Diabetes & Metabolic Syndrome: Clinical Research & Reviews xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Review

SGLT-2 inhibitors: Their pleiotropic properties

Natalia G. Vallianou[a,*], Eleni Geladari[a], Christos E. Kazazis[b]

[a] Department of Internal Medicine, Evangelismos General Hospital, Athens, Greece
[b] Horonary Lecturer at Leicester University, Samos, Greece

ARTICLE INFO

Article history:
Available online xxx

Keywords:
Sodium-glucose-co-transporters 2 inhibitors
Glycosuria
Kidney
Angiotensin (1–7)
Cardiovascular risk
Safety profile

ABSTRACT

Type 2 diabetes mellitus has become a global pandemic. Nowadays, it is estimated that approximately 415 million people all over the world have diabetes. The sodium glucose co-transporters 2 inhibitors are a new class of glucose-lowering agents, which act through a novel mechanism by producing a decline in glucose re-absorption in the kidney, thereby increasing glycosuria and decreasing serum glucose levels. Data suggest that apart from lowering HbA1c, they produce a small but significant weight loss and a small decrease in blood pressure. Also, they possess nephro-protective potential. These drugs are demonstrated to restore intra-glomerular pressure by increasing angiotensin (1–7), which exerts vasodilatory and anti-inflammatory effects. Their profile on cardiovascular events is still under investigation. In this review, the pleiotropic potential of this novel class of glucose-lowering levels will be discussed. Further research is warranted to determine their safety in the long term.

Contents

1. Introduction

Type 2 diabetes mellitus has become a global pandemic. Nowadays, it is estimated that approximately 415 million people all over the world have diabetes. By 2040, this will rise to 642 million people [1]. Diabetes mellitus is on the rise globally. Rates in developing countries are increasing due to the tidal pacing of obesity. Deaths from diabetes are accessed to increase 50% by 2025 world widely. Eighty percent of these deaths will occur in low and middle income countries [2].

There are two types of Sodium Glucose Co-Transporter Inhibitors: SGLT-1 and SGLT-2. SGLT-1 is expressed at high levels in the intestine and is also expressed in the kidney, heart, and skeletal muscle, whereas SGLT-2 is almost exclusively expressed in the kidney [3]. Renal SGLT-2 expression is increased in hyperglycemic mice and in humans with type 2 diabetes mellitus [4–6]. It took researchers approximately 200 years from the isolation of phlorizin, a chemical substance found in apple tree bark that inhibits sodium–glucose co-transporters, to the approval of the first medications inhibiting SGLT-2 for treatment of type 2 diabetes mellitus [7,8]. Phlorizin, a natural product that non-selectively

Abbreviations: SGLT-2 Inhibitors, sodium glucose co-transporter 2 inhibitors; SGLT-1 Inhibitors, sodium glucose co-transporter 2 inhibitors; GLUTs, glucose transporters; FPG, fasting plasma glucose; eGFR, estimated glomerular filtration rate; RAAS, renin angiotensin aldosterone system; HbA1C, glycosylated hemoglobin; ACE, angiotensin converting enzyme; AT1, angiotensin; SBP, systolic blood pressure.

* Correspondence to: 5 Pyramidon str, 19005, Municipality of Marathonas, Athens, Greece.
E-mail address: natalia.vallianou@hotmail.com (N.G. Vallianou).

http://dx.doi.org/10.1016/j.dsx.2016.12.003
1871-4021/

inhibits SGLT-1 and SGLT-2, normalized plasma glucose concentrations and reversed insulin resistance in animal models of diabetes [8,9]. Phlorizin has been used for many years as a research tool to study the physiology of GLUTs [10]. Although phlorizin is an effective SGLT-2 inhibitor, it is not a drug candidate because of its poor absorption after oral administration; inhibition of SGLT-1, which may cause nausea and diarrhea; and metabolism to phloretin, an inhibitor of GLUT1 [11–13]. To overcome the limitations of phlorizin, a number of oral SGLT-2 inhibitors, derived from the basic structure of phlorizin, have been synthesized and are in clinical development for the treatment of type 2 diabetes mellitus. Nowadays, we have many SGLT-2 inhibitors in our armamentarium in the fight against type 2 diabetes mellitus, such as dapagliflozin, canagliflozin, empagliflozin, ipragliflozin, ertugliflozin, topogliflozin, and luseogliflozin [14].

2. Sodium glucose co-transporters inhibitors and their mode of action

The Sodium Glucose Co-Transporter 2 Inhibitors (SGLT-2) inhibitors comprise a new class of oral glucose-lowering agents that fight hyperglycemia by reducing renal glucose reabsorption and increasing urinary glucose excretion [15–17]. Thus, SGLT-2 inhibitors work independent of insulin and b-cell function, focusing on the kidney.

Under normal circumstances, 180 g of glucose is filtered by the kidney on a daily basis. Almost all of this is then re-absorbed into the circulation by means of SGLTs. SGLTs bring sodium and glucose into cells using the sodium gradient created by sodium/potassium ATPase pumps, which are located at the basolateral side of the cells. 10% of renal glucose re-absorption occurs via SGLT-1, and approximately 90% occurs via SGLT-2, which is located in the early proximal tubule [18].

However, if the serum glucose levels rise above 200 mg/dL as in the case of diabetic patients, some glucose is excreted in the urine, too. In particular, among patients with type 2 diabetes, renal tubular re-absorption of glucose is enhanced [19,20]. The above-mentioned increase in renal glucose re-absorption is attributed to an up-regulation of the expression of SGLT-2 transporters. Hyperglycemia has been demonstrated to up-regulate the expression of SGLT-2 transporters [21,22]. The increased number of SGLT-2 transporters results in increased glucose re-absorption. Nevertheless, in spite of the enhanced glucose re-absorption, untreated hyperglycemia leads to serum glucose levels, which are frequently above the renal threshold, thus resulting in glycosuria [23,24].

3. SGLT-2 inhibitors and glycemic control

SGLT-2 inhibitors are effective in lowering plasma glucose when used as monotherapy or in combination with other oral agents/insulin. These results have been documented in large multicenter studies. Although metformin is the first choice for treating type 2 diabetes mellitus, it sometimes causes intolerable gastrointestinal side effects in several patients. In such patients, SGLT-2 inhibitors can be used as monotherapy, and in clinical trials, they lowered fasting plasma glucose by 20–46 mg/dL and HbA1c by 0.54–1.45% in patients with baseline HbA1c 7%–9.1% compared with placebo. The addition of SGLT-2 inhibitors as an add-on therapy to metformin results in fasting plasma glucose (FPG) lowering by 15–40 mg/dL and HbA1c by 0.54–0.77% compared with placebo in patients with mean baseline HbA1c between 7.9% and 8.2%. The SGLT-2 inhibitors are also effective in ameliorating glycemia in triple combination with metformin and either sulfonylureas, DPP-4 inhibitors, or glitazones, with fasting plasma glucose lowered by 20–38 mg/dL and HbA1c lowered by 0.4–1.03% in patients with mean HbA1c 7.8–8.1% The addition of SGLT-2 inhibitors in patients inadequately controlled on insulin and mean HbA1c 8.3–8.5% is related to improved glycemic control with FPG lowered by 6–63 mg/dL and HbA1c lowered by 0.39–1.27%, while modest weight reduction (1.31–3.5 kg) and lower insulin needs (9–19 units), without increasing major hypoglycemic episodes, were recorded [25].

4. SGLT-2 inhibitors and weight loss

Caloric loss together with osmotic diuresis leading to transient fluid loss accounts for the weight reduction associated with the use of SGLT-2 inhibitors, especially during the early treatment period. In patients treated with SGLT-2 inhibitors, a progressive weight loss is typically observed within the first 12–26 weeks, followed by maintenance of the decreased body weight with only minimal further reduction after 26 weeks. In the phase 3 clinical studies, SGLT-2 inhibition typically provided mean weight loss of 2–5% (1.5–6 kg) [27,28]. While fluid loss may contribute to the initial weight reduction associated with SGLT-2 inhibitors, the majority of the steady-state weight loss appears to be the result of fat loss. Indeed, in studies with DEXA measurement of body composition, approximately 70% of weight loss was attributed to fat and numerically greater reductions occurred in visceral compared with subcutaneous adipose tissue [29,30]. It is noteworthy that treatment with empagliflozin or dapagliflozin also shifted substrate utilization from carbohydrate to lipid metabolism [31,32].

Ferrannini et al. documented that people with type 2 diabetes who took an SGLT-2 inhibitor had an increase in glucagon and hepatic glucose production [33]. This has a plausible explanation that there is SGLT-2 expression in the α-cells in the pancreas. This will need further investigation [34]. Thus, it remains to be elucidated whether the addition of SGLT-2 inhibitors with agents such as dipepitdyl-peptidase-4 inhibitor (DPP-4) inhibitors or glucagon like peptide 1 receptor agonist in the clinical setting will have extra beneficial effects [35,36].

5. Pathophysiology of diabetic kidney disease

Endogenous changes such as increased production of adipocytokines, reactive oxygen species, activation of protein kinase C β, up-regulation of transforming growth factor (TGF)-β1 and formation of advanced glycation end products (AGEs) lead to accumulation of extracellular matrix, thickening of the glomerular basement membrane and ultimately glomerular sclerosis and tubule-interstitial fibrosis [37].

On the other hand, hemodynamic changes result in hyperfiltration, an early event in the course of type 2 diabetes, which usually precedes the diagnosis of diabetes [38,39]. Hyper-filtration is documented to be followed by a gradual and progressive decrease in glomerular filtration rate (GFR). Specifically, hyperfiltration leads to early glomerular death, which in turn results in higher filtration rates and loss of the remaining glomeruli; thereby a decline in GFR and end stage renal disease eventually pursues [40]. In diabetes, glomerular hyper-filtration is suggested to be due to glomerular hemodynamic and tubular mechanisms. Hyperglycemia-induced dys-regulation of the glomerular afferent and efferent arteriole tone, ie higher decrease in afferent arteriolar tone compared with efferent arteriolar tone is mostly driven by a regional up-regulation of angiotensin II. The hemodynamic mechanism behind this dys-regulation is perplexed, but it is noteworthy that the efferent glomerular arteriole is 10–100 times more sensitive to the vasoconstrictive properties of angiotensin II than the afferent one and this might account for the imbalance between the afferent and the efferent arteriolar tone and the

Please cite this article in press as: N.G. Vallianou, et al., SGLT-2 inhibitors: Their pleiotropic properties, Diab Met Syndr: Clin Res Rev (2016), http://dx.doi.org/10.1016/j.dsx.2016.12.003