Review

Update on the use of Sodium Glucose Cotransporter Type 2 inhibitors in kidney transplant patients

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Review

Update on the Use of Sodium Glucose Cotransporter Type 2 Inhibitors in Kidney Transplant Patients

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Abstract: Sodium glucose cotransporter type 2 inhibitors are a new class of drugs acting on cardiovascular system, renal and metabolism in a multiple way. Indeed, even their principal action is on the transporter of sodium and glucose in the convoluted distal tubule, they have multiple actions as antifibrotic and endothelial protective action. Their principal mechanism consist in the loss of sodium and glucose. Therefore, they have effect on blood pressure and glucose metabolism. In a first period their use has been in the diabetic general population, later on some studies documented their activity in non-diabetic general population, in heart failure in chronic kidney disease. Only in recent years several small studies documented their efficacy in diabetic and non-diabetic kidney transplant patients, larger studies are few and very recent and open new ways for these drugs

Keywords. sodium-glucose- cotransporters type 2 inhibitors; glucose reabsorption; sodium reabsorption; randomized clinical trials; diabetes; heart failure; chronic kidney disease; kidney transplantation

Introduction

Since 2015, sequential randomized controlled trials (RCTs) have documented the efficacy of Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors in improving both kidney and cardiovascular outcomes. This was firstly documented in general population, later in patients with diabetes [1]. By 2020, 4 compounds (empagliflozin, canagliflozin, dapagliflozin and ertugliflozin) were studied in 47,000 patients with diabetes. Due to its action, later on these compounds were studied in patients with chronic kidney disease with or without diabetes. More recently, SGLT2 inhibitors have been used in kidney transplant patients. Several studies document the heart and renal protective effect in particular empaglifozin [2], canaglifozin [3], dapaglifozin [4].

Mechanism of action

The SGLT2 inhibitors mechanism of action is complex and exerted on heart, metabolism (Figure 1A) and renal (Figure 1B). The cardio protective effect includes direct cardiovascular effect and is manifested through improvements in cardiac parameters, decrease in heart failure as well as promotion in cardiac remodeling. In addition, there is an effect on cardiac fibrosis by modulating macrophage phagocytosis and downregulating of reactive oxygen and nitrogen specific pathways [5]. The indirect cardiovascular effect is exerted through the action on renal system. Additionally, the heart effect is exerted by the improvement of endothelial dysfunction and by the effect on sympathetic nervous system that lead to vasodilation, reduction of heart rate, reduction of preload and reduction in blood pressure.

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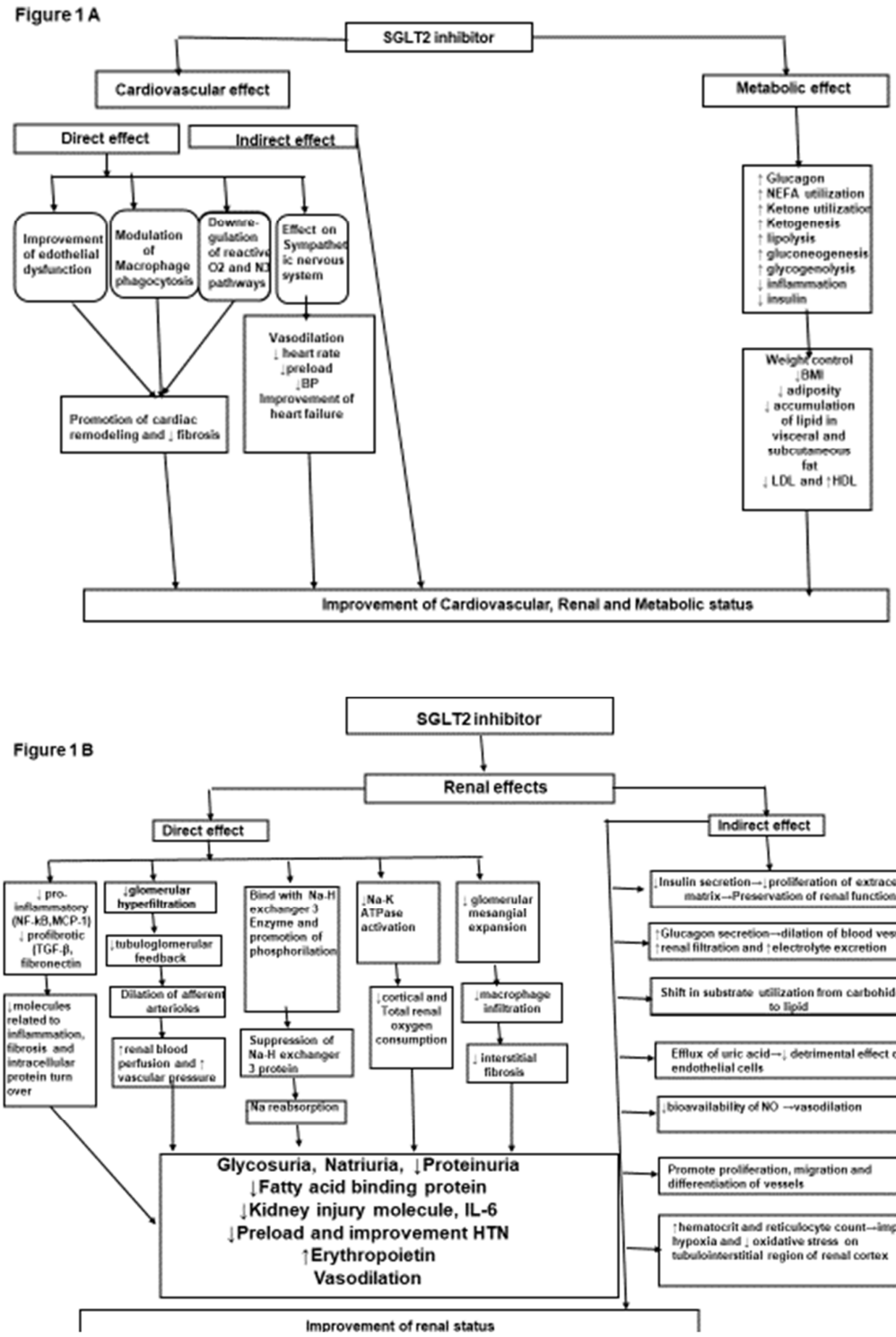

Figure 1. A SGLT2 action on heart and metabolism. **B** Action of SGLT2 on the kidney.

The metabolic effect is exerted by increase in glucagon, increase in non-esterified fatty acids (NEFA), increase in ketone utilization, increase in lipolysis, increase in gluconeogenesis, and decrease of insulin. All these facts lead to a decrease in body weight, decrease in LDL and increase in HDL.

In addition, the renal effects of SGLT2 inhibitors are exerted by a direct and an indirect effect. A reduction in proinflammatory and profibrotic molecules, decrease in glomerular hyper filtration with

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dilation of afferent arterioles and increase in renal blood perfusion mediate the direct effect. By binding to Na+-H+ exchanger 3 enzyme there is a reduction in Na+ reabsorption. Finally there is a reduction in glomerular mesangial expansion, a reduction in macrophage infiltration and a reduction in interstitial fibrosis [6]. All these facts lead to glycosuria, natriuresis, reduction in proteinuria, reduction in kidney injury molecules.

The indirect effect is induced by a reduced in insulin secretion, an increase in glucagon secretion, an increase in erythropoietin and an increase in hematocrit and reticulocyte count. Additionally, the renal indirect effect adds beneficial effect on the heart.

Factors as glycosuria, natriuresis and tubule-glomerular feedback induce a reduction in body weight, reduction of blood pressure and improvement in HbA1c [7,8]. The ketone metabolism induced by glycosuria improves the heart failure (HF) [9]. Additionally, SGLT2 Inhibitors produce cardio renal benefits by promoting adaptive cellular reprogramming to induce a state of fasting mimicry. This happens by activating the sirtuin 1/AMP activated protein kinase (SIRT1/AMPK) pathway that have an antioxidant and anti-inflammatory effect, an enhanced autophagic flux and an activation of hypoxia- inducible factor (HIF-2α). The latter stimulates erythrocytosis. [10–14]. In addition, the SGLT2 inhibitors improve the endoplasmic reticulum stress [15,16]. Finally, Canagliflozin reduces inflammation and fibrosis biomarkers as documented in diabetic kidney disease [17].

All SGLT2 inhibitors are metabolized in less than 24 hours by O-glucuronization. In particular, they are only in part metabolized by cytochromes. SGLT2 inhibitors slightly inhibit CYP3A4 and ABCB1 [18]. Concerning canagliflozin, has been documented a 23% increase of cyclosporine in the blood [19].

Due to its complex mechanism of action SGLT2 inhibitors have been used principally in patients affected by type 2 diabetes, often in association with other antidiabetic drugs. In general population its efficacy has been documented in patients affected by heart failure and by metabolic diseases.

More recently, in consideration that type 2 diabetes, heart disease and metabolic diseases are often related to chronic kidney diseases and kidney transplantation and concur to their poor outcomes, several small and large studies have been made to investigate the SGLT2 inhibitors effect in kidney disease and kidney transplantation

It should also considered that several adverse events have been reported with the use of SGLT2 inhibitors.

SGLT2i act inhibiting the co-transportation of sodium-glucose in the proximal part of convoluted tubule, where 90% of glucose is reabsorbed [20,21]. As collateral effect, SGLT2 inhibitors may cause urinary and genital infections because of the osmotic diuresis. In older people, an additional collateral effect is the hypotension due the loss of volume.

Other less frequent adverse events are euglycemic diabetic acidosis, distal limb amputation and acute kidney injury [22]. Physiologically, SGLT2 inhibitors cause a vasoconstriction of the afferent arterial that may rarely cause a reduction in GFR. Euglycemic ketoacidosis is more frequent in type 1 diabetes, principally in kidney transplant patients. An increased risk of lower extremity amputation was seen in the CREDENCE trial with the use of Canagliflozin [23].

SGLT2i Action on Heart, Metabolism and Kidney in Patients without Diabetes

Multiple RCTs have examined the therapeutic effectiveness of SGLT2 inhibitors in patients affected by type 2 diabetes mellitus. Notably several studies have documented the effectiveness of SGLT2 inhibitors in non-diabetic patients affected by heart, metabolic, renal dysfunction.

Anker et al. [24] on 1874 patients documented that Empagliflozin decreased the risk of cardiovascular death and total hospitalization for heart failure (HF) by 25, 30% and decreased the rate of decline of eGFR (estimated glomerular filtration rate) and risk of adverse effect by 50%.

Diaz-Cruz et al. [25] documented that 3 months of Dapaglifozin decreased blood pressure by lowering 24 hours systolic blood pressure (SBP), nighttime SBP, mean arterial pressure, nocturnal hypertension.

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Petrie et al. [26] demonstrated that Dapaglifozin was effective in reducing cardiovascular mortality and morbidity in patients with HF and reduced Ejection Fraction (EF).

Anker et al. again [27] documented on 5988 patients that Empaglifozin reduced the risk of cardiovascular deaths or hospitalization for HF in patients with left ventricular ejection fraction (LVEF) of 40% regardless of presence or absence of diabetes.

Several trials are looking at the efficacy of SGLT2 inhibitors on metabolic outcomes in patients without diabetes.

Bays et al. [28] documented that in overweight and obese subjects without diabetes, Canagliflozin significantly reduce body weight compared to placebo.

Neeland et al. [29] documented that Empagliflozin reduced endogenous glycerol-gluconeogenesis in obese adults without diabetes. Additionally, SGLT2 inhibitors may prevent type 2 diabetes in obesity.

Faerch et al. [30] demonstrated that treatment with Depagliflozin and interval-based exercise lead to similar but small improvements in glycemic variability compared to control and metformin therapy.

Finally, Veelen et al. [31] documented that Depagliflozin treatment of prediabetes insulin resistant individuals for 14 days resulted in significant metabolic adaptations, skeletal muscle metabolism, improved fat oxidation and mitochondrial oxidative capacity.

SGLT2 inhibitors trials looking at the efficacy of SGLT2 inhibitors on renal outcomes.

Heerspink et al. [32] in the DAPA-CKD trial on 4304 patients, documented the effect of Dapagliflozin were similar in participants with or without diabetes. It proven the most effective class of drug to prevent CKD progression since discovery of renin-angiotensin-system (RAS) inhibitor.

Harrington et al. [33] in the EMPA-KIDNEY trial on 6609 patients demonstrated that Empagliflozin lowered the risk of disease progression from kidney disease or death from CVD compared to placebo.

Most patients included in the above trials were affected by IgA nephropathy. As a result, the EMPA-KIDNEY and DAPA-CKD trials showed a 51% reduction in the risk of CKD progression in IgA nephropathy [34].

SGLT2 Inhibitors in Kidney Transplant Patients

The above-mentioned rationale also applies to kidney transplant patients, whose outcomes is deeply influenced by post-transplant diabetes, cardiovascular diseases and metabolic dysfunction.

A particular caution should be observed in treating kidney transplant patients because the incidence of infections (urinary tract infections and genital infections) could be enhanced by the immunosuppression. In addition, the incidence of acute kidney injury and the ketoacidosis encountered sometimes after transplantation could be enhanced by the SGTL2 inhibitors use.

Probably, this has been the cause of the less frequent use of SGLT2 inhibitors in kidney transplant patients until recently. Indeed, recently two large studies [35,36]

The potential benefits of SGLT2 inhibitors in CKD and kidney transplant patients are documented in Figure 2.

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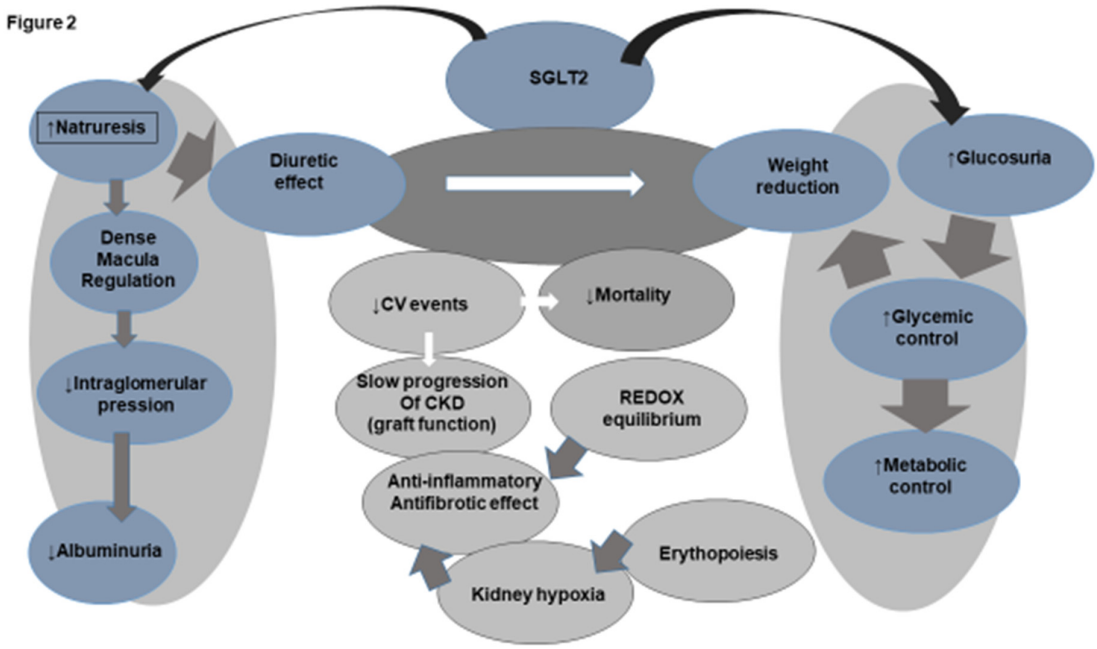

Figure 2. Potential benefits of SGLT2 inhibitors in chronic kidney disease and renal transplants.

SGLT2 inhibitors have a direct effect on the tubular co-trans carrier that increases natriuresis and glycosuria. Indirectly, increased natriuresis has been shown to decrease glomerular hyper filtration by regulating the dense macula. This effect leads to a decrease in renal hyper filtration and albuminuria, which has been historically associated with a slowing of the progression of CKD. Additionally, this increase in natriuresis results in a diuretic effect. In addition, another direct effect of SGLT2 inhibitors is that of the reduction in glycosuria reabsorption, which means better glycemic control and a better control of the metabolic profile thanks to the effects also demonstrated by these drugs (weight loss, improved lipid profile. The most important demonstrated benefits of these drugs are the reduction in the risk of cardiovascular events, reduced mortality from cardiovascular and renal causes, and the slowing of the progression of CKD. However, these great benefits may in part be ascribed to a beneficial balance between oxidant and antioxidant pathways that are associated with anti-inflammatory or antifibrotic effects or even an erythropoiesis stimulation.

The most important studies on kidney transplant patients are reported on Table 1. We may observe that only recently two large studies have been reported [35,36]. Previous studies, consisting in only one RCT, several case series and retrospective studies, could not give an answer of long-term efficacy and safety. In addition, as immunosuppression is more intensive in the first year after transplantation, the majority of the studies on SGLT2 inhibitor in kidney transplant patients have excluded patients in the first period after transplantation.

Table 1. More studies that are relevant for SGLT2 inhibitors on kidney transplant recipients.

Author, Year, Study type, Follow-up	Basal eGFR (ml/min)	Effect in Renal Function (eGFR mL/min/1.73)	Proteinuria (uPCR) g/d/(uACR mg/g	Adverse Events
Rajasekeran, (37) 2017, CS n6, 8mo	78.6±18.2	No differences	NA	Cellulitis
Shah, (38) 2019, PS n25, 8mo	86±20	No differences	NA	None
Schwaiger,(39) 2019, PS, n14, 12mo	55.6±20.3	Decrease and then stabilize	ΔuACR: -25 ΔuACR: -73	UTI 5

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Halden, (40) 2019, RCT, n44, 6mo	66±10.5	No differences	NA	UTI 3
Mahling, (41) 2019, PS, n10, 6mo	57±19.3	No differences	NA	UTI 2
Attallah, (42) 2019, CS, n25, 12mo	NA	Decrease and than stabilize	ΔuPCR -0.6 g/d	UTI 2
Kong, (43) 2019, PS, n42, 12mo	60.36±17	No differences	ΔuACR No significant change	Acute cystitis 3
Alkindi,(44) 2020, CS, n8, 12mo	75.8±13.4	No differences	NA	UTI 1
Song, (45) 2021, RS, n50, 6mo	66.7	No differences	NA	UTI 7
Lemke,(46) 2021, RS, n39, 12mo	NA	No differences	NA	UTI 6, Ketoacidosis 1
S-Fructuoso,(36) 2022, MCO, n339, 12mo	58.4 (56.2-60.6)	No differences	ΔuPCR: -230 at 6 mo	UTI 14%, AKI 1.8%
Lim, (35) 2022, OR, PSM, n2083, 63mo	S: 66.9±17.7 C: 68.4±20.1	Decrease, stabilization and amelioration	ΔuPCR: the urine PCR significantly decreased after SGTLi p=0.005	NA

Due to these limitations, all these studies [37–46] were less potent to studies on general population or renal patients in terms of the number of patients enrolled and the quality of study design. However, the benefits observed in these studies were similar to those observed in the general population [47–50]. Similarly, the incidence of side effects observed in this series of kidney transplant patients was mcg/mg; p<similar to that observed in general population [51]. Two studies just recently have shed new light on the efficacy of SGLT2 inhibitors in kidney transplant patients. Lim et al. [35] enrolled 2083 kidney transplant recipients from six Korean hospitals. 226 patients assumed SGLT2 inhibitors. Patients were observed for 63 months and the multivariate analysis consistently showed a decreased risk of death-censored graft failure and serum creatinine doubling in the SGTL2 inhibitors users. A 15.6% of the SGLT2 inhibitors users showed acute eGFR dip during the first month, but the eGFR recovered thereafter. The risk for infections was very low as documented in previous studies [39,40].

In the other large observational study [36], 339 diabetic kidney transplant patients were given SGLT2 inhibitors for 6 month's treatment. The most frequent side effect was urinary tract infection (14%) and the risk factor for developing UTI were a prior episode and the female sex. The efficacy evaluated at 6 months was a reduction in body weight (-2.22 kg), a reduction in blood pressure, in fasting glycemia, serum acid decreased of 0.44 mg/dl as well as urinary protein creatinine ratio. Hemoglobin level rose 0.44g/dl. According to the authors, SGLT2 should be prescribed in these patients, only with caution for UTI.

Conclusions and Recommendation

An acute reduction of eGFR at the beginning of treatment with SGLT2 inhibitors in kidney transplant patients is due to a feedback tubuloglomerular and is followed by an eGFR stabilization. The study of Kwon et al. [52] evaluated the dapagliflozin efficacy on microalbuminuria. Urinary albumin creatinine ratio (UACR) at 6 months was reduced (118.9 ±231.0 mcg/mg to 82.7±152.1mcg/mg; p, 0.009).

A recent meta-analysis [50] documented that the use of SGLT2 inhibitors reduced the mean of HbA1c of 0.57% and the most relevant reductions were observed in patients with the highest levels.

The treatment with SGLT2 inhibitors reduced the body weight in the majority of patients as documented in the meta-analysis of Chewcharat et al. [50]

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The most common side effects in kidney transplant patients is the urinary tract infection, whose incidence is 11.5%, similar to the incidence reported in a previous meta-analysis [53].

On these bases, the following recommendation should be followed.

a) Start treatment with SGLT" inhibitors at least 6 months after transplantation

b) Start treatment if no previous rejection happened

c) Start treatment in patients with no history of UTI 6 months before starting therapy

d) No history of vascular disease

Legends to Figure 1A,B: NFKB, nuclear factor kappa B; MCP 1 Monocyte chemoattractant protein 1; TFGβTransforming growth factor β; NEFA Non-esterified fatty acids; NO Nitric oxide; O2 Oxygen; N2 Nitrogen; LDL low density lipoprotein; HDL High density lipoprotein

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Conflicts of Interest: Maurizio Salvadori, Alberto Rosati and Giuseppina Rosso do not have any conflict of interest in relation with the manuscript.

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