Cardiorenal Protection with Sodium-Glucose Co-Transporter 2 Inhibitors

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Sodium-glucose co-transporter 2 (SGLT2) is a family of glucose transporter proteins localized in the proximal tubule of the nephron, responsible for the majority of filtered glucose and sodium reabsorption, and SGLT2 inhibitors (SGLT2-Is) are novel drugs for the treatment of T2DM and heart failure.

SGLT2 inhibitors diabetes mellitus cardiorenal protection

1. Introduction

Sodium-glucose co-transporter 2 (SGLT2) is a family of glucose transporter proteins localized in the proximal tubule of the nephron, responsible for the majority of filtered glucose and sodium reabsorption, and SGLT2 inhibitors (SGLT2-Is) are novel drugs for the treatment of T2DM and heart failure [1][2].

SGLT2-Is reduce the renal threshold for glucose excretion, resulting in an increase in urinary glucose excretion and a decrease in blood glucose levels. This reduces glucotoxicity and improves whole-body β-cell function and insulin sensitivity [3][4].

The precursor of SGLT-Is, the phlorizin, was isolated from the root of the apple tree in 1835, and its glycosuric properties were identified a century later [5][6].

In the last decade, several SGLT2-Is have been developed as derivatives of this drug, including dapagliflozin, canagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, and tofogliflozin. In addition to their structural differences, these agents have different half-lives and selectivity for SGLT2 co-transporters. The United States Food and Drug Administration and the European Union currently have approved only the first four SGLT2-Is [7]. In contrast, ipragliflozin, tofogliflozin, and luseogliflozin have been authorized in Japan [8][9].

The protective effect of SGLT2-Is on the reduction of acute and chronic cardiovascular (CV) events is well known [10]. Therefore, early clinical trials of SGLT2-Is focused on improving glucose plasma levels and other diabetes-related effects. However, the CV benefits observed in several studies generated considerable interest in their therapeutic benefits beyond glycemic control, and a number of cardiovascular outcome studies have been conducted over the past six years. Unexpectedly, these drugs have shown a reduction in the risk of cardiovascular disease in general, with particularly marked effects on CV death and hospitalization for HF [11][12].

A number of large clinical trials have been conducted to evaluate the safety and efficacy of SGLT2-Is in patients with diabetes and established vascular disease, multiple cardiovascular risk factors, or renal failure and in patients with established HF and reduced ejection fraction, with and without T2DM [13]. The most important results of the EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcomes Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose) trial showed that T2DM patients who were at high risk for CV disease had early reductions in major CV and renal sequelae [14]. This included a significant reduction in CV death and hospitalization for HF in patients treated with empagliflozin. Subsequent large trials with other SGLT2-Is, such as canagliflozin (CANVAS (Canagliflozin Cardiovascular Assessment Study) [15] and CREDENCE (Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy) trials [16]) and dapagliflozin (DECLARE-TIMI 58 (Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes) trial [17]), confirmed these observations in a broader population of primary and secondary prevention patients [18][19]. O'Hara et al., in a recent review, showed that the administration of dapaglifozin in non-diabetic patients may prevent the onset of overt diabetes mellitus [20]. This observation came from the results of a pre-specified pooled analysis of the DAPA-CKD [21] and DAPA-HF [12] trials and raises the possibility of an expanded target patient population.

In addition, SGLT2-Is showed a lower risk of CKD, even in non-diabetic patients [11]. Research to date to identify the mechanisms of action of SGLT2-Is has yielded impressive results. The lack of consistent glucose dependence of cardiorenal protection, with no significant difference between subjects with and without T2DM and across levels of glucose control in T2DM patients, suggested a predominant role of non-glucose-mediated pathways [11][12].

In the kidney, SGLT2-Is act by restoring sodium/fluid homeostasis; they have pleiotropic effects on calcium/phosphate homeostasis, magnesium levels, glomerular tubular feedback, and energy metabolism. In the heart, they modulate the cardiac sodium-hydrogen exchanger. Other effects include systemic metabolic and hemodynamic adjustments, the attenuation of mitochondrial dysfunction, and the stimulation of autophagy [22].

2. SGLT2 Inhibition and Kidney Protection

In healthy adult men, maximal glucose tubular transport (TmG) is approximately 375 mg/min, which correlates with 300 mg of glucose per day [23][24]. During normoglycemic and hypoglycemic conditions, filtered glucose is completely reabsorbed at the proximal convoluted tubules by means of SGLT2, as the glucose filtration rate is lower than TmG. Glycosuria appears when glycemia exceeds the threshold level of 180 mg/d. Underlying this is the action of SGLT2, located below Bowman's capsule in the S1 segment of the proximal tubule, and sodium-glucose co-transporter 1 (SGLT1), located in the S2–S3 segment below [25]. Around 80–90% of filtered glucose is reabsorbed by SGLT2, and the remainder by SGLT1. SGLT2 has high transport capacity, but lower affinity for glucose, unlike SGLT1. Patients with T2DM present higher expression of SGLT2s in the proximal tubule compared to healthy individuals [26].

During hyperglycemia, as glucose and sodium reabsorption are coupled, increased glucose reabsorption leads to increased sodium reabsorption, which is responsible for hypertension in diabetic subjects. The increased extracellular fluid volume resulting from the hyperabsorption of sodium also causes an atrial natriuretic peptide rise

and vasodilatation of the glomerular afferent arteriole. In addition, a low sodium concentration detected at the macula densa activates the renin–angiotensin–aldosterone system (RAAS), with increased production of angiotensin II (ATII) and vasoconstriction of the efferent arteriole [27]. Vasodilation of the afferent arteriole by nitric oxide, adenosine, and prostanoids and vasoconstriction of the efferent arteriole by ATII result in increased endoglomerular filtration pressure with glomerular hyperfiltration, which damages the mesangial structure and causes inflammation, fibrosis, renal damage, and albuminuria [28]. SGLT2 inhibition leads to an increased concentration of sodium chloride in the tubular fluid, which may trigger a cascade that reduces the GFR by afferent glomerular arteriole constriction. SGLT2-I-mediated diuresis and natriuresis also reduce the concentration of circulating natriuretic peptides, which contributes to vasoconstriction of the efferent arteriole [27]. Moreover, the macula densa sensing of an increased sodium concentration activates the tubuloglomerular feedback, which causes vasoconstriction of the afferent arteriole and suppresses renin production by juxtaglomerular cells, reducing RAAS system activation and enhancing efferent glomerular arteriole vasodilation, which further reduces GFR and glomerular hyperfiltration. SGLT2-Is reduce active tubular transport work and, thereby, reduce the energy demand and oxygen consumption in the kidney [29], showing that it is precisely reduced cortical oxygenation that predicts the progressive decline in renal function. Thus, by reducing glomerular hyperfiltration and hyperglycemia, SGLT2 inhibition also decreases albuminuria, tubular growth, and tubulo-interstitial inflammation. SGLT2-I cardiovascular outcome trials in diabetes mellitus patients demonstrated that empagliflozin, canagliflozin, and dapagliflozin reduce hyperfiltration at the onset of therapy and slow the decline in estimated glomerular filtration rate (eGFR) in the long-term. This might be due to an improvement in mitochondria integrity and function, tubular energy, and autophagy. Darshi M et al. showed that diabetes increases the urinary ratio of lactate to pyruvate, thus inducing an increase in glycolysis at the expense of mitochondrial oxidation [30], and they demonstrated that this dangerous process was reversed by SGLT2-I administration. In addition, dapagliflozin treatment improves mitochondrial function in diabetics, increasing urinary metabolites linked to mitochondrial metabolism compared with a placebo, suggesting that SGLT2 inhibition may improve mitochondrial function in diabetes [31]. Lee et al. showed that empagliflozin treatment improved mitochondrial fragmentation and enhanced renal proximal tubule cell autophagic activity under hyperglycemia by involving the AMP-activated protein kinase (AMPK) and the mammalian target of rapamycin (mTOR) signaling pathways, resulting in reduced apoptosis and tubulo-interstitial fibrosis [32], so empaglifozin improved tubular mitochondrial dynamics and increased autophagic activity. Autophagy is a mechanism that allows healthy renal tubules and podocytes to maintain their structural and functional integrity by counteracting oxidative stress. In the diabetic kidney, excessive oxidative stress is not adequately limited [33] as the autophagy process is impaired, resulting in the dysfunction and death of podocytes and tubular cells [34].

3. SGLT2 Inhibition and Heart Protection

While the nephroprotective action has solid evidence, the mechanisms responsible for SGLT2-I-related cardioprotection are still not well understood. Today, gliflozins represent one of the “four pillars” of therapy for reduced ejection fraction heart failure (HFrEF), to be introduced immediately in combination with ARNI (or ACE inhibitors/sartan), beta-blockers, and mineralocorticoid antagonists in recommendation class IA. The first published study, DAPA-HF [35], evaluated the efficacy of dapaglifozin vs. placebo on a primary endpoint of worsening HF, i.e.,

hospitalization, and cardiovascular death in 4744 patients with HFrEF, regardless of the presence of diabetes. The primary endpoint was reduced in 26% of patients. Similar results were recently obtained with empaglifozin in the Emperor Reduced study [36], which demonstrated a superior reduction in adverse events of empaglifozin to placebo. Among the cardioprotective effects are certainly the vascular and hemodynamic ones. The glycosuric action is associated with a diuretic action [37][38], resulting in increased reabsorption of interstitial edema and a reduction in preload and afterload with positive hemodynamic effects. According to the Frank–Starling law, the cardiomyocyte contractility is directly related to cell distension and preload, but overdistension impairs contractility and leads to a reduction in cardiac output. Therefore, natriuresis and diuresis associated with SGLT2 pathway inhibition may improve cardiac contractility by reducing the plasma volume, preload, and myocardial overdistension. The reduction in blood pressure and afterload induced by gliflozins represent another important mechanism that improves cardiac function [39]. Osmotic diuresis is responsible for the reduction in blood pressure values; in particular, treatment with SGLT2-Is is associated with a significant decrease in blood pressure—an average reduction of approximately 3–4.5 mmHg for systolic blood pressure and 1–2 mmHg for diastolic blood pressure compared to baseline levels [40]. The results of four placebo-controlled studies showed that canagliflozin causes a significant reduction in systolic blood pressure compared to placebo, with a dose-dependent effect (−4.00 mmHg at the 100 mg dosage and −5.0 mmHg with 300 mg) [41]. The same analysis showed that 67.1% and 69.9%, respectively, of patients treated with canagliflozin 100 and 300 mg reached the target value of systolic blood pressure <140 mmHg (32.2% and 39.8%, respectively, for the target value <130 mmHg). Canaglifozin has been shown to return the urine volume to pre-treatment levels after 3 months of treatment, although the blood pressure reduction persists [42], suggesting that, besides diuresis, also other mechanisms contribute to the reduction in arterial pressure, such as nephron remodeling, endothelial function improvement, arterial stiffness reduction, and loss of body weight related to caloric loss through glycosuria [27]. The glycosuria-related reduction in body weight and adipose tissue also leads to a reduction in insulin resistance [43]. In addition, there is a change in adipose tissue expression of adipokines and leptin with a reduction in inflammation and oxidative stress at the endothelial level [44].

In patients with HF there is a decreased ATP availability with a shift from the mitochondrial oxidation of glucose to glycolysis. SGLT2 inhibition, on the other hand, increases free fatty acid oxidation, stimulating ketogenesis and shifting substrate use towards fat; this improves mitochondrial function, cardiomyocyte energy efficiency, and ventricular contractile performance [45][46]. In detail, SGLT2-Is are associated with increased ketogenesis as a consequence of the reduced renal glucose reabsorption [39]. Ketone bodies are produced in the liver and are utilized as energy-efficient substrates in extrahepatic tissue, including the heart and kidneys. β-Hydroxybutyrate (β-HB) is the predominant ketone body utilized in the heart; it is converted to acetoacetate via β-hydroxybutyrate dehydrogenase 1 and activated by the succinyl-CoA:3-oxoacid CoA transferase to form acetoacetyl CoA. Acetoacetyl-CoA undergoes a thiolysis process to form acetyl-CoA and then enters the tricarboxylic acid cycle to produce adenosine triphosphate (ATP) for cardiac contraction [47]. SGLT2-Is can raise the level of β-HB to around 0.6 mmol/L in patients with diabetes and to around 0.3 mmol/L in those without diabetes [45]. SGLT2-Is also reduce

epicardial adipose tissue, which could result in the reduction of leptin and RAAS components, which are involved in cardiac vascular inflammation and fibrosis [48].

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