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Clinical pharmacology of sodium glucose cotransporter 2 inhibitors

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Abstract

SGLT2 inhibitors represent a new class of glucose-lowering drugs that act through the inhibition of glucose reabsorption at the proximal tubular cells of the kidney. There are 3 drugs of this class currently available in Europe and United States of America: empagliflozin, dapagliflozin and canagliflozin. These compounds selectively inhibit the reabsorption of glucose in the kidney by almost 30-50% and the resulting glucosuria is translated to meaningful reductions is serum glucose. Apart from their effects on carbohydrate homeostasis these drugs also affect human metabolism in various ways. Thus, they reduce blood pressure, arterial stiffness and body weight, decrease serum concentrations of insulin and increase those of glucagon and shift energy metabolism towards the utilization of fatty acids and ketone bodies. In two recent clinical trials empagliflozin and canagliflozin were found to reduce cardiovascular events and to preserve renal function in patients with type 2 diabetes and established cardiovascular disease. In this review, we summarize the knowledge on the metabolic effects of SGLT2 inhibitors, discuss the potential mechanisms that underlie the cardioprotective and renoprotective effect of these drugs and present their side effects and the possible contraindications to their use.

Key words: SGLT2 inhibitors; dapagliflozin; empagliflozin; canagliflozin, ketone bodies; euglycemic ketoacidosis; glucosuria

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Introduction

Every day approximately 180 gr of glucose are filtered in the renal glomeruli. However, under normal circumstances only traces of this metabolite are found in the urine since the greater proportion of the filtered load of glucose is actively reabsorbed by sodium-coupled transport across the brush border membrane of the proximal tubule and then returned to the circulation by glucose transporters. This active transfer is facilitated mainly by a low affinity, high capacity system controlled by sodium glucose transporter-2 (SGLT2) in the early convoluted segment of the proximal tubule [1].

In hyperglycemic conditions the filtered load of glucose is increased. When the reabsortive capacity of the proximal tubule is surpassed glycosuria ensues and considerable amounts of glucose are lost in the urine. In patients with diabetes the glucose reabsorption capacity in the proximal tubule is upregulated. These changes in renal glucose reabsorption are considered to significantly contribute to the maintenance of hyperglycaemia in patients with diabetes and provide a strong rationale for inhibition of SGLT2 as a mean to better control glucose levels [1].

The understanding of the renal handling of glucose in diabetic individuals led to the development of specific SGLT2 inhibitors that recently reached the clinical practice. There are 3 drugs of this class currently available in Europe and United States of America: Empagliflozin, dapagliflozin and canagliflozin. These compounds selectively inhibit the reabsorption of glucose in the kidney by almost 30-50% and the resulting glucosuria is translated to meaningful reductions is serum glucose. Indeed, the administration of these drugs reduce HbA1c by approximately 0.6-0.9% and this reduction reflects a decrease in both fasting and postprandial hyperglycemia. The resulting decrease in glucotoxicity leads to an improvement in endogenous insulin production and to an increase in tissue insulin sensitivity. In addition, the loss of calories attributable to glucose into the urine results in a moderate weight loss of about 3-5 Kgr [2].

A study that resulted in a paradigm change in the treatment of type 2 diabetes was the EMPA-REG trial. This study enrolled 7020 patients with type 2 diabetes and established cardiovascular disease which randomized to receive empagliflozin 10 and 25mg or placebo [3,4]. The median observation time was 3,1 years. The incidence of the primary outcome was 10.5% in the empagliflozin group and 12.1% in the placebo group (relative risk 0.86; 95.02% CI 0.74 to 0.99, p<0,04). No significant difference was observed in the incidence of myocardial infarctions or stroke. However, empagliflozin reduced cardiovascular mortality (3.7%, *vs*. 5.9%; 38% relative risk reduction), heart failure hospitalizations (2.7% *vs* .4.1%, 35% relative risk reduction), and total mortality by 32%. In addition, the subsequent analysis of the EMPA-REG data reveled a reduction in the incidence or the renal composite outcome (progression to macroalbuminuria, doubling of the serum creatinine level, initiation of renal-replacement therapy, or death from renal disease) by 39% [5]. In the same line were the results of the CANVAS program examining the effects of canagliflozin on vascular events in patients with type 2 diabetes and high cardiovascular risk [6]. The rate of the primary outcome was lower with canagliflozin than with placebo (occurring in 26.9 *vs*. 31.5 participants per 1000 patient-years; hazard ratio, 0.86; 95% confidence interval [CI], 0.75 to 0.97; P<0.001 for noninferiority; P=0.02 for superiority). Although on the basis of the prespecified hypothesis testing sequence the renal outcomes are not viewed as statistically significant, the results showed a possible benefit of canagliflozin with respect to the progression of albuminuria (hazard ratio, 0.73; 95% CI, 0.67 to 0.79) and the composite outcome of a sustained 40% reduction in the estimated glomerular filtration rate, the need for renal-replacement therapy, or death from renal causes (hazard ratio, 0.60; 95% CI, 0.47 to 0.77) [6].

These drugs can decrease blood pressure (BP) by 5-6 mmHg/ 1-2 mmHg. [7] A post- hoc analysis of a clinical study suggested that this reduction of BP is greater in diabetic patients treated with calcium channel blockers and β-blockers but not with diuretics, a finding which implies that natriuresis may play a prominent role in the drugs' antihypertensive effect. [8]

Table 1. Mechanisms of the antihypertensive effects of SGLT2 inhibitors

Natriuresis leading to volume depletion and conversion of a non dipping salt sensitive profile to a dipping non salt sensitive one
Decrease of glucose levels and insulin resistance
Improvement in arterial stiffness
Decrease in body weight
Decrease in sympathetic nervous system activity
Decrease in serum uric acid levels
Local inhibition of the renal renin- angiotensin axis

Table 2. Mechanisms of weight loss observed with SGLT2 inhibitors

Loss of calories due to glucosuria
Natriuresis and osmotic diuresis-induced volume depletion
Increased fatty acid oxidation for energy supply

In **table 1** the underlying mechanisms of the reduction in BP are shown. [7,9] It has been suggested that this reduction in BP can, at least in part, contribute to the beneficial cardio-renal effects observed in the EMPA-REG trial. [10]

A significant weight loss by approximately 2-3 kg is commonly found after SGLT2 inhibitors administration which is associated with visceral fat reduction. [11] However, this decrease is lower than anticipated from the loss of calories due to glucosuria since an increase in energy intake has been described. [12] In **table 2** the underlying mechanisms of the drugs'-associated weight loss are shown. Small decreases in triglyceride (TRG) levels and increases in HDL cholesterol levels are commonly observed after SGLT2 inhibitors administration possibly due to weight loss. [13,14] However, no change in HDL functionality was recently found. [15] A small increase in LDL cholesterol is noticed after SGLT2 inhibitors administration. Even though it was initially thought to be related to diuresis–induced hemoconcentration, this small increase is possibly due to a decrease in LDL receptors activity. (**Fig.1**) [16]

As shown in **table 3**, SGLT2 inhibitors despite their diuretic effects are not associated with electrolytes depletion. On the contrary, small increases in serum potassium and magnesium concentrations have been found in clinical trials, which are more evident in patients with reduced renal function as well as in patients consuming drugs affecting potassium homeostasis. [14, 17, 18] It has been proposed that the canagliflozin–associated normalization of serum magnesium in hypomagnesemic patients may potentially associated with improved cardiometabolic outcomes. [19] Interestingly a small increase in serum phosphate levels due to increased

Table 3. Effects of SGLT 2 inhibitors on serum electrolytes

Small increases in serum potassium levels possibly due to decreased insulin levels, mainly observed in patients with reduced renal function or those receiving drugs affecting potassium homeostasis, such as ACE inhibitors, sartans, heparin, spironolactone, non-steroidal anti-inflammatory drugs, etc.
Small increases in serum magnesium levels
Small increase in serum phosphate levels due to an increase of phosphate reabsorption in the proximal tubules leading to increased PTH secretion and possibly to detrimental effects on bone metabolism (not confirmed)

Table 4. SGLT2 inhibitors and absence of hypoglycaemia: underlying mechanisms

They do not increase insulin secretion
The increase in SGLT-1 activity limits the excess glucosuria
The resulting hyperglucagonemia can increase liver glucose production
The increased lipolysis increases the glucose availability to the cerebral tissue

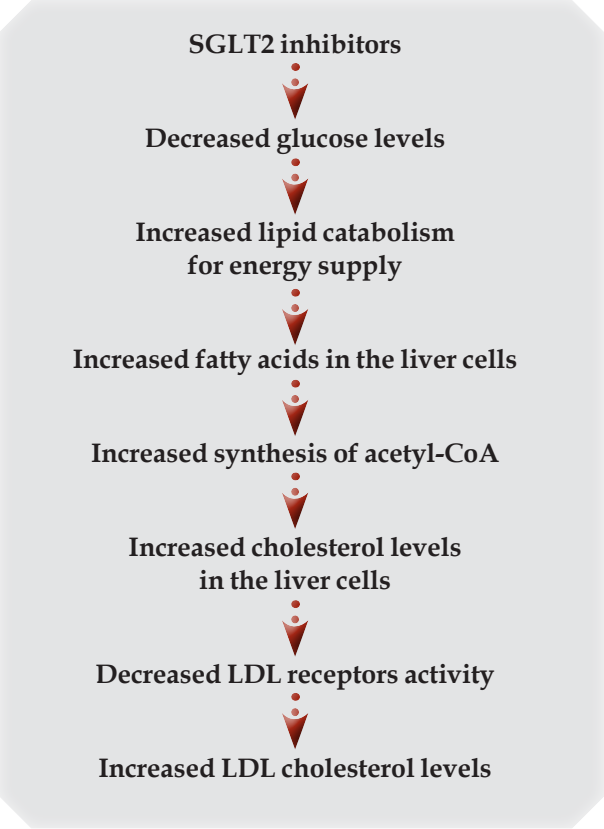

Figure 1. Mechanism of the SGLT2 inhibitors –mediated increase of LDL cholesterol levels. Acetyl-coA: acetyl-coenzyme A

phosphate reabsorption along with sodium in the renal tubules via the Na^{+}-PO_4^{3-} cotransporters is observed leading to increased PTH levels and subsequently to a detrimental effect on bone homeostasis. [20-22] Even though some studies have shown an increase in bone fractures after drugs' administration, this finding has not been confirmed in a recently published meta-analysis. [23] Thus, the increased fracture risk observed in some clinical trials with canagliflozin may be related to weight loss, as well as to drug-associated hypotension. [24-26] However, FDA suggests that canagliflozin should be used with caution in high risk patients for bone fractures. [27]

As shown in **figure 2** the SGLT2 inhibition-associated decreased glycemia results in a decreased glucotoxicity leading to both improvement of insulin resistance and insulin secretion. [28-30] Furthermore, increased glucagon secretion by the pancreatic alpha cells has been repeatedly reported due to both decreased glycemia but also to a direct effect of SGLT2 inhibition on these cells. The result hyperglucagonemia–associated increased hepatic glucose production limits the hypoglycemic

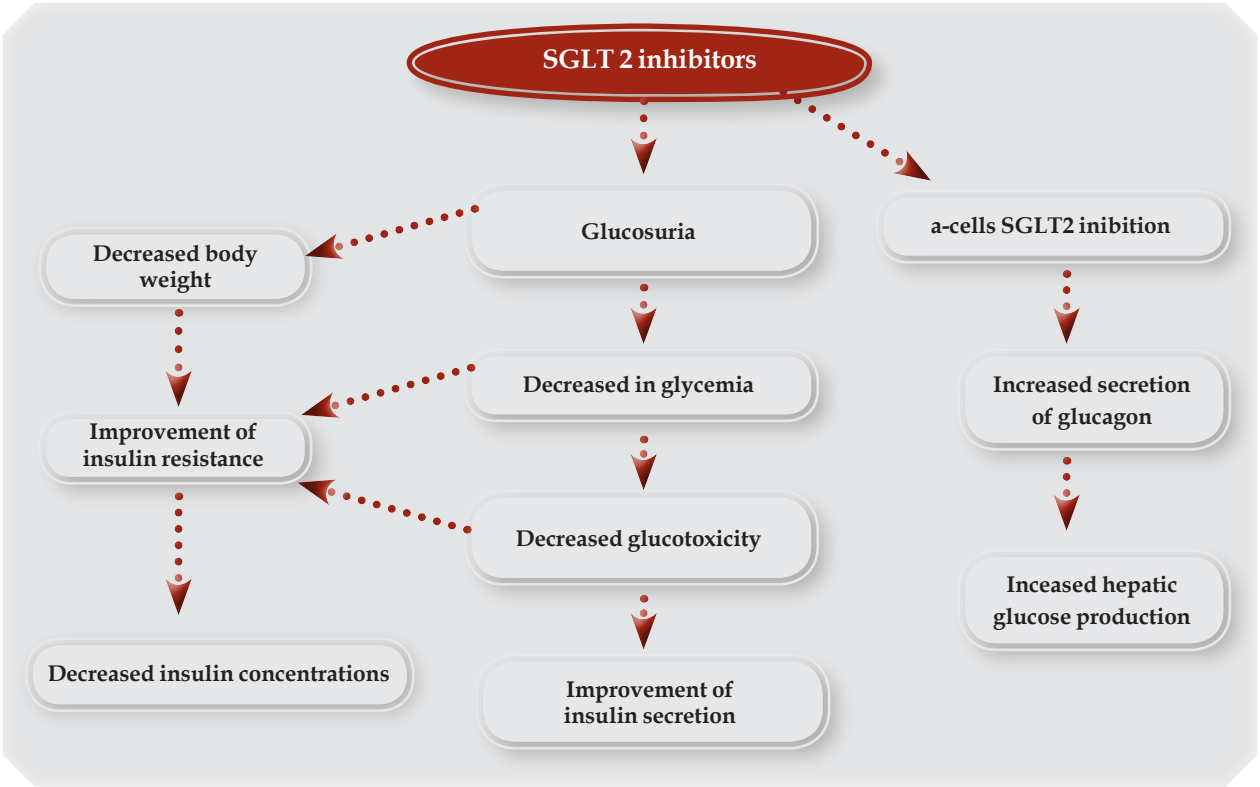

Figure 2. Effects of SGLT2 inhibitors on the carbohydrate metabolism

potential of these drugs but also minimises the risk of hypoglycemia. [28-30] In fact, a significant advantage of these drugs is the absence of hypoglycemia (**Table 4**). [30] In **table 5**, the adaptive metabolic responses to SGLT2 inhibitors are shown. Thus, these drugs can increase glucose reabsorption in distal parts of the proximal renal tubules to avoid excess glucosuria through an increase in SGLT-1 activity, increase the carbohydrate intake, increase the hepatic glucose production as well as fat oxidation. [12,28-31]

As previously mentioned EMPA-REG has clearly demonstrated the renoprotective effects of empagliflozin. [5] Initially, the administration of the drugs of this class is followed by a decrease in glomerular filtration rate (**Fig. 3a**) due to both natriuresis-induced hypovolemia and to the increased sodium supply to the macula densa-induced vasoconstriction of the afferent arterioles. [5, 32] However, chronic administration is associated with nephroprotection (decrease in albuminuria and decrease in the rate of the decline of renal function) due to both glucose dependent and glucose independent mechanisms. (**Fig. 3b**) [24,32-34]

The increased tubuloglomerular balance associated with SGLT2 inhibitors is considered the main nephroprotective mechanism. Thus, the drug- associated increase in the sodium supply to the macula densa is followed by vasoconstriction of the afferent arterioles leading to a decrease in the intraglomerular pressure and subsequently to a long-term nephroprotection. [24, 32-34] However, a drug-related decrease in renal hypoxia due to the increased erythropoietin (EPO) concentrations and mainly to the increased ketogenesis (see below for details) are also considered as major nephroprotective mechanisms. In fact, β-hydroxybutyrate is considered as an effective renal energy fuel which may improve the oxygenation of renal tissues. [35,36]

The adverse effects of SGLT2 inhibitors are shown in **table 6**. Urinary tract infections and mainly genital infections are by far the most common adverse effects of these drugs. [24, 37, 38] Even though the long-term nephroprotection of these

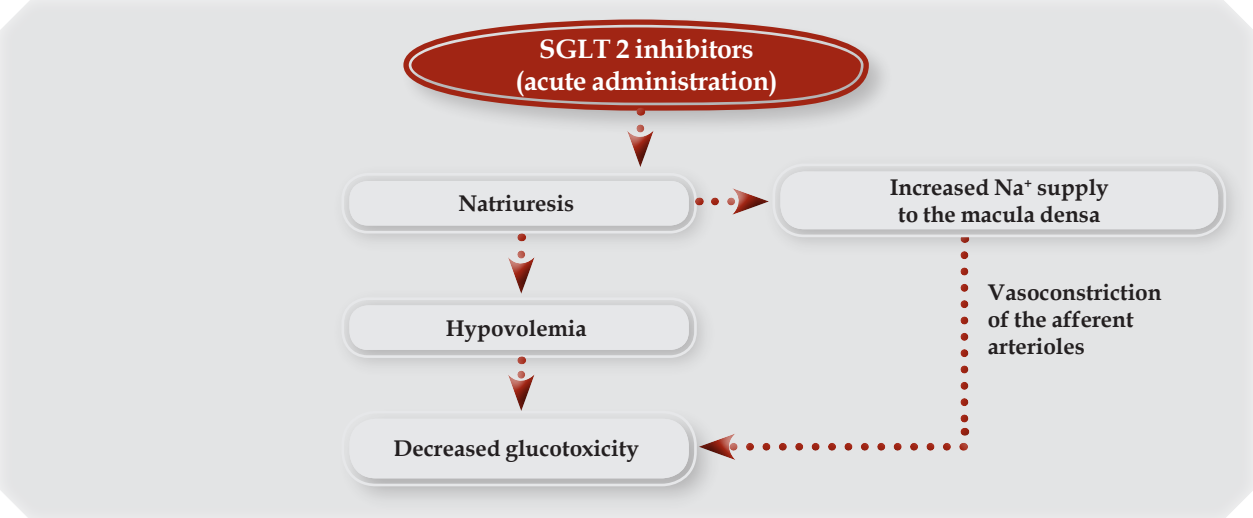

Figure 3a. Effect of SGLT2 inhibitrs on renal function (acute administration)

Table 5. **SGLT2 inhibitors and metabolic adaptive responses**
Increased SGLT-1 mediated glucose reabsorption in the distal parts of the proximal renal tubules
Increased hepatic glucose production (due to the hyperglucagonemia)
Increased dietary intake of carbohydrates
Increased fat oxidation leading to the production of ketones

Table 6. **SGLT2 inhibitors: Side effects**
Increased incidence of genital infections (mycotic infections due to candida)
Increased incidence of urinary tract infections
Euglycemic diabetic ketoacidosis
Increased incidence of bone fractures (?) associated with small increases in serum phosphate and PTH levels but also with weight loss
Acute deterioration of renal function, especially in elderly patients with extracellular volume depletion as well as in patients receiving drugs affecting renal function, including diuretics (mainly furosemide), RAS blockers or NSAIDS
Small increases in LDL cholesterol levels
Increased risk of leg amputations (?)

RAS: renin angiotensin system, NSAIDs: non steroid anti-inflammatory drugs, PTH: parathormone

Table 7. SGLT2 inhibitors: contraindications

Decreased GFR (<45-60ml/min): Decreased efficacy
Conditions predisposing to diabetic ketoacidosis (surgery, trauma, infection, acute diseases, etc.)
Coexistent hypovolemia, especially in patients administered drugs affecting renal function, such as diuretics (mainly furosemide), renin-angiotensin blockers or nonsteroidal anti-inflammatory agents
Patients with Type 1 diabetes mellitus

Table 8. SGLT 2 inhibitors and cardioprotection: potential mechanisms

Decrease of glucose levels and insulin resistance without associated hypoglycemia
Drug-induced diuresis leading to decreased cardiac preload, decreased myocardial wall tension, and ventricular arrhythmias, without SNS overactivity as well as without electrolyte abnormalities
Maintenance of euvolemia leading to decreased risk of hospitalization for heart failure
Decrease of body weight and visceral fat as well as of epicardial fat with potential beneficial effects (decrease of fibrosis and inflammation, improvement of cardiac function, decrease of cardiac arrhythmias)
Decrease of BP and arterial stiffness as well as restoration of the dipping profile of BP resulting in a decrease of cardiac afterload
Decrease in serum uric acid levels
Nephroprotection leading to cardioprotection
Increased glucagon levels resulting in an improvement of myocardial cells function
Increased ketogenesis leading to an improvement of tissue hypoxia (shift in fuel energetics)
Increased hematocrit (due to hemoconcentration or to a direct drugs' effect on erythropoietin production) leading to an improvement in myocardial and renal tissue oxygenation
Increased activity of SGLT-1 in the heart leading to an improvement of myocardial function and to a decrease in cardiac arrhythmias
Small increase in serum magnesium levels, which can decrease the incidence of cardiac arrhythmias
Decreased NHE activity in myocardial cells leading to increased calcium in mitochondria and increased energy supply
Increased activation of AT2 receptors and angiotensin 1-7 pathway leading to vasodilation (in patients also receiving RAS blockers)
Antioxidant , anti-inflammatory and anti-apoptotic properties
Decreased intracellular sodium in the myocardium leading to decreased risk of arrhythmias and to an improvement in myocardial function (effects on mitochondrial function)

NHE: Na+/H+ exchanger, AT2: angiotensin II receptor type II, RAS: renin angiotensin system

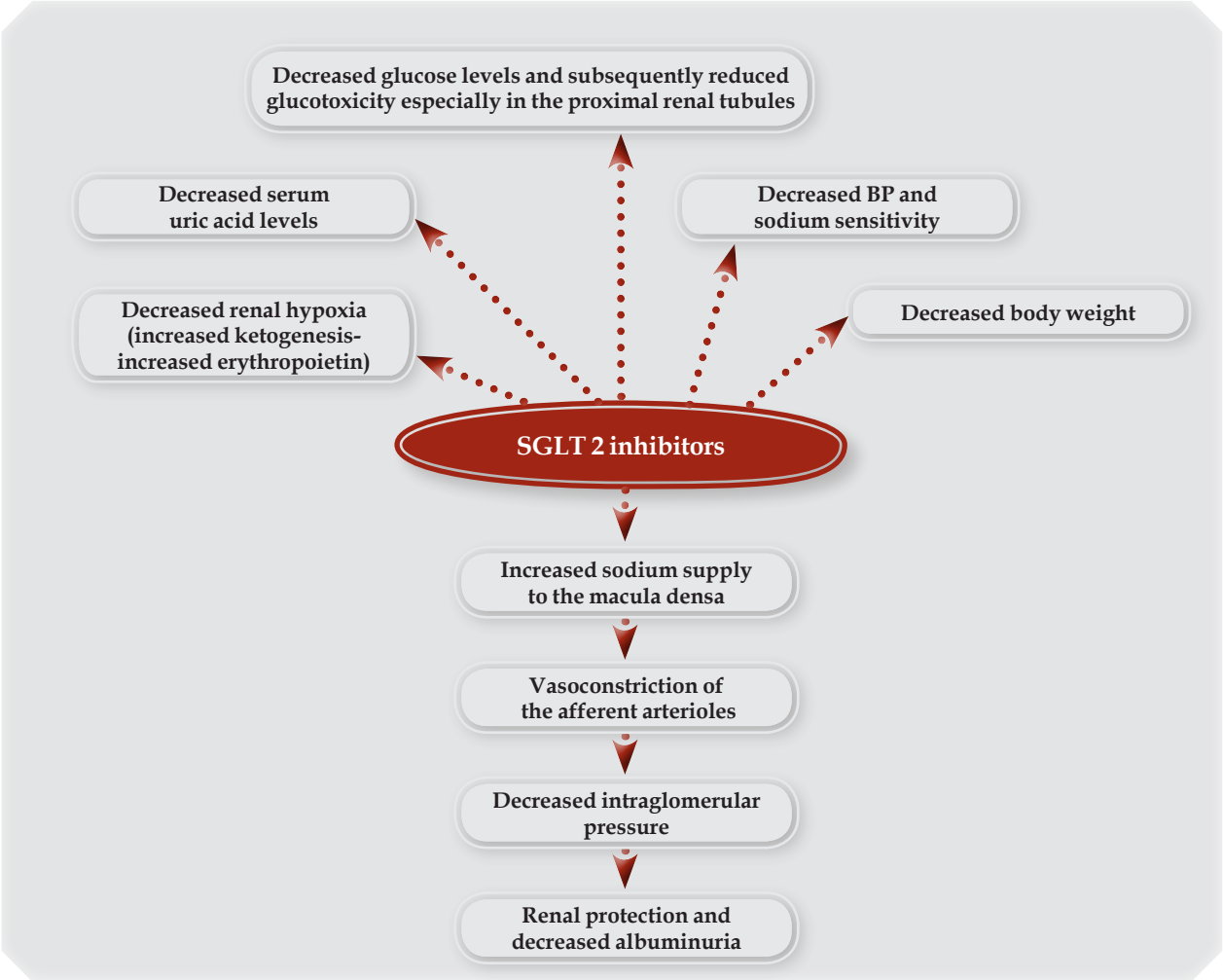

Figure 3b. Effects of SGLT2 inhibitors on renal function (chronic administration)

drugs has been confirmed, acute deterioration of renal function, especially in elderly patients with underlying nephropathy, in individuals with coexistent volume depletion as well as in those receiving drugs affecting renal hemodynamics has been repeatedly reported and noticed by both FDA and EMEA. [24, 37-40] A rare but important side effect of these drugs is the development of euglycemic diabetic ketoacidosis [DKA] (which is also reported such as ketoacidosis with less than anticipated glucose levels) characterized by a high anion gap metabolic acidosis without profound hyperglycemia. DKA is mainly due to increased liver ketogenesis and increased renal ketones reabsorption (the latter mechanism has not been verified). Increased liver ketogenesis is due to increased glucagon/ insulin ratio in the liver cells as well as to increased lipolysis in the adipose tissue. [41-43]. Both EMEA and FDA have recently released clear recommendations concerning the prevention, the early diagnosis and the appropriate treatment of DKA. Thus, these drugs should not be used in patients predisposed to ketoacids production (such as patients with acute infections, trauma, surgical patients as well as patients with acute diseases) as well as in patients with type I diabetes mellitus. Furthermore, drug cessation is indicated when nonspecific symptoms suggestive of DKA are present. Additionally, these drugs should not be used in patients with decreased eGFR (<45-60 ml/

min) due to their limited efficacy but also in patients with extracellular volume depletion and especially in those receiving drugs affecting renal function (**Table 7**). [44,45]

The EMPA-REG trial also clearly showed the cardioprotective effects of empagliflozin (decreased cardiovascular mortality and decreased hospitalization for heart failure) findings also replicated to some extent in the CANVAS program with canagliflozin. [3,4,6] However, no change in the incidence of non-fatal myocardial infarction or stroke was noticed in these studies suggesting that the beneficial cardiovascular effects are not related to the drugs' effects on the atherosclerotic process but to other mechanisms. The proposed mechanisms are shown in **table 8** and include their diuretic action, which is not associated with electrolyte abnormalities or increased symphathetic drive, leading to a decrease in preload, myocardial stretch and ventricular arrhythmias, the restoration of euvolemia along with a decrease of intracellular sodium levels, the decrease in blood pressure along with a restoration of a dipping profile in BP, and the improvement of myocardial cells oxygenation due to the increased ketogenesis, to increased erythropoietin concentrations as well as to decreased Na^+-H^+ exchanger (NHE) activity in myocardial cells. However, other mechanisms may be implicated including the decrease of glucose levels and subsequently the reduced glycotoxicity as well as the decreased insulin resistance, the decrease in body weight and visceral fat including epicardial fat, the decrease in uric acid levels, the increase in serum magnesium levels, as well as the hyperglucagonemia. [24,33, 34, 46-48]

Conflict of Interest

All authors declare no conflict of interest.

Περίληψη

Κλινική φαρμακολογία των αναστολέων των SGLT2 μεταφορέων

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Οι SGLT2 αναστολείς αποτελούν μια νέα κατηγορία αντιδιαβητικών φαρμάκων που δρουν διαμέσω της αναστολής της επαναρρόφησης γλυκόζης στα κύτταρα των εγγύς εσπειραμμένων σωληναρίων των νεφρών. Τρεις εκπρόσωποι αυτής της κατηγορίας κυκλοφορούν αυτή τη στιγμή στην Ευρώπη και την Αμερική: η εμπαγλιφλοζίνη, η καναγλιφλοζίνη και η ντααπαγλιφλοζίνη. Αυτές οι ουσίες αναστέλλουν εκλεκτικά την επαναρρόφηση γλυκόζης στους νεφρούς κατά 30-50% και η γλυκοζουρία που προκύπτει με αυτό τον τρόπο μεταφράζεται σε κλινικά σημαντική μείωση της γλυκόζης του ορού. Εκτός από την επίδρασή τους στην ομοιοστασία των υδατανθράκων αυτά τα φάρμακα επηρεάζουν τον ανθρώπινο μεταβολισμό με πολλούς τρόπους. Ετσι, μειώνουν την αρτηριακή πίεση, την αρτηριακή σκληρία και το σωματικό βάρος, μειώνουν τα επίπεδα της ινσουλίνης του ορού και αυξάνουν αυτά της γλυκαγόνης και προκαλούν μια εκτροπή του κυτταρικού μεταβολισμού προς τη χρήση κετονικών σωμάτων ως ενεργειακών υποστρωμάτων. Πρόσφατες μελέτες έδειξαν πως σε ασθενείς με διαβήτη και εγκατεστημένη καρδιαγγειακή νόσο η εμπαγλιφλοζίνη και η καναγλιφλοζίνη μειώνουν σημαντικά τα καρδιαγγειακά συμβάματα και συμβάλλουν στη διατήρηση της νεφρικής λειτουργίας. Στην παρούσα ανασκόπηση παρουσιάζουμε τη διαθέσιμη γνώση για τις μεταβολικές επιδράσεις των SGLT2 αναστολέων, συζητάμε τους πιθανούς μηχανισμούς που βρίσκονται πίσω από τις καρδιοπροστατευτικές και νεφροπροστατευτικές επιδράσεις αυτών των φαρμάκων και παρουσιάζουν τις ανεπιθύμητες ενέργειες και τις πιθανές αντενδείξεις στη χορήγησή τους.

Λέξεις ευρετηρίου: SGLT2 αναστολείς, ντααπαγλιφλοζίνη, εμπαγλιφλοζίνη, καναγλιφλοζίνη, κετονικά σώματα, ευγλυκαιμική κετοξέωση, γλυκοζουρία

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