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MINIREVIEWS

Chances and risks of sodium-glucose cotransporter 2 inhibitors in solid organ transplantation: A review of literatures

Marlene Schwarzenbach, Flavia Elena Bernhard, Cecilia Czerlau, Daniel Sidler

ORCID number: Marlene Schwarzenbach 0000-0003-2886-2721; Flavia Elena Bernhard 0000-0001-7385-9295; Cecilia Czerlau 0000-0002-9453-2766; Daniel Sidler 0000-0002-2435-5936.

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Marlene Schwarzenbach, Flavia Elena Bernhard, Cecilia Czerlau, Daniel Sidler, Department of Nephrology and Hypertension, University Hospital Insel Bern, Bern 3010, Switzerland

Corresponding author: Daniel Sidler, MD, PhD, Assistant Professor, Consultant Physician-Scientist, Senior Researcher, Department of Nephrology and Hypertension, University Hospital Insel Bern, Freiburgstrasse, Bern 3010, Switzerland. daniel.sidler@insel.ch

Abstract

Solid organ transplantation offers life-saving treatment for patients with end-organ dysfunction. Patient survival and quality of life have improved over the past few decades as a result of pharmacological development, expansion of the donor pool, technological advances and standardization of practices related to transplantation. Still, transplantation is associated with cardiovascular complications, of which post-transplant diabetes mellitus (PTDM) is one of the most important. PTDM increases mortality, which is best documented in patients who have received kidney and heart transplants. PTDM results from traditional risk factors seen in patients with type 2 diabetes mellitus, but also from specific post-transplant risk factors such as metabolic side effects of immunosuppressive drugs, post-transplant viral infections and hypomagnesemia. Oral hypoglycaemic agents are the first choice for the treatment of type 2 diabetes mellitus in non-transplanted patients. However, the evidence on the safety and efficacy of oral hypoglycaemic agents in transplant recipients is limited. The favourable risk/benefit ratio, which is suggested by large-scale and long-term studies on new glucose-lowering drug classes such as glucagon-like peptide 1 receptor agonists and sodium-glucose cotransporter 2 inhibitors, makes studies warranted to assess the potential role of these agents in the management of PTDM.

Key Words: Solid organ transplantation; Post-transplant diabetes mellitus; Antidiabetic treatment; Sodium-glucose cotransporter 2 inhibitors; Renoprotection

Core Tip: Literature review of efficacy and side effects of sodium-glucose cotransporter 2 inhibitors in diabetes management specifically in solid organ recipients.

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INTRODUCTION

Pre- and post-transplant diabetes mellitus in solid organ transplantation

Solid organ transplantation (SOT) has become the preferred treatment for end-stage organ failure. The outcomes have improved steadily since the first transplantation in the 60s and 70s[1,2]. The Organ Procurement and Transplantation Network/ Scientific Registry of Transplant Recipients annual data report from 2018 showed a 5-year survival for kidney transplantation of 65% for deceased donors and 90% for living donors. In heart transplantation the 5-year survival was 79.6% and in liver transplantation 76.6%[3-5]. With introduction of modern immunosuppressive regimens, severe rejection of allografts is nowadays rare and thereby fatal immunological organ failures are uncommon. Meanwhile, other complications prevail, notably infections, tumors and cardiovascular diseases[6,7].

Diabetes mellitus (DM) is one of the most prevalent chronic disease conditions in the long-term follow-up of SOT. DM that develops after SOT is called post-transplantation diabetes mellitus (PTDM) and is associated with cardiovascular disease and premature death[1,2]. Increased age and obesity are important risk factors of PTDM and since these conditions prevail in the overall population, the prevalence has steadily increased in the SOT cohorts as well[1]. The following Table 1 shows the current diagnostic criteria for PTDM defined by the American Diabetes Association[8].

For a formal diagnosis of PTDM, it is important to wait until the immunosuppression dosage has stabilised and the patients are with stable kidney allograft function. Although the oral glucose tolerance test is considered the gold standard, in practice hemoglobin A1c (HbA_{1c}) is much more often used for diagnosing PTDM. It should be noted that in the early post-transplant setting, PTDM cannot be ruled out despite normal HbA_{1c}, as transplant-related anaemia may still be present[9]

There is some variation in the reported incidence of PTDM in the literature due to heterogeneity of diagnostic criteria, length of follow-up, type of transplanted organ and immunosuppressive agents used. In kidney transplant recipients the PTDM incidence is reported as 10%-40% after 5 years, in heart transplantation 20%-30% and in liver transplantation 30%-40% at 5 years follow-up[1].

TREATMENT OF POST-TRANSPLANT DIABETES MELLITUS

Oral hypoglycaemic agents are the primary choice for treatment of type 2 diabetes mellitus (T2DM) in non-transplanted patients[1]. In contrast, insulin therapy is the preferred strategy to manage hyperglycaemia in the early postoperative period in transplant recipients[1,10,11]. Indeed, PTDM is perceived as a combined hit of defective insulin secretion and insulin resistance. Therefore, interventions for reducing insulin resistance and preserving β-cell function should be included in the optimal management of PTDM[11]. Starting insulin therapy early after diagnosis of hyperglycaemia to prevent β-cell glucotoxicity and overstimulation of vulnerable β-cell is hiding behind the idea called 'β-cell rest'[1]. In a proof-of-concept randomised controlled trial, renal transplant recipients with hyperglycaemia in the early transplant period showed a lower PTDM-rate in the 1 year follow-up if they were aggressively treated with intensive insulin regimens. The study demonstrated, that early basal insulin therapy is effective in reducing HbA_{1c} and decreasing PTDM over the long term[12]. Unfortunately, the evidence on the efficacy and safety of oral hypoglycaemic agents in transplant recipients are limited, and there is very little published data to guide therapeutic choices in the posttransplant setting[10,13]. Only dipeptidyl peptidase-4 inhibitors have been tested in an randomised controlled trial with good efficacy and tolerability. Also, metformin is associated with a number of cardio-metabolic benefits and could be a useful option for patients with good or only modestly impaired allograft function[11]. The favourable risk/benefit ratio, which is suggested by the limited clinical experience with newer classes such as incretins and sodium-

Table 1 Criteria for the diagnosis of diabetes mellitus in patients with and without solid organ transplantation

Criteria for the diagnosis of diabetes	
FPG	≥ 126 mg/dL (7.0 mmol/L), fasting means no caloric intake for at least 8 h
2-h PG	≥ 200 mg/dL (11.1 mmol/L) during OGTT
HbA_{1c}	≥ 6.5% (48 mmol/L)
	Random plasma glucose ≥ 200 mg/dL (11.1 mmol/L), in a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis

At least one of the above-named criteria must be fulfilled for the diagnosis of diabetes. 2-Hpg: 2-h-plasma glucose; FPG: Fasting plasma glucose; HbA_{1c}: Haemoglobin A1c; OGTT: Oral glucose tolerance test.

glucose cotransporter 2 inhibitors (SGLT2-inhibitors), makes studies warranted to assess the potential role of these agents in the management of PTDM[10,11].

As shown in the review by Hecking *et al*[12], different immunosuppressive therapies have different diabetogenic effects. The diabetogenic effect of therapy with corticosteroids and tacrolimus is well documented, and, compared to tacrolimus, cyclosporine is less diabetogenic. Belatacept and the mammalian target of rapamycin inhibitors present also an increased PTDM risk. Regarding basiliximab, no definitive statement is possible due to the lack of data. The few studies that have been done, have given different results. The treatment with anti-thymocyte globulin shows no risk of developing PTDM. Immunosuppression is the major modifiable risk factor for development of PTDM, but risk *vs* benefit analysis is required to balance risk of developing PTDM *vs* rejection. In selected patients with PTDM or at high risk of PTDM, switching tacrolimus to cyclosporine can be considered by the nephrologist/transplantation team provided that it does not compromise graft/patient outcomes[14,15].

The survival rate of kidney transplantation is superior to maintenance dialysis and is therefore the treatment of choice among eligible patients, including those with type 1 diabetes mellitus and end-stage renal disease. This patient group also has the option of simultaneous pancreas-kidney transplantation (SPKT)[16]. Several studies have shown that SPKT is associated with a better cardiovascular outcome compared to kidney transplantation alone[17-20]. To date, oral hypoglycaemic agents have very little relevance in the treatment for type 1 diabetes mellitus, neither in patients with unimpaired renal function nor in patients with kidney transplantation alone or SPKT.

MACRO- AND MICROVASCULAR COMPLICATIONS IN DIABETES MELLITUS IN GENERAL, AND IN SOT IN PARTICULAR

A large body of evidence shows the excessive long-term complication rate in patients suffering from DM, namely micro- and macrovascular events[21-24]. A large collaborative meta-analysis of 102 prospective studies demonstrated that DM patients suffer from an independent two-fold excess risk of vascular outcomes (coronary heart disease, ischaemic stroke, and vascular deaths)[25]. Importantly, in the presence of DM, the risk of classical cardiovascular risk factors was not additive yet synergistic in respect of vascular complications[26,27]. Coronary artery disease is the most common macrovascular complication registered. No other risk factor, except for cigarette smoking, increases the risk of myocardial infarction more than DM[22]. Not only the coronary but also the cerebral vessels are strongly affected by DM. Relative to non-diabetic population, patients with T2DM have a 150%–400% higher risk of stroke[24]. The most common microvascular complication is diabetic retinopathy. In the United States, 10000 new cases of blindness every year are due to this complication[28]. Furthermore, diabetic neuropathy is a second microvascular complication and associated with significant morbidity and mortality. Eighty percent of lower limb amputations are a consequence of peripheral neuropathy[29]. Thirdly, one of the leading causes of renal failure and end-stage renal disease requiring dialysis as renal replacement therapy is diabetic nephropathy[22].

Importantly, micro- and macrovascular cardiovascular co-morbidities are common in SOT, notably in kidney and heart transplant recipients[30,31]. First, patients are dependent on polypharmacy with a substantial risk of progressive atherosclerosis,

notably calcineurin inhibitors and steroids[2,32,33]. Systemic immunosuppression has been attributed to induce independently atherosclerosis, although the exact mechanisms are not well understood. Thirdly, SOT patients with polypharmaceutical regimens often do not tolerate sufficient doses of cardiovascular medications, notably statins, and therefore primary or secondary prevention cannot be optimised[1,2,34,35]. Last, SOT recipients have become older, more obese, and more polymorbid, which by itself suggests an excessive risk for cardiovascular events[33,36].

It has long been known that the optimal modality of renal replacement therapy is a renal transplantation, resulting in better quality of life and better life expectancy[37]. But a national cohort study from Taiwan showed that even renal transplant recipients still have a twofold higher annual cardiovascular mortality than the general population. The study also included heart, lung, and liver recipients and demonstrated that SOT recipients were at an approximately threefold risk of developing any type of vascular disease[30].

In conclusion, SOT recipients with DM are at highest risk of cardiovascular events due to excessive and cumulative classical and non-classical cardiovascular risk factors [30,31,38]. Therefore, antidiabetic medications like SGLT2-inhibitors, which may not only improve the diabetic status but may even reduce the risk of cardiovascular diseases, could have an extreme potential in treatment strategies[22].

INTRODUCTION OF SGLT2-INHIBITORS IN DIABETES MANAGEMENT

The SGLT2 is a renal high-capacity, low-affinity transporter in the proximal convoluted tubule and reabsorbs virtually all filtered glucose from the tubular lumen. In patients with T2DM, SGLT2 is significantly overexpressed to cope with increased tubular glucose load and glucosuria therefore appears only with prolonged and severe hyperglycaemia[39,40]. Reversible inhibitors of SGLT2 are approved as antidiabetic drugs for use in T2DM mellitus with or without cardiovascular complications[41]. By blocking glucose and sodium re-uptake in the proximal convoluted tubule, these compounds reduce the renal glucose reabsorption leading to increased urinary glucose excretion and natriuresis[39,42-44]. The SGLT2-inhibitors show a low risk of hypoglycaemia, are independent of endogenous insulin secretion and are not affected by pancreatic β-cell function or the degree of insulin resistance, which allows their use in any stage of type 2 diabetes[10,40,44].

The forced natriuresis leads to intravascular volume contraction and alters intrarenal haemodynamic. Therefore, apart from reduction of glucosaemia, SGLT2-inhibitors have a positive impact on the cardiovascular system and lower risk for kidney disease and cardiovascular events in high risk individuals. The EMPA-REG study reported strong evidence that empagliflozin protects against serious cardiovascular and renal complications[40,42,43,45,46].

An experimental *in vitro* model by Jin *et al*[47] showed that empagliflozin decreases tacrolimus-induced hyperglycaemia while increasing plasma insulin level. Further, a direct renoprotective effect was observed.

The CANVAS study showed a reduced incidence of fatal and non-fatal cardiovascular events in participants randomised to the canagliflozin group. Furthermore, the study showed, that participants assigned to canagliflozin experienced less likely a progression of albuminuria, reduction in eGFR and end-stage renal disease[45]. A growing body of literature suggests that SGLT2-inhibitors have a very potent vasoprotective activity and should therefore be introduced in patients at high risk of cardiovascular events, irrespective of their diabetes status[41]. Since the risk of hypoglycaemia is negligible, such interventions would be easily possible without posing the patient at risk for hypoglycaemia. Indeed, several trials to evaluate the effect of SGLT2-inhibitors on vascular endpoints in non-diabetic populations are ongoing.

POTENTIAL RISKS OF SGLT2-INHIBITORS

Adverse events have been reported in association with SGLT2-inhibitors including dyslipidaemia, urinary and genital tract infections, metabolic acidosis, normoglycaemic ketoacidosis, hypotension and bone fracture (reviewed in[48]). While some side effects are clearly associated with the mechanism of action of the drug class, other-namely fractures and non-ischaemia related amputations-have raised speculations about unwarranted off-target effects. Further research, including well-controlled real-life data, is mandatory, to further insights. SGLT-2 inhibitors may induce normogly-

Table 2 Retrospective studies, case series and prospective randomised and non-randomised studies investigating sodium-glucose cotransporter 2 inhibitors in solid organ transplantation recipients

Ref.	Type	Patients	Endpoint	Findings
Lo *et al*[13]	Review of 7 intervention studies	KTRs: 3: Insulin therapy (more or less intensive); 3: Dipeptidylpeptidase 4-inhibitors for new-onset diabetes after transplantation; 1: Pioglitazone with insulin to insulin alone for treating pre-existing diabetes	Effectiveness and safety of glucose-lowering agents in this population.	Safety and efficacy of glucose-lowering agents in transplant recipients are uncertain due to data being limited and of poor quality; more studies are required to confirm the effectiveness and safety of glucose-lowering agents.
Schwaiger *et al*[51]	Prospective, nonrandomised interventional pilot study	KTRs (n = 14, all received exogenous insulin therapy [< 40 IU per day (total)]	Intra-individual difference in 2-h glucose level between first OGTT at baseline and second OGTT after 4-wk empagliflozin monotherapy.	Glucose control under empagliflozin monotherapy was clinically inferior compared to prior exogenous insulin treatment (glucose levels during second OGTT higher than baseline); statistically significant reduction in body mass index, body weight and waist circumference; bacterial urinary tract infections in 3 patients during study period; empagliflozin can safely be used as add-on therapy, if PTDM patients are monitored closely.
Halden *et al* [50]	Single-centre, prospective, randomised, placebo con-trolled, double blinded study	KTRs (n = 49)	Investigation whether empagliflozin can be used safely to improve glucose metabolism in KTRs with PTDM.	Glycaemic control significantly improved compared with placebo; empagliflozin treatment was associated with a concomitant, significant reduction of body weight; one case of urosepsis observed, but relationship to drug treatment is uncertain; no significant differences between groups in adverse events, immunosuppressive drug levels or estimated glomerular filtration rate.
Cehic *et al* [52]	Retrospective, nonrandomised single-centre observational study	Heart transplant recipients (total n = 101, 22 empagliflozin, 79 alternative glucose-lowering therapies)	Investigate the safety of empagliflozin in postheart transplant diabetic population; focus on incidence of genitourinary infections; long-term (after 12 mo) effectiveness.	No genitourinary tract infections in the empagliflozin-treated group compared with 9 urinary infections in the control group; significant reduction in median body weight, median body mass index and median furosemide dose after 12 mo of treatment with empagliflozin; HbA_{1c} was reduced in the empagliflozin group, during patients in the control group experienced a mean increase in HbA_{1c}; although the reduction in HbA_{1c} was not statistically significant (P = 0.07), data suggest empagliflozin was efficacious for improving glycaemic control; overall, empagliflozin was well tolerated and can be safely used as a long-term option.
AlKindi *et al* [53]	Case series supported by literature review	KTRs (n = 8)	Description of the short-term experience of KTRs treated with empagliflozin (n = 6) and dapagliflozin (n = 2).	Significant reduction in HbA_{1c}, weight and BMI; no episodes of severe hypoglycaemia or symptomatic ketoacidosis during the study period; the use of SGLT2 inhibitors among diabetic renal transplant patients was both effective and safe.
Rajasekeran *et al*[54]	Case series (n = 10)	KTRs (n = 6) and SPKTR (n = 4)	Description of the short-term experience of KTR and SPKTR treated with canagliflozin.	No urinary or mycotic infections diagnosed during treatment; one patient experienced hypoglycaemia that did not require hospitalization; one patient developed cellulitis; no patients experienced acute rejection or acute kidney injury. In this small cohort, canagliflozin was generally well tolerated. They observed an overall improvement in glycaemic control, weight and blood pressure.
Peláez-Jaramillo *et al*[55]	Literature review	LTR	Current knowledge on the epidemiology, pathogenesis, course of disease and medical management of PLTDM.	PLTDM should be screened for, timely diagnosed and intensively managed. Clinicians in charge of caring for LTR should bear in mind key concepts about PLTDM.
Cigrovski Berkovic *et al*[56]	Literature review	LTR	Exploration of the relationships and mechanisms between diabetes mellitus and liver disease bevor and after liver trans-plantation, especially in the term of non-alcoholic fatty liver disease.	The pharmacological management of PTDM is still complicated because there are no published randomised clinical trials about effectiveness and safety of antihyperglycaemic agents.
Attallah *et al* [57]	Case series (n = 8)	KTRs	Description of the short-term experience of KTR treated with empagliflozin.	The use of empagliflozin to manage diabetes mellitus after kidney transplantation was tolerated; small number and in general mild side effects.
Beshyah *et al* [58]	Mixed methods: Case report,	KTRs	Case report: Off-label use of dapagliflozin in a	The index case suggests the safe use of SGLT2 inhibitors by renal transplant recipients. It seemed that physicians

	surveys of physicians' opinions, and a review of the literature	patient with diabetes mellitus and renal transplantation.	are willing to use SGLT2 inhibitors in such patients if the renal function is satisfactory.

BMI: Body mass index; HbA_{1c}: Haemoglobin A1c; KTR: Kidney transplant recipient; LTR: Liver transplant recipients; OGTT: Oral glucose tolerance test; PLTDM: Post-liver trans-plant diabetes mellitus; PTDM: Post-transplant diabetes mellitus; SGLT2: Sodium-glucose cotransporter 2.

caemic ketoacidosis, notably in settings of dehydration and acute kidney injury. Interestingly, none of the three large prospective trails (CANVAS, DECLARE and EMPA-REG) revealed a side-effect signal in this perspective[49].

The glucose-lowering effect of SGLT2-inhibitors depends on glycemia levels and glomerular filtration rate and is progressively eased as renal function decreases. Meanwhile, the non-glycaemic effects of this drug class, including blood pressure control and reduction of albuminuria, seem independent of kidney function[42,43]. Currently, SGLT2-inhibitors are indicated for patients with an eGFR of 45 mL/min/1.73 m^2 or above, although the CANVAS study included patients with eGFR of 30-45 mL/min/1.73 m^2 with similar treatment efficacy and side effects. Similar to treatment with ACE-Inhibitors or sartans, SGLT2-inhibiors induce an early and reversible reduction of eGFR in the first weeks of treatment due to decreased intraglomerular pressure[44].

The expertise of SGLT2-inhibitors in SOT is limited, and prospective trials currently not available[13]. Recently published articles are summarised in Table 2. Halden *et al* [50] investigated in a randomised, double-blinded trial the safety and efficacy of 10 mg/d empagliflozin or placebo in 49 kidney patients with PTDM, at least 1 year transplant history and an allograft function of 30 mL/min/1.73 m^2 or above[2,50]. They observed a small, yet significant improvement of HbA_{1c} and increased weight loss in the intervention group. Interestingly, the magnitude of glucose reduction was dependent on eGFR and baseline HbA_{1c}. Adverse events were rare and indifferent among the groups[50]. In line, several retrospective cohort studies in kidney transplant recipients under SGLT2-inhibitors reported a high tolerability of the drug class with minimal infectious/ infectious complications[51,53,54,57,58]. So far, a renoprotective effect of SGLT2-inhibitors in kidney transplant recipients has not been demonstrated, yet is under active investigation (see below).

A recently published retrospective single-centre observational study analysed the outcome of 22 heart transplant recipients treated with empagliflozin compared to 79 matched controls on alternative glucose-lowering therapies. After 12 mo treatment, empagliflozin-treated patients showed a reduction in body weight, improvement of HbA_{1c} and diminished diuretic requirements that was not seen in the control group. No difference in blood pressure, renal function or incidence of infections, notably genitourinary tract infection, was seen among the groups[52].

Cleary, PTDM is an emerging problem among liver transplant recipients, and optimal treatment modalities have not yet been identified[55,56]. In our literature search, we did not identify prospective trials investigating safety and efficacy of SGLT2-inhibitors in liver transplant recipients. Nevertheless, these agents seem attractive for the future treatment of patients with orthotopic liver transplantation[49,55].

Currently, several prospective trials investigating SGLT2-inhibitors in SOT are registered. The Renji Hospital in China investigates (NCT03642184) change from baseline in eGFR in stable kidney transplanted patients randomised to empagliflozin or linagliptin. The EMPTRA-DM trial from Vienna (NCT03113110) investigates glucose control in 16 stable kidney transplant recipients who receive empagliflozin as add-on to standard PTDM treatment.

CONCLUSION

In conclusion, a large body of evidence underscores the beneficial effect of SGLT2-inhibitors in diabetes management, reduction of cardiovascular events and weight loss intervention in diabetic and non-diabetic patients with high cardiovascular risk. In SOT, treatment is well tolerated with limited side effects, importantly no signs for excessive incidence of genitourinary infections. Prospective trials are needed to elucidate the potential effect of SGLT2-inhibitors after SOT, notably in respect of early

and late glycaemic control and reno- and cardiovascular protection.

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