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REVIEW

Sodium–Glucose Cotransporter Protein 2 Inhibitors: Novel Application for the Treatment of Obesity-Associated Hypertension

Yilan Hu[1,2], Jiaqi Bao[1,2], Zhicheng Gao[1,2], Lifang Ye[2], Lihong Wang[1,2]

[1]The Second Clinical Medical College, Zhejiang Chinese Medical University, Hangzhou, People's Republic of China; [2]Heart Center, Department of Cardiovascular Medicine, Zhejiang Provincial People's Hospital, Affiliated People's Hospital, Hangzhou Medical College, Hangzhou, People's Republic of China

Correspondence: Lihong Wang, Heart Center, Department of Cardiovascular Medicine, Zhejiang, Provincial People's Hospital, Affiliated People's Hospital, Hangzhou Medical College, Hangzhou, People's Republic of China, Email wanglhnew@126.com

Abstract: Obesity is becoming increasingly prevalent in China and worldwide and is closely related to the development of hypertension. The pathophysiology of obesity-associated hypertension is complex, including an overactive sympathetic nervous system (SNS), activation of the renin–angiotensin–aldosterone system (RAAS), insulin resistance, hyperleptinemia, renal dysfunction, inflammatory responses, and endothelial function, which complicates treatment. Sodium–glucose cotransporter protein 2 (SGLT-2) inhibitors, novel hypoglycemic agents, have been shown to reduce body weight and blood pressure and may serve as potential novel agents for the treatment of obesity-associated hypertension. This review discusses the beneficial mechanisms of SGLT-2 inhibitors for the treatment of obesity-associated hypertension. SGLT-2 inhibitors can inhibit SNS activity, reduce RAAS activation, ameliorate insulin resistance, reduce leptin secretion, improve renal function, and inhibit inflammatory responses. SGLT-2 inhibitors can, therefore, simultaneously target multiple mechanisms of obesity-associated hypertension and may serve as an effective treatment for obesity-associated hypertension.

Keywords: sodium-glucose cotransporter protein 2 inhibitors, obesity-associated hypertension, metabolism, neuro-humoral regulation, inflammation

Introduction

Since the 1990s, China's economy has grown rapidly and people's lifestyles have changed considerably,[1] with a concurrent rapid increase in the prevalence of obesity. China now has the largest number of people with obesity worldwide.[2,3] Obesity is a major risk factor for non-communicable diseases, presenting a great public health and economic burden.[3,4]

Hypertension is one of the most common complications of obesity, as well as a major risk factor for stroke, myocardial infarction, heart failure, and chronic kidney disease.[5] It is estimated that by 2025, approximately 1.5 billion people worldwide will be affected by hypertension.[6] A study including one million people in China from 2014 to 2017 showed that nearly half of adults aged 35–75 years suffer from hypertension, with approximately 22.5% of the people with hypertension being obese.[7]

Obesity-induced hypertension has diverse, interrelated pathogenic mechanisms, which complicates treatment. Many patients with obesity struggle to control their weight and blood pressure through diet and lifestyle changes and require treatment with drugs, such as orlistat, liraglutide, or bariatric surgery.[8] First-line treatments for obesity-related hypertension currently include angiotensin-converting enzyme (ACE) inhibitors, angiotensin II (ANG II) receptor blockers, and calcium channel blockers.[9]

Sodium-glucose cotransporter 2 is mainly expressed in the proximal convoluted tubules of the kidney and is involved in glucose reabsorption. SGLT-2 inhibitors, a new class of drugs currently used to treat type 2 diabetes mellitus (T2DM), reduce blood glucose levels by increasing glucose excretion in the urine. This mechanism is insulin-independent, thus reducing the risk of hypoglycemia. More and more evidence suggests that SGLT-2 inhibitors have renal and

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cardiovascular protective effects in both diabetic and non-diabetic patients; thus, they are used in the treatment of heart failure and chronic kidney diseases.[10–13] In addition, SGLT-2 inhibitors have been found to reduce body weight and blood pressure. Weight loss is a critical component in the treatment of patients with obesity-related hypertension. Therefore, SGLT-2 inhibitors may be a new option over the current first-line drug treatment of obesity-related hypertension. This review discusses the beneficial effects of SGLT-2 inhibitors targeting the pathogenic mechanisms of obesity-associated hypertension (Figure 1).

Obesity-Associated Hypertension, SGLT-2 Inhibitors, and the Sympathetic Nervous System

Over-activation of the sympathetic nervous system (SNS) in patients with obesity is associated with insulin resistance, hyperinsulinemia, obstructive sleep apnea, and renin–angiotensin–aldosterone system (RAAS) activation.[14] Increased sympathetic nerve activity (SNA) is an important mechanism for the development of hypertension.[15,16] However, SNS activation in patients with obesity varies between tissues. Animal and human studies using norepinephrine-spillover assessment and microneurographic measurements found increased SNA in the kidney and skeletal muscle, whereas cardiac SNA tends to be normal or may even be reduced.[17–20] In a canine renal denervation model fed a high-fat diet, sodium retention and elevated blood pressure were greatly attenuated compared with controls,[21] and in hypertensive patients with obesity, catheter-based renal denervation significantly reduced blood pressure for at least 3 years,[22] which suggests that renal nerves play a key role in SNS activation and therefore in blood pressure in patients with obesity. Correlative studies in obese mice have shown that dapagliflozin decreases intrarenal tyrosine hydroxylase and norepinephrine.[23] Dapagliflozin also reduced renal SNA, thereby reducing blood pressure and inhibiting weight gain in a mouse model of neurogenic hypertension.[24] In a diabetic rabbit model, empagliflozin reduced SNS activity to similar levels as those of non-diabetic rabbits.[25] Furthermore, ApoE-deficient mice treated with empagliflozin had significantly lower norepinephrine levels and suppressed SNA compared with controls.[26] SGLT-2 inhibitors also improve the circadian rhythm of SNA,[27,28] which may improve blood pressure. Although several

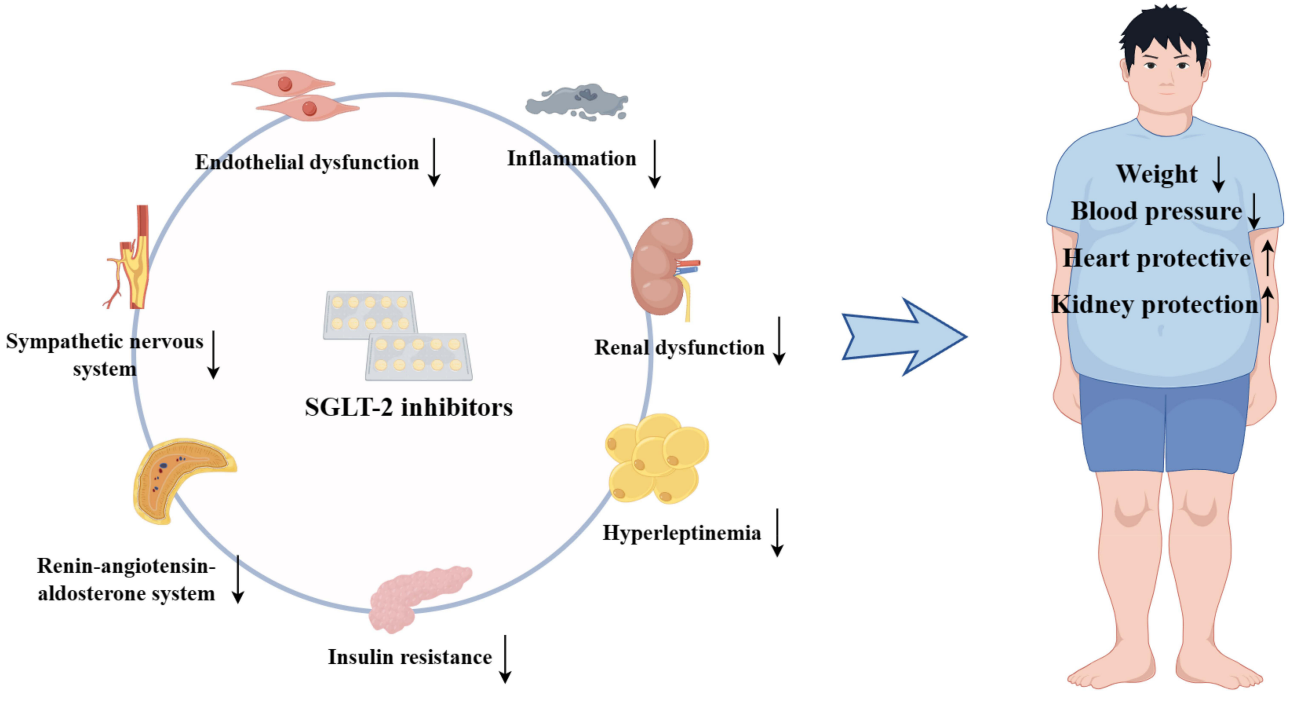

Figure 1 The mechanisms of SGLT-2 inhibitors for the treatment of obesity-associated hypertension. Taking sympathetic nervous system, renin-angiotensin-aldosterone system, insulin resistance, hyperleptinemia, renal insufficiency, inflammatory response and endothelial function as the main aspects, can improve the body weight and blood pressure of patients with obesity-related hypertension, and better protect the heart and kidney function.

studies have demonstrated that SGLT-2 inhibitors inhibit SNS activation, the exact mechanism remains unclear and requires experimental studies in humans.

Obesity-Associated Hypertension, SGLT-2 Inhibitors, and the Renin–Angiotensin–Aldosterone System

The renin–angiotensin–aldosterone system (RAAS) is a hormonal cascade that plays an important role in blood pressure regulation. Several important components of the RAAS, including plasma renin activity, angiotensinogen (AGT), ACE activity, ANG II, and aldosterone, are moderately elevated in patients with obesity, especially visceral obesity.[29] RAAS activation occurs in patients with obesity even in the presence of obesity-related volume expansion and sodium retention, and may be associated with SNS hyperactivation, renal compression, and adipose tissue dysfunction.[30] Adipose tissue can produce and secrete ANG II.[31] In addition, AGT is closely related to ANG II production, and white adipose tissue is second only to the liver as a source of AGT.[32] Moreover, adipocyte AGT-deficient mice fed a high-fat obesogenic diet do not develop elevated blood pressure, whereas control mice fed the same diet exhibit elevated plasma ANG II concentrations and blood pressure.[33] In addition to ANG II stimulating adrenal aldosterone secretion in patients with obesity, adipocytes have been shown to produce aldosterone[34] that induces sodium retention, which in turn leads to increased blood pressure. ACE inhibitors, ANG II receptor blockers, and saline cortical receptor antagonists have all been shown to reduce blood pressure in patients with obesity,[35–37] highlighting the important role of the RAAS in obesity-associated hypertension. In high-fat diet-induced diabetic mice, canagliflozin inhibits AGT and attenuates hypertension.[38] In obese rats with T2DM, 12 weeks of dapagliflozin treatment not only lowered glucose levels but also reduced RAAS activation.[39] The macula densa, a chemoreceptor located in the glomerulus, regulates renin secretion in a sodium-dependent manner, thereby affecting RAAS activity. As SGLT-2 is a sodium-glucose cotransporter, SGLT-2 inhibitors reduce sodium reabsorption in the proximal tubule,[40] which leads to increased sodium delivered to the macula densa, reducing renin release and activating the RAAS.[41] In contrast, some studies have shown that sodium reabsorption is reduced in the proximal tubule and that polyureic natriuretic stimulation induced by SGLT-2 inhibitors activates systemic RAAS in patients with diabetes but does not affect intrarenal RAAS.[42–44] Furthermore, no significant changes in plasma aldosterone levels are seen in patients treated with SGLT-2 inhibitors, which may be related to the aldosterone circadian rhythm.[42,45] Overall, the effects of SGLT-2 inhibitors on the RAAS are complex and controversial, and although several studies have shown that SGLT-2 inhibitors attenuate RAAS activation, further research is required.

Obesity-Associated Hypertension, SGLT-2 Inhibitors, and Insulin Resistance

Obesity is often accompanied by hyperinsulinemia and insulin resistance, which play an important role in the development of hypertension.[46] Animal experiments have shown that insulin promotes renal sodium reabsorption through activation of sodium/proton exchange protein 3 (NHE3) and epithelial sodium channels, thereby leading to sodium retention.[47–49] In addition, under normal physiological conditions, insulin stimulates endothelial nitric oxide (NO) production, exerting anti-inflammatory and vasodilatory effects. Insulin-resistant states impair the selectivity of the insulin-stimulated O pathway, and compensatory hyperinsulinemia may activate mitogen-activated protein kinase, leading to vasoconstriction, water and sodium retention, and increased inflammatory responses.[50] Furthermore, hyperinsulinemia may increase SNS activity and activate the RAAS, thereby elevating blood pressure,[51–53] but this theory is currently controversial and requires further investigation. SGLT-2 inhibitors increase glucose excretion in an insulin-independent manner, lowering glucose levels, reducing glucose toxicity, and improving insulin sensitivity.[54] In obese mice, dapagliflozin effectively reduces plasma insulin levels and improves pancreatic β-cell function after 10 weeks of treatment.[55] Dapagliflozin also improves pancreatic injury, attenuates hyperinsulinemia, and reduces body weight in rats fed a high-fat diet by modulating the AMPK/mTOR signaling pathway, a major regulatory pathway for cell growth.[56] Moreover, in a clinical study of pre-diabetic patients with insulin resistance, those treated with oral empagliflozin were found to have a more significant reversal of insulin resistance and lower blood pressure than the control group.[57] Furthermore, several studies have reported that SGLT-2 inhibitors reduce insulin resistance in patients with diabetes[58,59] with greater efficacy than metformin.[60,61] Therefore, as insulin resistance is associated with metabolic activity, SGLT-2 inhibitors may be beneficial for the treatment of obesity and related metabolic diseases.

Obesity-Related Hypertension, SGLT-2 Inhibitors, and Hyperleptinemia

Leptin is an adipose-derived cytokine that suppresses appetite and increases energy expenditure.[62] Leptin also stimulates the SNS, affecting cardiac and renal function.[63] However, in people with obesity, high levels of leptin in circulating plasma induce a leptin-resistant state, which affects the appetite-suppressing effects of leptin but does not attenuate SNS activation.[64] This selective leptin resistance suggests that hyperleptinemia may elevate blood pressure primarily through modulation of SNS activity, as demonstrated in experimental animal models.[65,66] Furthermore, studies have shown that in the obese state, hyperleptinemia decreased NO availability and attenuated the vasodilatory effects of NO.[67] Leptin is one of the most studied adipokines, and SGLT-2 inhibitors have been shown to improve metabolism by modulating adipokine levels.[68] In obese rats, leptin levels and body mass index were significantly reduced by empagliflozin treatment.[69] After 16 weeks of dapagliflozin treatment, serum leptin levels significantly decreased, and blood glucose and blood pressure significantly improved in patients with poor glycemic control.[70] Furthermore, in patients with T2DM, dapagliflozin reduced circulating leptin levels, improved metabolism, and reduced cardiovascular risk.[68,71,72] A recent clinical study showed that empagliflozin significantly reduced leptin levels compared with other glucose-lowering drugs used to treat patients with obesity and T2DM, such as biguanides and sulfonylureas.[73] In addition, leptin levels are proportional to adiposity, and SGLT-2 may reduce leptin secretion via its weight-loss effect.[74] As leptin is a major contributor to obesity and elevated blood pressure, leptin may be a potential target for SGLT-2 inhibitors in the treatment of obesity-associated hypertension.

Obesity-Associated Hypertension, SGLT-2 Inhibitors, and Renal Dysfunction

Obesity increases sodium reabsorption by the kidneys through physical compression of the kidneys, RAAS activation, and increased SNS activity,[5] thereby leading to sodium retention, increased extracellular fluid, and increased blood pressure. During the early stages of weight gain, there is an increase in renal blood flow and glomerular hyperfiltration, which leads to increased sodium reabsorption. Following excessive weight gain, the kidneys are compressed by surrounding adipose tissue, which causes increased sodium reabsorption in the loop of Henle, thus indirectly increasing renin secretion and RAAS activation.[75] RAAS and SNS activation increases sodium reabsorption in the renal tubules, causing sodium retention. Moreover, patients with obesity often exhibit hyperinsulinemia, dyslipidemia, and inflammation, the combination of which leads to renal insufficiency.[76] Renal insufficiency has been demonstrated to cause hypertension in both animal experimental models and humans.[77] In a double-blind, randomised trial involving patients with T2DM and kidney disease, long-term canagliflozin treatment reduced the risk of kidney failure, doubling of the creatinine level, or death from renal causes compared with placebo, with lower blood pressure and body weight.[78] A further clinical study indicated that empagliflozin reduces the risk of kidney disease progression and hospitalisation of patients with chronic kidney disease, with or without T2DM.[79] SGLT-2 inhibitors improve renal tissue viability by ameliorating oxidative damage through reduced glucose reabsorption.[80] In addition, SGLT-2 inhibitors reduce uric acid concentration,[81] thereby reducing renal injury.[82] SGLT-2 inhibitors also inhibit NHE3 activity, which can cause sodium retention.[83,84] Although the potent renoprotective activity of SGLT-2 inhibitors has been demonstrated, specific studies in patients with obesity-associated hypertension are still required.

Obesity-Associated Hypertension, SGLT-2 Inhibitors, and Inflammation

Obesity is recognised as a chronic low-grade inflammatory disease, and chronic inflammation plays an important role in the development and progression of hypertension.[85] Obesity is characterised by excess adipose tissue, which secretes various adipokines that are involved in metabolic and inflammatory responses.[86] Fat accumulation leads to adipocyte dysfunction and increased secretion of pro-inflammatory factors, such as tumor necrosis factor α, interleukin-6, interleukin-1 β, and resistin.[87] In addition, several animal and human studies have shown that obesity increases the number of macrophages.[88,89] Macrophages can alternate between the classically activated M1 phenotype, which is associated with increased production of pro-inflammatory factors, and the alternatively activated M2 phenotype, which repairs damaged tissue and prevents inflammation.[90,91] In patients with obesity, macrophage polarisation is shifted from M2 to M1, resulting in increased production of pro-inflammatory factors,[92] which induce inflammation, insulin resistance, oxidative stress, and endothelial dysfunction, thereby leading to vascular sclerosis and increased peripheral vascular resistance,[93,94] and ultimately hypertension. Numerous studies have demonstrated the

anti-inflammatory effects of SGLT-2 inhibitors.[95–98] For example, empagliflozin reduces the amount of adipose tissue and the size of adipocytes and attenuates inflammation in ApoE-deficient mice fed a Western diet.[99] Moreover, in spontaneously hypertensive rats, continuous feeding of empagliflozin for 30 days improved inflammatory response and blood pressure.[100] Dapagliflozin pretreatment of macrophages obtained from healthy humans reduced M1 polarisation by bacterial lipopolysaccharide in vitro, thus reducing the M1/M2 ratio and blocking pro-inflammatory factor secretion.[101] Additionally, in C57BL/6 mice with lipopolysaccharide-induced lung injury, canagliflozin reduced the M1/M2 macrophage ratio in vivo and contributed to attenuating the inflammatory response.[102] In addition, empagliflozin attenuated inflammation, ameliorated endothelial dysfunction, and counteracted atherosclerosis in ApoE-deficient mice.[103] Overall, SGLT-2 inhibitors reduce the amount of adipose tissue and the size of adipocytes, and modulate macrophage phenotypic transformation, thereby reducing inflammation.[104] In recent years, numerous studies have demonstrated the anti-inflammatory effects of SGLT-2 inhibitors, suggesting additional indications for these drugs.

Obesity-Associated Hypertension, SGLT-2 Inhibitors, and Endothelial Function

Endothelial cells are involved in the regulation of vascular function through mediators such as NO.[105] Our blood vessels are surrounded by adipose tissue known as perivascular adipose tissue (PVAT), which is able to regulate endothelial and vascular smooth muscle function through endocrine and paracrine effects and secretion of biologic factors (eg, contractile and relaxing factors).[106] In obese patients, with the increased presence of PVAT, leading to dysregulation of its secretory function, it affects the homeostasis of the vascular system, leading to endothelial dysfunction.[107] Other unfavourable factors of endothelial function, such as insulin resistance and inflammatory response, are also present in obese patients, as mentioned previously. When endothelial dysfunction occurs, endothelial nitric oxide synthase (eNOS) function and activity are altered, more reactive oxygen species (ROS) are produced, and enzyme "uncoupling" occurs, leading to an increased likelihood of cardiovascular disease, such as hypertension and atherosclerosis.[108,109]

Previous animal and clinical studies have demonstrated the effects of SGLT-2 inhibitors on vascular endothelial cells and vasoprotective effects. A prospective study in patients with T2DM revealed a decrease in blood pressure and a certain improvement in vascular function after 6 weeks of treatment with empagliflozin compared with a placebo control group.[110] Furthermore, it was shown that patients with T2DM who had good glycaemic control after 2 days of acute treatment with dapagliflozin had a significant improvement in whole-body endothelial function, which may demonstrate that the effects of SGLT-2 inhibitors on the vascular system are rapid and direct.[111] Although many studies have demonstrated the vasoprotective effect of SGLT-2 inhibitors, the mechanism has not been fully elucidated and may be related to their ability to reduce ROS production, increase NO utilisation, and reduce oxidative stress.[112–115] Therefore, in patients with obese hypertension, early administration of SGLT-2 inhibitors may be able to improve their vascular function, benefiting the cardiovascular system and reducing the incidence of cardiovascular emergencies.

Conclusions

The increasing prevalence of obesity places a significant burden on human health and the healthcare system. The development of hypertension is closely related to obesity. Factors influencing obesity-associated hypertension are diverse and include, but are not limited to, SNS overactivity, RAAS activation, insulin resistance, hyperleptinemia, renal dysfunction, inflammatory responses, and endothelial function. Among them, SNS, RAAS, and renal function interact with each other. Insulin resistance and hyperleptinemia often exist at the same time, resulting in increased SNS activity and changes in vascular endothelial function. Inflammation is related to insulin resistance and dysfunction. These complex pathological mechanisms complicate the treatment of obesity-associated hypertension. SGLT-2 inhibitors have received significant research interest in recent years, and their clinical indications are constantly expanding. SGLT-2 inhibitors can simultaneously target multiple mechanisms of obesity-associated hypertension and may therefore be effective for the treatment of obesity-associated hypertension. However, few clinical studies have investigated SGLT-2 inhibitors for obesity-associated hypertension, and large-scale clinical trials are required to investigate the efficacy of SGLT-2 inhibitors for obesity-associated hypertension.

Disclosure

The authors report no conflicts of interest in this work.

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