin (1–7)/type 2 angiotensin II receptor pathway.[25] As previously known, most patients involved in the major cardiovascular outcome trials of SGLT2 inhibitors were on angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers. Through the activation of nonclassic RAAS pathways, SGLT2 inhibitors may promote vasodilatation, enhance sodium excretion, and offer antiproliferative and antiinflammatory effects.[26]

In contrast, SGLT2 inhibitor-induced sympathetic nervous system inhibition has been suggested as a potential mechanism for its cardiovascular protective effect.[27,28] Renal sympathetic nerve activation is implicated in CKD progression by mediating renal interstitial inflammation and fibrosis through the stimulation of intrarenal angiotensin II and activation of α2 adrenoreceptors.[29,30] Renal denervation, in contrast, has demonstrated protective antiinflammatory effects on the heart and kidneys in various animal models.[31,32] A preclinical study by Hasan *et al*. revealed that canagliflozin, when used in chronic sympathetic nervous system overactivation model, could augment antiinflammatory and antioxidant signaling pathways.[33] This finding suggests immunomodulatory impact of SGLT2 inhibitors via sympathetic nervous system deactivation.

Suppression of Inflammatory Signaling by SGLT2 Inhibitors

NOD-, LRR-, and Pyrin Domain-Containing Protein 3 (NLRP3) Inflammasome

The inflammasome is a multiprotein complex that activates inflammatory responses by promoting the release of proinflammatory cytokines in response to infection or cellular stress. NLRP3 inflammasome activation plays a significant role in driving sterile inflammation, leading to cardiovascular complications in patients with diabetes.[34] Key products of NLRP3 inflammasome activation include IL-1β and IL-18, which play a pivotal role in both the initiation and progression of atherosclerosis.[35,36] The use of SGLT2 inhibitors can suppress the activation of NLRP3 inflammasome. A recent small randomized controlled trial conducted by Kim *et al*. demonstrated that the use of SGLT2 inhibitors in patients with diabetes with a high cardiovascular risk leads to a significant suppression of NLRP3 inflammasome activation and the decreased secretion of IL-1β and TNF-α from circulating macrophages, as compared to the sulfonylurea-treated group, irrespective of glycemia control.[37] Their *ex vivo* study further elucidated that this effect might be mediated by an increased serum beta-hydroxybutyrate level and the decreased serum insulin level.

Nuclear Factor Kappa-B (NF-κB), Mitogen-Activated Protein Kinase, and Janus Kinase/Signal Transducer and Activator of Transcription Signaling Pathways

NF-κB, mitogen-activated protein kinase, and Janus kinase/signal transducer and activator of transcription are critical signaling pathways in the immune system.[38] They mediate immune activation and differentiation by regulating gene expression, cytokine production, and immune cell function. SGLT2 inhibitors have shown some evidence to exert their antiinflammatory effects via those signaling pathways in multiple *in vivo* and *in vitro* studies irrespective of glucose concentration.[39-43] An *in vitro* study using LPS-stimulated RAW 264.7 macrophages demonstrated that empagliflozin attenuated the release of proinflammatory cytokines and proinflammatory mediators such as nitric oxide or prostaglandin E2 via downregulating the NF-κB, mitogen-activated protein kinase, and Janus kinase/signal transducer and activator of transcription signaling pathways.[41] Another *in vitro* study involving human ventricular cardiac myoblasts revealed that empagliflozin mitigated the high glucose-induced DNA demethylation changes in NF-κB and superoxide dismutase 2 genes, and this finding was correlated with the decreased reactive oxygen species level and lower IL-6 gene expression.[42] The exact mechanism or receptor target that led to this effect upon SGLT2 inhibition on innate cells and myocytes was not determined.

Modulation of Nutrient Deprivation and Surplus Signaling by SGLT2 Inhibitors

As described in a well-written review article by Packer,[44] SGLT2 protein behaves like an energy sensor by discerning the nutritional excess status when there is increased glucose in the proximal renal tubules. This signal parallels changes in other nutrient sensors, including adenosine monophosphate-activated protein kinase (AMPK), sirtuins, and mammalian target of rapamycin (mTOR). These 3 master regulators orchestrate the cellular catabolic and anabolic responses according to the environmental challenges. AMPK and sirtuins mediate nutrient deprivation signaling whereas mTOR pathway is activated by a surplus of environmental amino acids. We review how SGLT2 inhibitors

regulate the nutrient deprivation and surplus signaling in the next section.

AMPK Pathway

AMPK pathway is activated when the adenosine triphosphate-to-adenosine monophosphate ratio is low. AMPK signaling promotes catabolism and decreases anabolism, resulting in increased adenosine triphosphate production. Activation of AMPK weakens oxidative stress, proinflammation pathways, apoptosis, and mitochondrial dysfunction.[45] Several studies showed that the use of SGLT2 inhibitors induced increased phosphorylation of AMPK and the activity of the AMPK pathway.[46,47] The use of empagliflozin improved sunitinib-induced cardiac dysfunction by restoring AMPK-mediated autophagy.[46] In another study, it was demonstrated that canagliflozin could mitigate cisplatin-induced kidney damage through an AMPK-dependent mechanism.[47] These studies also revealed the cardiorenal protective effects of SGLT2 inhibitors are abolished by AMPK inhibition.

Sirtuins

The sirtuin family, encompassing SIRT 1 to 7, plays a vital role in preserving homeostasis by detecting the body's bioenergy demands and fine-tuning cellular nutrient allocation accordingly.[48] The cardiovascular benefits of caloric restriction are known to be partially mediated by SIRT1, because it enhances lipolysis, augments insulin sensitivity, and limits proinflammatory macrophage activity.[49,50] Notably, chronic inflammation leads to diminished SIRT expression, and various studies have elucidated the antiinflammatory properties of SIRT1 in atherosclerosis and CVD.[51,52] The use of SGLT2 inhibitors can induce nutrient deprivation status by its glucosuric effect and amplify SIRT1/PGC-1α/FGF21 signaling pathway.[53] The activation of the sirtuin pathway is believed to contribute partially to the cardiorenal protective effect associated with SGLT2 inhibitors.

mTOR Pathway

The mTOR pathway not only integrates signals from the nutritional microenvironments but also plays a crucial role in regulating immune function, establishing a vital link between metabolism and the immune system.[54] The activation of mTOR signaling is related to clinical cardiomyopathy and nephropathy.[55,56] Several studies have reported the suppressive effect of SGLT2 inhibitors on mTOR pathway.[57,58] A recent in-depth single-cell transcriptional study in young patients with diabetes by Schaub *et al*. reported that the use of SGLT2 inhibitor induced less expression of mTORC1 in all nephron segments and phosphorylated S6 protein, an mTORC1 activity marker.[59] SGLT2 inhibitors restored the mTORC1-signaling pathway toward healthy control levels in all tubular segments. This study suggested that the SGLT2 inhibitor treatment can ameliorate the metabolic disturbance of kidney tubules via mTORC1 signaling in patients with diabetes.

Metabolic Reprograming of T Cell Response by SGLT2 Inhibitors

Several studies have unveiled the impact of SGLT2 inhibitors on T cell effector function and differentiation via metabolic reprograming.[12,60] A recent study by Jenkins *et al*. demonstrated that *in vitro* exposure to canagliflozin inhibits T cell receptor signaling, leading to compromised ERK and mTORC1 activity in T cells. In addition, canagliflozin inhibited mitochondrial glutamate dehydrogenase and complex I in T cells, whereas another SGLT2 inhibitor, dapagliflozin, had no effect on T cells. The impaired T cell receptor response induced by canagliflozin led to compromised metabolic reprogramming and T cell effector function.[12] In addition, the study showed when CD4 T cells from patients with autoimmune disease were treated with canagliflozin *in vitro*, they produced less proinflammatory cytokines and exhibited reduced activation. These findings suggest that canagliflozin may attenuate pathogenic T cell function in autoimmunity. Importantly, SGLT2 is minimally expressed on T cells, suggesting an SGLT2-independent mechanism of action of canagliflozin, which may vary across different SGLT2 inhibitors.

Another *in vitro* experiment involving T cells isolated from immune thrombocytopenia patients revealed that empagliflozin increased the regulatory T cell subset while decreasing the Th1 and Th17 T cell subsets.[60] This effect was counteracted by the use of an mTOR agonist. This study suggests that SGLT2 inhibitors may modulate the metabolic reprogramming of CD4 T cells through the mTOR signaling pathway.

Augmented Autophagy and Mitochondrial Function by SGLT2 Inhibitors

Starvation-mimicking conditions, induced by the glucosuric effect of SGLT2 inhibitors, can trigger pleiotropic effects, including the enhancement of autophagy. There has been a growing attention on the role of autophagy in renal inflammation and renal senescence.[61] The suppression of autophagy is associated with the progression of diabetic nephropathy, including mesangial expansion, thickening of glomerular basement membrane, and podocytopathy.[62] Korbut *et al*. demonstrated that caloric reduction, induced by significant glycosuria through empagliflozin, could promote autophagy in *db*/*db* mice.[63] In this experiment, SGLT2 inhibitors also mitigated mesangial expansion, podocyte foot process effacement, and urinary albumin excretion.

SGLT2 inhibitors can alleviate mitochondrial dysfunction in renal tubules by reducing the proximal tubular workload through the inhibition of sodium and glucose reabsorption.[64,65] Given that aberrant mitochondrial homeostasis and elevated reactive oxygen species levels can contribute to renal inflammation and fibrosis, the mitochondrial protective properties of SGLT2 inhibitors demonstrated in numerous preclinical studies hold promise as an immunomodulatory agent in chronic renal inflammatory conditions, preventing acute kidney injury-to-CKD transition.[63,66]

Insulin Lowering and Insulin Sensitizing Effect of SGLT2 Inhibitors

SGLT2 inhibitors do not rely on insulin or islet beta-cells to achieve their glucose-lowering effects. Insulin-lowering effect is one of the distinctive characteristics of SGLT2 inhibitors when compared to insulin secretagogues such as sulfonylureas or glinides, as well as exogenous insulin. In addition, several studies involving patients with type 2 diabetes have demonstrated that SGLT2 inhibitors increase the insulin sensitivity as evidenced by increased peripheral glucose uptake.[67,68] Because elevated insulin levels and insulin resistance can induce inflammation, mitochondrial dysfunction, mesangial proliferation, and dysfunction of podocytes and endothelial cells in kidneys,[69] the impact of SGLT2 inhibitors on insulin level and peripheral insulin sensitivity may offer a partial explanation for their renal protective effects.

Alleviation of Ectopic Fat Deposition and Adipose Tissue Inflammation by SGLT2 Inhibitors

Ectopic fat deposition around the kidney and the heart can induce local tissue inflammation. Perirenal fat is known to affect the progression of diabetic nephropathy and ectopic fat deposition in the heart can induce the development of coronary artery disease and heart failure by secreting a cocktail of cytokines, adipokines, microRNAs, and cellular mediators.[70] Okuma *et al.*[71] revealed that the use of ipragliflozin reduced leptin production from the perirenal fat tissue and this was associated with attenuated high-fat diet-induced inflammation, fibrosis, and cell death in perirenal fat tissue in mice. SGLT2 inhibitors have also shown to reduce the epicardial fat mass independent of weight loss in patients with diabetes.[72,73]

Several studies suggest the positive impact of SGLT2 inhibitors in obesity-induced adipose tissue inflammation. SGLT2 inhibitors can regulate the recruitment of macrophages and induce M2-like polarization within adipose tissue macrophages.[74,75] SGLT2 inhibitors can improve insulin sensitivity and inflammation in white adipose tissue and liver through the polarization to M2-like macrophages. By inhibiting SGLT2 and promoting glucose excretion through urine, SGLT2 inhibitors can enhance fat utilization through AMPK activation in muscle.[74] In addition, SGLT2 inhibitors encourage the browning of white adipose tissue, thereby inducing thermogenesis and increasing overall energy expenditure.[75] Several studies have also explored the influence of SGLT2 inhibitors on adipokines such as leptin and adiponectin and its impact on antiinflammatory effect.[76,77] These multifaceted effects contribute to improvement in obesity, alleviation of inflammation, and enhanced insulin sensitivity.

Alleviation of Vascular Inflammation

Several preclinical studies suggested that the use of SGLT2 inhibitors may improve vascular function by attenuating endothelial cell activation and vascular inflammation, and by improving vaso-relaxation and arterial wall stiffness.[78–80] In a human substudy of the EMPA-HEART Cardiolink-6 trial by Hess *et al.*, empagliflozin administration increased the circulating pro-vascular progenitor cells and shifted the balance of circulating monocytes toward M2 polarization.[81] These findings were concomitant with reduced systemic oxidative stress and decreased inflammatory granulocytes. The collective changes suggested that the use of SGLT2 inhibitors may generate a microenvironment that is permissive to blood vessel regeneration, reversing the oxidative stress-induced regenerative cell exhaustion.

The use of SGLT2 inhibitors can also enhance the stability of atherosclerotic plaque. A study revealed that atherosclerotic plaques of patients with diabetes express increased level of SGLT2 as compared to those from individuals without diabetes, and the use of SGLT2 inhibitors could induce more stable plaque phenotype.[14] A recent clinical study by the same investigators also unveiled the data from patients with multivessel nonobstructive coronary artery disease, demonstrating that the use of SGLT2 inhibitors improves the stability of atherosclerotic coronary plaque.[82] This was evidenced by an increase in coronary fibrous cap thickness and a decrease in the degree of lipid deposition within atherosclerotic plaques.

Enhanced Urinary Uric Acid Excretion by SGLT2 Inhibitors

SGLT2 inhibitors gained attention for their ability to induce uricosuria, although the exact mechanism remains elusive.[83,84] A recent meta-analysis by Banerjee *et al.* revealed that SGLT2 inhibitors significantly reduce the acute gout events or gout flares and the need to initiate new antigout medications.[85] Hyperuricemia

exhibits a strong association with a diverse range of cardiovascular conditions, including hypertension, coronary artery disease, and kidney disease.[86,87] It is also believed that inflammation is partially mediating this correlation. Several studies have provided evidence that elevated uric acid levels can trigger a proinflammatory response through NF-κB signaling, resulting in the infiltration of inflammatory cell and the activation of endothelial cells.[88,89] In a study using dotinurab, a selective inhibitor of cardiac urate transporter-1 which reduces uric acid uptake by cardiomyocytes, there was a significant reduction in cardiac fibrosis, inflammatory responses, and cardiac dysfunction in obese mice fed a high-fat diet.[90] Whether the uricosuric effect of SGLT2 inhibitors induces immunomodulatory effect and contributes to its cardiovascular benefit requires further investigation.

EXPANDING THE ANTIINFLAMMATORY POTENTIAL OF SGLT2 INHIBITORS BEYOND RENAL AND CARDIOVASCULAR SYSTEMS

Recent clinical studies have explored the immunomodulatory effects of SGLT2 inhibitors on various organ systems, extending beyond the kidney and heart. In this section, we review the immunological implication of SGLT2 inhibitors on serum biomarkers and multiple organ systems beyond just kidney and heart, leveraging available clinical data with further complementation from preclinical data.

Serum Biomarkers

Numerous proinflammatory biomarkers, such as C-reactive protein, IL-6, TNF-α, and adipokines, have been established to be significantly associated with the development of CVD and CKD.[91,92] In addition, the leptin-to-adiponectin ratio is recognized as a reliable and predictive biomarker for several metabolic disorders, such as CVD, type 2 diabetes, and insulin resistance.[93,94] Inflammatory cytokines can induce endothelial dysfunction and elevate extracellular matrix turnover, ultimately resulting in tissue fibrosis.[95] The influence of SGLT2 inhibitors on the reduction of proinflammatory biomarkers has been explored in various human studies, indicating a promising antiinflammatory potential of SGLT2 inhibitors.[96-98]

More intriguingly, the *post hoc* analysis of the Canagliflozin Cardiovascular Assessment Study unveiled a significant correlation between the decrease of TNF receptor-1 and TNF receptor-2 levels and reduced risk of adverse kidney outcomes among a canagliflozin-treated group. In a recent meta-analysis conducted by Wang *et al.*, the effects of SGLT2 inhibitors on inflammation-related biomarkers were comprehensively assessed across various randomized controlled trials.[99] The key findings from this analysis revealed reductions in ferritin, C-reactive protein, leptin, plasminogen activator inhibitor-1, along with an increased adiponectin levels when compared to placebo-controlled studies. These findings suggest a promising application of SGLT2 inhibitors for immunomodulation in metabolic disorders.

The Immunological Influence of SGLT2 Inhibitors on Nonalcoholic Fatty Liver Disease

There is a growing interest in the potential benefits of SGLT2 inhibitors for the treatment of nonalcoholic fatty liver disease, a condition that arises when the liver's capacity to regulate metabolic energy substrates becomes overwhelmed due to excessive dietary intake.[100] This surplus of energy leads to dysfunction in hepatocytes and triggers *de novo* lipogenesis in the liver.[101] The imbalance between lipogenesis and lipolysis results in the accumulation of free fatty acids within liver cells, causing hepatocellular damage, apoptosis, inflammation, and eventual fibrosis.[102] A recent meta-analysis has demonstrated that the use of SGLT2 inhibitors can improve hepatic steatosis and fibrosis in patients with diabetes with nonalcoholic fatty liver disease.[103] The protective mechanisms of SGLT2 inhibitors against nonalcoholic fatty liver disease appears to be mediated by the promotion of lipolysis and β-oxidation of free fatty acids in mitochondria, which in turn reduces oxidative stress, hepatic inflammation, and apoptosis.[11,104,105]

SGLT2 Inhibitors in Neuroinflammatory Disease

Growing evidence support the beneficial role of SGLT2 inhibitors in neuroinflammatory diseases, including cognitive dysfunction and cerebral atherosclerosis.[106] Contrary to earlier beliefs, recent studies confirmed the expression of SGLT2 in specific brain areas, such as the hippocampus and cerebellum.[107,108] Because of its lipid-soluble characteristics, SGLT2 inhibitors can penetrate the central nervous system with a brain-to-serum ratio ranging from 0.3 to 0.5, allowing it to exert its immunomodulatory function within the central nervous system.[106]

The use of SGLT2 inhibitors can mediate a neuroprotective effect either by directly modulating central nervous system inflammation or indirectly by ameliorating the systemic inflammation outside the central nervous system. For instance, the use of dapagliflozin reduced cerebral inflammation, as evidenced by decreased NF-κB signaling in high-fat diet-induced obese rats. This finding correlated with the prevention of cognitive decline and the restoration of hippocampal synaptic plasticity. By using a complex mouse model combining Alzheimer's disease and diabetes, Hierro-

Bujalance *et al.*[109] revealed that empagliflozin usage reduced microglia burden, a marker of brain inflammation. The empagliflozin-treated group also exhibited improvements in senile plaque burden and amyloid-β levels, as well as an overall enhancement in learning and memory compared to the control group. In another study conducted by Jayarathne *et al.*,[110] it was demonstrated that canagliflozin can lead to notable reductions in age-associated hypothalamic gliosis along with a decrease in inflammatory cytokine production by microglia in old male mice. Moreover, the utilization of canagliflozin resulted in the down-regulation of mTOR signaling in the hypothalamus and hippocampus in old male mice.

Systemic inflammation is recognized to play a critical role in neuroinflammation by disrupting the integrity of the blood-brain barrier, impairing the endothelium of brain microvessels, and inducing a shift in the phenotype of astrocytes and microglia toward a proinflammatory state.[106] The indirect immunomodulating mechanism of SGLT2 inhibitors in neuroprotection largely overlaps with the systemic antiinflammatory effect of SGLT2 inhibitors, which have been extensively discussed in the aforementioned sections.

FUTURE IMPLICATIONS OF HARNESSING THE IMMUNOMODULATORY EFFECTS OF SGLT2 INHIBITORS FOR VARIOUS MEDICAL CONDITIONS

Aging

The persistent, low-grade sterile inflammation is a pivotal factor in the process of aging and the development of age-related illnesses, commonly referred to as "inflamma-aging."[111] This phenomenon is thought to be driven by several fundamental mechanisms, including cell senescence, mitochondrial dysfunction, oxidative stress, impaired autophagy, activation of inflammasomes, and alterations in the composition of gut microbiota.[112,113] Although there is limited clinical data due to the challenges of studying aging in humans, there exists a substantial body of preclinical evidence supporting the potential of SGLT2 inhibitors in the realm of antiaging. A recent review article by Schönberger *et al.* highlights the potential benefit of SGLT2 inhibitors in the aging process, driven by their antiinflammatory, antioxidative, and favorable metabolic properties.[114] IL-6, a well-known cytokine in gerontology society, is strongly associated with the aging-related diseases including diabetes, CVD, and mortality. Studies have demonstrated that the use of SGLT2 inhibitors can reduce circulating IL-6 levels.[13,115] Furthermore, the glucosuria induced by SGLT2 inhibitors is considered to mimic caloric restriction, a known factor in slowing down the aging process.[116]

Autoimmune Nephritis

Although most of the large randomized controlled trials excluded patients with autoimmune kidney diseases due to potential necessities of acute immunosuppression, the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease trial sought to assess the impact of dapagliflozin in combination with RAAS blockades in renal outcome among CKD populations, including those with IgA nephropathy.[117] This study revealed a remarkable 39% reduction in the primary outcome, defined as a ≥50% decline in estimated glomerular filtration rate, end-stage kidney disease, or death from cardiovascular or renal causes, with SGLT2 inhibitor use among the general CKD population. The results were even more striking among patients with IgA nephropathy, with an unprecedented 71% reduction in the primary outcome.[118] This substantial improvement far exceeded the efficacy of RAAS blockades alone, indicating a potential additional benefit of SGLT2 inhibitors in patients with autoimmune kidney diseases.

Even though the utilization of SGLT2 inhibitors in autoimmune nephritis is increasingly gaining attention, there exists very limited data regarding the efficacy and safety of SGLT2 inhibitors in populations with antineutrophilic cytoplasmic autoantibody-associated glomerulonephritis and lupus nephritis. Only 2 studies related to lupus nephritis were identified on www.clinicaltrials.gov (NCT05748925 and NCT05704088). CVD continues to be a paramount cause of mortality, alongside malignancy and infection, with CKD standing out as a robust predictor of unfavorable prognosis for patients with antineutrophilic cytoplasmic autoantibody-associated glomerulonephritis and lupus nephritis.[119] Therefore, it is imperative that future prospective controlled studies be implemented to furnish additional evidence regarding the potential impact of SGLT2 inhibitors to improve kidney and cardiovascular health among individuals with antineutrophilic cytoplasmic autoantibody-associated glomerulonephritis and lupus nephritis.

Solid Organ Transplant Recipients

The seminal randomized controlled trials examining the efficacy of SGLT2 inhibitors did not include solid organ transplant recipients due to concerns that these agents might promote infection, compromise graft function, and alter immunosuppressive drug levels.[1–4,20] Consequently, there is only limited evidence regarding the use of SGLT2 inhibitors in this specific patient population.

The utilization of SGLT2 inhibitors in solid organ transplant recipients is an attractive prospect, particularly given the high prevalence of both preexisting and *de novo* posttransplant diabetes mellitus, as well as the elevated cardiovascular risk observed in this population.[120,121] Numerous observational studies and systemic reviews have explored the safety and efficacy of SGLT2 inhibitors in kidney transplant recipients.[122,123] However, the clinical benefits of SGLT2 inhibitors on cardiovascular and kidney health in the transplant population remain inconclusive due to substantial heterogeneity in study population and limited power in most of these investigations.[124]

Therefore, it remains imperative to conduct further assessments of the efficacy and safety of SGLT2 inhibitors in kidney transplant recipients through prospective controlled studies; in particular the potential increased risk in urinary tract infections and fungal infections. Several ongoing studies were identified on www.clinicaltrials.gov, enrolling various types of transplant recipients and focusing on diverse aspects of clinical outcomes (NCT04965935, NCT06013865, NCT05013112, NCT04906213, NCT05788276, NCT05938712, NCT04918407, NCT04743453, and NCT03642184 for kidney transplant recipients; NCT05321706 for heart transplant recipients; NCT05042505 for liver transplant recipients; and NCT03113110 for all posttransplant diabetes mellitus).

CONCLUSION

SGLT2 inhibitors have demonstrated pleiotropic effects that extend well beyond their initial role as a hypoglycemic agent (Figure 2), prompting investigators to

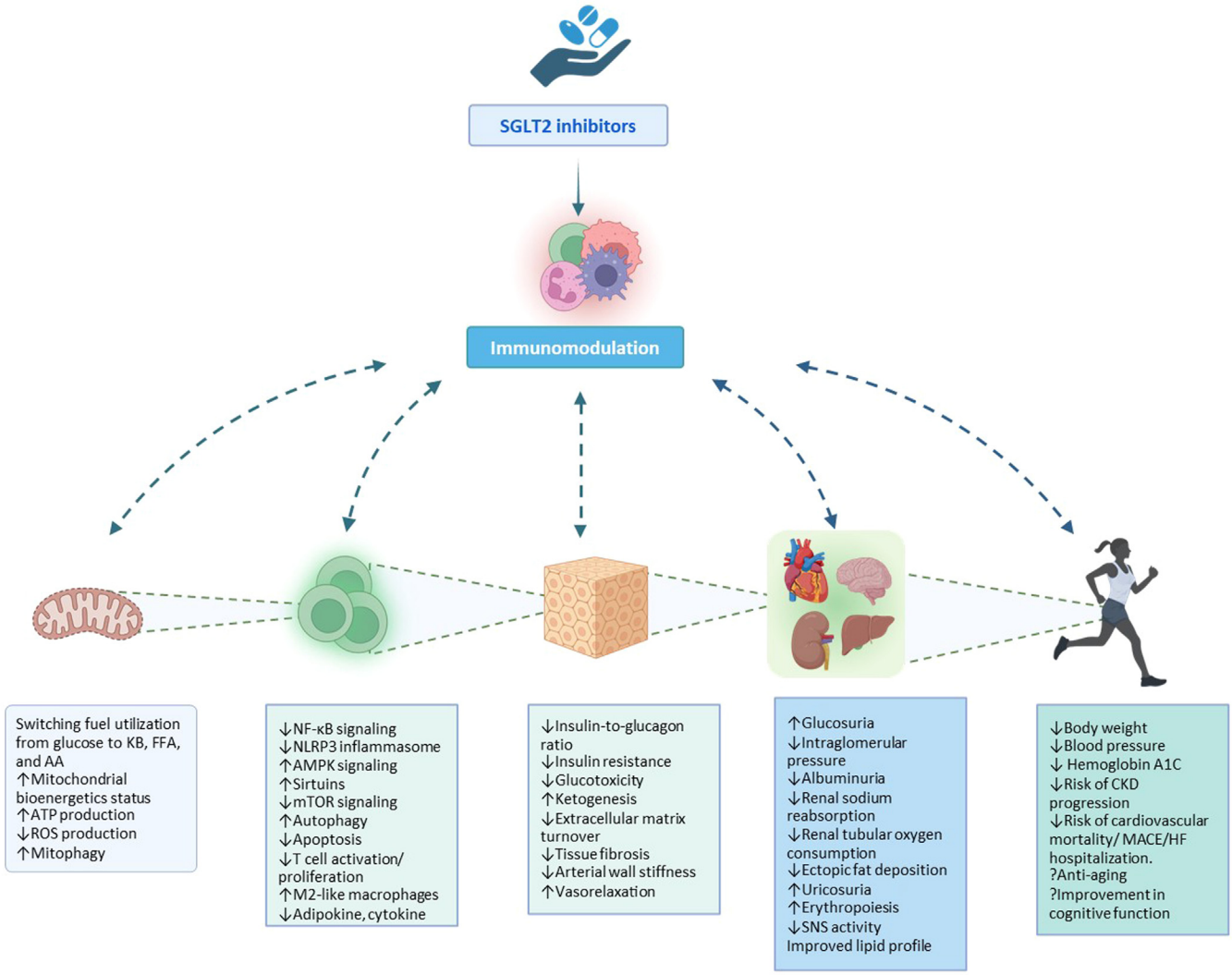

Figure 2. Potential multifaceted impact of SGLT2 inhibitors via immunomodulation and its crosstalk over multilayer of biological system. AA, amino acid; AMPK, 5′ adenosine monophosphate-activated protein kinase; ATP, adenosine triphosphate; CKD, chronic kidney disease; FFA, free fatty acid; HF, heart failure; KB, ketone body; MACE, major adverse cardiovascular event; mTOR, mammalian target of rapamycin; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; ROS, reactive oxygen species; SGLT2 inhibitors, sodium-glucose cotransporter-2 inhibitors; SNS, sympathetic nervous system. Created with BioRender.com.

conduct further investigations. Through extensive preclinical studies, SGLT2 inhibitors have been shown to exert immunomodulatory effects, either directly or indirectly influencing various targets and pathways crucial for immune activation. Amid the influx of new data, the challenge still remains in understanding the dominant mechanism of the significant benefits on cardiovascular and renal outcome. Bridging this knowledge gap and translating this information from research back to bedside will hopefully lead to more precise and targeted use of SGLT2 inhibitors in patients with proinflammatory conditions.

DISCLOSURE

The study was supported in part by the Harold and Ellen Danser Endowed/ Distinguished Chair in Transplantation at Massachusetts General Hospital (Boston, MA, USA) and the National Institute of Health (NIH) -grant R01AI143887 (to LVR). LVR has received research funding unrelated to this topic from Brystol-Meyers Squibb, Visterra, Natera, Caredx, Sanofi and AstraZeneca. SAL declared no competing interests.

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