

The new antidiabetic agents: cardiovascular and renal protection in post-transplant diabetes mellitus

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ABSTRACT

Post-transplant diabetes mellitus (PTDM) is a metabolic alteration in organ transplant patients, with an incidence ranging from 2% to 65%. PTDM leads to an increased risk of organ rejection, infections, cardiovascular (CV) events, and reduced survival. The incidence of PTDM depends on various factors occurring in the post-transplant period, from changes in lifestyle and eating habits, with subsequent increase of visceral weight and fat, to the direct action of immunosuppressive drugs. In recent years, cardiovascular outcome studies have shown that two drug classes, glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose-cotransporter-2 inhibitors (SGLT-2i) have cardiovascular and renal protection effects on patients with type 2 diabetes, substantially modifying the guidelines on the therapeutic management of these patients. Given the effects on glycometabolic control and the several glucose-independent effects, GLP-1RAs and SGLT-2i potentially play a predominant role in the management of PTDM. The evidence gathered so far in the literature is still limited. Though no drug interactions are present, GLP-1RAs may still interfere with the absorption of immunosuppressants due to the effect of slowing gastric emptying. On the other hand, SGLT-2i already increases the risk

of genitourinary infections, which could be more frequent and severe in immunosuppressed patients. Nevertheless, both drug classes appear to be safe and effective in transplanted patients, and though further controlled prospective studies are necessary, their mechanism of action, glucose-independent effects, and cardiovascular and renal protection effects seem to fully respond to the metabolic changes caused by PTDM.

INTRODUCTION

In 2017, approximately 139,000 organ transplants were carried out worldwide, of which 65% kidney, 23% liver, 6% heart, 4% lung, and 2% pancreas (Global Observatory on Donation and Transplantation - World Health Organization).

Diabetes mellitus that occurs after transplantation is defined as new onset diabetes after transplantation (NODAT). However, since the glucidic alteration may be present prior to transplantation and unknown, in 2013 an international consensus meeting recommended the use of the term post-transplant diabetes mellitus (PTDM)¹. Besides, pre-transplant type 2 diabetes, because of the prognostic and management implications resulting from immunosuppressive therapy, may not be addressed independently from PTDM recommendations.

The incidence of PTDM is estimated at approximately 40% in kidney transplantation, 25% in heart transplantation, 32% in lung transplantation, and 18% in liver transplantation².

The identification and management of PTDM is crucial in view of the increased risk of organ



rejection, infections, cardiovascular (CV) events, and the reduced survival of patients with diabetes compared to patients with normoglycemia^{3,4}. Even without a definite diabetes mellitus, metabolic syndrome, the incidence of which increases progressively over time after transplantation, is associated with a higher incidence of CV events⁵.

Almost all immunosuppressive drugs, including glucocorticoids, calcineurin inhibitors and, to a lesser extent, mammalian target of rapamycin (mTOR) selective inhibitors play a key role in the development of PTDM⁶⁻⁸. Immunosuppressant therapy potentially leads to the development of a dysglycemic state due to both a direct cytotoxic action on pancreatic beta cells with inhibition of basal insulin secretion and after glycemic stimulus, and to induction of insulin resistance, with inhibition of basal and postprandial insulin secretion and decreased glucose uptake in peripheral tissues.

Other factors also increase the risk of developing diabetes in these patients. Lifestyle changes after transplantation, with increased appetite and return to a less stringent diet, sometimes result in increased weight and visceral fat, with related metabolic abnormalities. Post-surgery hyperglycemia, certain donor characteristics, post-transplant pharmacological procedures, and the treatment of acute rejection can affect the risk of developing PTDM⁹⁻¹².

Non-pharmacological treatment is a key component of PTDM management. Healthy lifestyle and regular physical activity should be the first steps to be taken in the event of prolonged hyperglycemia after transplantation. However, in most cases, drug therapy is essential to counteract hyperglycemia and its deleterious effects on vascular macro- and microcirculation.

The primary goal of drug therapy is to reduce the CV risk in these patients. To date, there are no unique recommendations on the selection of the most suitable hypoglycemic agent for PTDM. Some centers do not distinguish between T2D and PTDM and, in fact, choosing patient-tailored therapies and goals based on the current guidelines for the treatment of T2D would be ideal¹³. Nevertheless, transplant patients inherently have a higher CV risk due to comorbidity, surgery, and immunosuppressive drugs. The increased survival rate of transplant recipients have shown that the incidence and prevalence of cardiovascular disease (CVD) in patients with PTDM are higher compared to non-transplanted diabetic patients³.

Immunosuppressive therapy is an important challenge for the management of post-transplant diabetes for several reasons. First, the immunosuppressant regimen changes over time. In particular, corticosteroids are gradually reduced in the post-transplant period, and sometimes discontinued, and then re-administered in case of acute rejection. This means that a more aggressive glucose-lowering treatment with insulin is needed immediately after transplantation, and that insulin can be reduced or discontinued later on during the follow-up, and then be used again in case of rejection. Second, there may be pharmacokinetic interactions between glucose-lowering agents and immunosuppressive drugs¹⁴. Finally, nephrotoxicity resulting from the use of certain immunosuppressive drugs limits the use of certain hypoglycemic drug classes over time. For this reason, often only insulin therapy is considered a valid choice in PTDM patients. Given the growing number of transplants worldwide, a proportional and significant increase in the incidence of PTDM has to be considered.

The aim of this study is to analyze the current evidence on two new pharmacological classes that, due to their effects on glycometabolic control and to the numerous glucose-independent effects, have a potentially predominant role in the management of PTDM: glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT-2i).

CARDIOVASCULAR OUTCOME TRIALS ON NEW ANTIDIABETIC AGENTS

Since 2008, the United States Food and Drug Administration and, later, the European regulatory authorities, on the basis of some negative reports recorded after the marketing of rosiglitazone, have requested pharmaceutical industries to demonstrate the cardiovascular safety of the new hypoglycemic drugs before or immediately after their marketing authorization, through ad hoc controlled clinical studies, commonly known as cardiovascular outcome trials (CVOTs)¹⁵. A common feature of these randomized, double-blind studies is to compare the new drug with placebo, which is understandable from the perspective of evaluating safety first, but does not give any indication of superiority over other available drugs. CVOTs have a specific and well-defined primary goal, generally consisting of the 3-point MACE (major adverse cardiovascular events), which is a composite end-point of death for cardiovascular causes, heart attack,

and non-fatal stroke. Almost all CVOTs conducted since 2008 therefore meet these criteria but, though these studies are designed to demonstrate non-inferiority, SGLT-2i and GLP-1RAs have demonstrated cardiovascular and renal protection.

GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONIST (GLP-1RAs)

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by L cells of the intestine in response to food ingestion, which stimulates endogenous insulin secretion in a glucose-dependent manner. GLP-1 reduces blood sugar by stimulating insulin release, suppressing high levels of glucagon, delaying gastric emptying, and reducing food intake. Furthermore, GLP-1 has been shown to promote the growth and proliferation of beta cells in animal models¹⁶.

Incretin-based therapies have been used for almost a decade as additional agents to conventional therapy, and as initial treatment for some patients. There are two therapeutic approaches that target the incretin system for the reduction of blood glucose.

Dipeptidyl peptidase 4 (DPP-4) inhibitors block the enzyme accountable for removing circulating endogenous GLP-1, thus enhancing its effects. On the other hand, glucagon-like peptide-1 receptor agonists (GLP-1RAs) are glucagon-like peptide-1 analogues which are resistant to degradation by DPP-4¹⁷.

The latter category has been shown to be safe and effective in reducing glycated hemoglobin

(HbA1c) without directly causing hypoglycemia and, unlike the DPP-4 inhibitors, has passed several trials that showed a clear association with reduction of cardiovascular risk and renal protection.

Except for the EXSCEL¹⁸ and ELIXA¹⁹ studies, which, as required by drug regulatory authorities, showed only the cardiovascular safety of exenatide and lixisenatide, respectively, all other CVOTs on GLP-1RAs also demonstrated higher cardiovascular efficacy compared to placebo. In the LEADER study, liraglutide demonstrated a statistically significant reduction in the incidence of MACE, especially for decreased cardiovascular mortality²⁰. In addition, liraglutide had positive effects on the progression of nephropathy, mainly due to a reduction in microalbuminuria²¹. The SUSTAIN-6 study conducted with semaglutide, a long-acting once-weekly analogue, showed a significant reduction in the incidence of the primary outcome, in this case mainly driven by a reduction in non-fatal stroke²². In the Harmony Outcomes study, albiglutide showed cardiovascular benefits on MACE, the driver of which was a 25% reduction in the risk of fatal or non-fatal myocardial infarction²³. Finally, dulaglutide, administered on a weekly basis, was associated with lower incidence of cardiovascular adverse events compared to placebo in a large cohort of diabetic patients with and without prior cardiovascular disease in the REWIND study, the first cardiovascular outcome study designed to demonstrate the superiority of GLP-1RAs treatment over standard care²⁴.

Table 1. Summary of large cardiovascular outcomes trials for glucagon-like peptide-1 receptor agonists

TRIAL NAME	N PATIENTS	TREATMENT	ENROLLEMENT CRITERIA	PRIMARY OUTCOME	PRIMARY OUTCOME RESULTS	MEDIAN FOLLOW-UP
LEADER (20) 2015	9340	Liraglutide once daily vs. placebo	≥50 years old, T2D with at least one co-existing CVD or ≥60 years old with at least on CV risk factor	CV death, non-fatal MI, non-fatal stroke	13.0% in liraglutide vs 14.9% in placebo group (HR 0.87, 95% CI 0.78-0.97, p<0.001 for non-inferiority, p=0.01 for superiority)	3.8 years
ELIXA (19) 2015	6068	Lixisenatide once daily vs. placebo	≥30 years old, T2D and ACS within 180 days of screening	CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina	13.4% in lixisenatide vs 13.2% in placebo group (HR 1.02, 95% CI 0.89-1.17, p<0.01 for non-inferiority, p=0.81 for superiority)	2.1 years
SUSTAIN-6 (22) 2016	3297	Semaglutide once weekly vs. placebo	≥50 years old, T2D with established CVD, chronic heart failure or chronic kidney disease, or age ≥60 with at least one cardiovascular risk factor	CV death, non-fatal MI, non-fatal stroke	6.6% in semaglutide vs 8.9% in placebo group (HR 0.74, 95% CI 0.58-0.95, p<0.01 for non-inferiority, p=0.02 for superiority)	2.1 years
EXSCEL (18) 2018	14752	Exenatide once weely vs. placebo	Adults with T2D, 70% with previous cardiovascular events and 30% with no history of cardiovascular events	CV death, non-fatal MI, non-fatal stroke	11.4% in exenatide vs 12.2% in placebo group (HR 0.91, 95% CI 0.83-1.00, p<0.001 for non-inferiority, p=0.06 for superiority)	3.4 years
HARMONY OUTCOMES (23) 2019	9463	Albiglutide once weekly vs. placebo	≥40 years old, T2D and established coronary, cerebrovascular or peripheral arterial disease	CV death, non-fatal MI, non-fatal stroke	7% in albiglutide vs 9% in placebo group (HR 0.78, 95% CI 0.68-0.90, p<0.0001 for non-inferiority, p=0.0006 for superiority)	1.6 years
REWIND (24) 2019	9901	Dulaglutide once weekly vs. placebo	≥50 years old with T2D who had either a previous cardiovascular event or cardiovascular risk factors	CV death, non-fatal MI, non-fatal stroke (designed for superiority)	12.0% in dulaglutide vs 13.4% in placebo group (HR 0.88, 95% CI 0.79-0.99; p=0.026 for superiority)	5.4 years

ACS, acute coronary syndrome. CI, confidence interval. CVD, cardiovascular disease. HR, hazard ratio. MI, myocardial infarction. T2D, type 2 diabetes.

These results have led to an update of current North American and European guidelines on the management of T2D, recommending GLP-1RAs as a second-line therapy after metformin for CVD patients, primarily with atherosclerotic disease^{25,26}. Table 1 summarizes the largest CVOTs for GLP-1RAs.

THE ROLE OF GLP-1RAs IN PTDM

Apart from the already described direct and indirect effects on blood sugar, GLP-1 has potentially anti-hypertensive, anti-inflammatory, anti-apoptotic, and immunomodulatory effects²⁷. These effects are the basis of a likely intrinsic cardiovascular protection of GLP-1RAs, which allows a greater survival of the graft, as suggested by Wang et al²⁸ in a recent study on cardiac allograft vasculopathy in a murine model. On the other hand, there is substantial evidence of the beta-cell protection effect obtained in pancreatic islet transplantation²⁹⁻³¹. In a recent study on human islets transplanted into immunodeficient mice, Dai et al³² showed that tacrolimus and sirolimus-induced beta-cell dysfunction (i.e. impaired insulin secretion in fasted and/or stimulated conditions, increased amyloid deposition and islet macrophage infiltration, disrupted insulin granule formation) can be prevented by GLP-1RAs. Moreover, as in T2D, also in PTDM it has been shown that, in conjunction with a reduced insulin secretion, there is a reduced ability to suppress circulating glucagon levels, which GLP-1RAs can restore³³.

GLP-1RAs are cleared by proteolytic degradation, glomerular filtration, or both, and are therefore not involved in any pharmacological interactions with immunosuppressants³⁴. As these drugs slow gastric emptying, the absorption of immunosuppressants may be modified. However, gastric emptying does not seem to affect the exposure of immunosuppressive drugs^{35,36}, even when this is a consequence of the use of liraglutide, as demonstrated by Pinelli et al³⁷ in the first case series on diabetic patients after kidney transplantation. In a retrospective study of 7 kidney transplant patients in poor diabetic control, Liou et al³⁸ found an improvement in glycometabolic control, with the maintenance of an optimal tacrolimus concentration over time, even with some dosage modifications. GLP-1RAs were also safe and effective in some subsequent retrospective studies in patients transplanted with kidney, liver, combined kidney/liver, or heart. Krisl et al³⁹ showed reductions in HbA1c levels and weight loss in 19 of 20 patients

treated with liraglutide or exenatide. In 2019, Singh et al⁴⁰ analyzed data from 63 patients with PTDM at 6, 12, and 24 months. No increased risk of tumors, CVD, rejection or mortality from any cause was found, gastrointestinal adverse effects were rare, and no change in the dose of immunosuppressants was necessary. Interestingly, the improvement trend in the renal function observed in this population included 72% of patients in stage 3 and stage 4 chronic renal failure. Even more recently, in a retrospective study of 19 patients, Thangavelu et al⁴¹ confirmed the efficacy of GLP-1RAs, which seem to improve glycemic control and reduce body weight, without affecting tacrolimus levels or transplant outcomes in the short term. Finally, the first comparative study of dulaglutide and liraglutide for the management of PTDM was conducted in 2020⁴². In this retrospective study of 88 patients, Singh et al⁴² observed an increased efficacy of dulaglutide on glucose control and renal function.

Nevertheless, all GLP-1RAs studied have demonstrated good safety in terms of side effects, and no interference with immunosuppression. Metabolic benefits were maintained over 2 years of follow-up, suggesting that GLP-1RAs are a valuable option for long-term treatment of PTDM^{40,42}. Table 2 summarizes the reported studies on GLP-1RAs in PTDM.

SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS (SGLT-2i)

In the kidney of healthy individuals, the amount of glucose reabsorbed through the sodium-glucose-cotransporters-1 (SGLT-1) and -2 (SGLT-2) is equal to the amount of glucose filtered by the glomerulus. Glucose reabsorption by the proximal tubule increases linearly as the glucose concentration increases, up to a theoretical threshold of ~ 180 mg/dL. The SGLT-2 transporter mediates about 90% of renal glucose reabsorption by coupling glucose transport to the electrochemical sodium gradient. The remaining glucose is reabsorbed through SGLT-1. After this threshold, the glucose flow is too high, and the glucose transport system becomes saturated. All filtered glucose that exceeds this threshold is then excreted. In diabetes, SGLT-2 is overexpressed and thus increases the ability to reabsorb glucose. Therefore, instead of allowing the kidney to excrete excess filtered glucose into the urine and correct hyperglycemia, the SGLT-2 transporter works at higher rates and maintains high glucose concentration in the plasma⁴³. Inhibition of SGLT-2 decreases the maximum reabsorption capaci-

Table 2. Summary of reported studies on glucagon-like peptide-1 receptor agonist use in post-transplant diabetes mellitus

STUDY	TYPE OF STUDY (N PATIENTS)	TREATMENT	ORGAN TRANSPLANTED	SAFETY	GLYCEMIC CONTROL	EFFECT ON WEIGHT	RENAL FUNCTION	FOLLOW-UP
Pinelli et al (37) 2013	Case series (n=5)	Liraglutide once daily	Kidney	Mild symptoms, no hypoglycemia; tacrolimus and maintenance corticosteroid doses remained unchanged, no biopsy proven evidence of acute rejection	Trend of postprandial glucose reduction	Trend of body weight reduction	No patients experienced stage 1 acute kidney injury	21 days
Krisi et al (39) 2014	Retrospective (n=20)	Liraglutide or long-acting release (LAR) exenatide	Kidney, lung, heart, liver, combined	No adverse effects on immunosuppressive drug levels or creatinine	Trend of HbA1c reduction	Trend of body weight reduction	Trend of creatinine reduction	10 months (mean)
Liou et al (38) 2018	Retrospective (n=7)	Liraglutide once daily	Kidney	Mild symptoms but no hypoglycemia, no serious adverse events.	HbA1c reduction (p=0.047), nadir glucose reduction (p=0.047)	Nadir body weight reduction (p=0.032)	Nadir creatinine reduction (p=0.044), best eGFR increase (p=0.024)	19.4 months (mean)
Singh et al (40) 2019	Retrospective (n=63)	Dulaglutide once weekly	Kidney, heart, liver, liver/kidney	6.3% non-severe hypoglycaemic events; 1.5%-3% GI mild symptoms.	HbA1c reduction (p<0.001 at 6mo, p=0.07 at 12mo, p=0.23 at 24 mo)	Body weight reduction (p<0.003 at 6mo, p<0.001 at 12mo, p<0.03 at 24 mo)	No creatinine difference (p=0.05 at 6mo, p=0.87 at 12mo, p=0.14 at 24 mo)	24 months
Thangavelu et al (41) 2020	Retrospective (n=19)	Exenatide, liraglutide, dulaglutide or semaglutide	Kidney, heart, liver	No serious adverse effects, mild GI symptoms, no differences in FK506 level	HbA1c reduction and decreases in total daily dose of insulin	Weight and BMI reduction	No significant change in eGFR	12 months
Singh et al (42) 2020	Retrospective comparison study (n=88)	Dulaglutide once weekly (63 patients) vs. Liraglutide once daily (25 patients)	Kidney, heart, liver, liver/kidney	No adverse events, including pancreatitis, pancreatic cancers, thyroid cancers or injection site infection in either group. Non-severe hypoglycaemia and GI side effects higher in liraglutide compared to dulaglutide group	HbA1c reduction with no difference between groups	Weight and BMI reduction, significantly greater in the dulaglutide compared to liraglutide	Renal function improvement in favor of dulaglutide	24 months

BMI, body mass index. eGFR, estimated glomerular filtration rate. GI, gastrointestinal. HbA1c, hemoglobin A1C. Mo, months.

ty of the proximal tubule and lowers the renal threshold for glucose. Therefore, there will be abundant glycosuria associated with fluid loss, osmotic diuresis, and a calorie loss of about 240 calories per day⁴⁴.

Empagliflozin was the first SGLT-2i studied in a CVOT, the EMPA-REG OUTCOME⁴⁵. The primary endpoint (reduction of MACE) was achieved and a superiority in cardiovascular protection was demonstrated, mainly related to a reduction of cardiovascular mortality, independently of the effects on blood sugar, body weight, and blood pressure. Notable results were also achieved for secondary end-points such as hospitalization for decompensated heart failure (-35%) and all-cause mortality (-32%). Positive effects on the progression of diabetic nephropathy were also reported in the trial. In the CANVAS study, canagliflozin also demonstrated superiority in the reduction of the primary endpoint associated with less progression of renal failure, and a significant reduction of hospitalization for heart failure⁴⁶. The CANVAS reported an unexplained increase of the risk of amputations, which, nevertheless, have been found to be quite limited in number, and have not been observed in subsequent observational studies. The DECLARE-TIMI

58 study with dapagliflozin⁴⁷, included a significant number of patients without known atherosclerotic disease and, though it did not show a significantly lower MACE rate compared to placebo, it demonstrated the superiority of dapagliflozin over another primary composite outcome of cardiovascular death or hospitalization for heart failure. The latest CVOT conducted on a SGLT-2i (ertugliflozin) is the VERTIS CV, that basically confirmed a consistent class effect, even if superiority was not achieved⁴⁸.

In all SGLT-2i trials, cardioprotective effects were evident just a few months after treatment initiation compared to the placebo group. This effect is different from the one observed with GLP-1RAs, suggesting that mechanisms other than the atherosclerotic process are involved, and they concern cardiovascular hemodynamics and metabolism⁴⁹. Diuresis, natriuresis, ketone metabolism, and direct myocardial effects at the basis of SGLT-2i actions have recently increased the interest in the use of these drugs even in non-diabetic patients with heart failure. Based on the results obtained with the DAPA-HF study⁵⁰, FDA recently approved dapagliflozin for the treatment of heart failure with reduced ejection fraction.

Thanks to the robust results shown by CVOTs,

Table 3. Summary of large cardiovascular outcomes trials for sodium-glucose cotransporter-2 inhibitors

TRIAL NAME	N PATIENTS	TREATMENT	ENROLLEMENT CRITERIA	PRIMARY OUTCOME	PRIMARY OUTCOME RESULTS	MEDIAN FOLLOW-UP
EMPA-REG OUTCOME (45) 2015	7020	Empagliflozin 10 mg or 25 mg vs. placebo	HbA1c: 7.0-10.0%, pre-existing CVD (99% with history of CVD)	CV death, non-fatal MI, non-fatal stroke	10.5% in empagliflozin vs 12.1% in placebo group (HR 0.86, 95% CI 0.74-0.99, p<0.001 for non-inferiority, p=0.04 for superiority)	3.1 years
CANVAS (46) 2017	10142	Canagliflozin 100 mg or 300 mg vs. placebo	HbA1c: 7.0-10.5%, pre-existing CVD if ≥30 years old or > 2 CV risk factors if ≥ 50 years old	CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina	26.9 in canagliflozin vs 31.5 participants per 1000 patient-years in placebo group (HR 0.86; 95% CI 0.75-0.97, p<0.001 for non-inferiority, p=0.02 for superiority)	3.6 years
DECLARE-TIMI 58 (47) 2019	17160	Dapagliflozin 10 mg vs. placebo	HbA1c: 6.5-12.0%, pre-existing CVD or multiple risk factors for atherosclerotic CVD	i) CV death, non-fatal MI, non-fatal stroke ii) CV death or hospitalization for heart failure	i) 8.8% in dapagliflozin vs 9.4% in placebo group (HR, 0.93, 95% CI 0.84-1.03, p<0.001 for non-inferiority, p=0.17 for superiority) ii) 4.9% in dapagliflozin vs 5.8% in placebo group (HR 0.83, 95% CI 0.73-0.95, p=0.005 for superiority)	4.2 years
VERTIS CV (48) 2020	8246	Ertugliflozin 5 mg and 15 mg vs. placebo	HbA1c: 7.0-10.5%, established CVD involving the coronary, cerebrovascular, and/or peripheral arterial systems	CV death, non-fatal MI, non-fatal stroke	11.9% in ertugliflozin vs 11.9% in placebo group (HR 0.97, 95% CI 0.85-1.11, p<0.001 for non-inferiority, p=NS for superiority)	3.5 years

CI, confidence interval. CVD, cardiovascular disease. HR, hazard ratio. MI, myocardial infarction. NS, not significant. T2D, type 2 diabetes.

SGLT-2i have also recently been included in the therapeutic algorithm of T2D and have been placed in the second line after metformin for patients with high cardiovascular risk. Also, they are preferable to GLP-1RAs in the case of patients with heart failure or stage 1-2 chronic kidney disease^{25,26}. Table 3 summarizes the largest CVOTs for SGLT-2i.

THE ROLE OF SGLT-2I IN PTDM

The mechanism of SGLT-2 overexpression at the tubular level is not clear, but appears to be associated with hyperinsulinemia and insulin resistance, which are typically present in patients with PTDM⁴³. Moreover, in an experimental model of tacrolimus-induced diabetes, SGLT-2 overexpression and increased urinary glucose excretion were found⁵¹. The same study also suggested the protective role of SGLT-2i on tacrolimus-induced glomerular damage, probably also due to renin-angiotensin-aldosterone system suppression. Extra-glycemic, cardiac hemodynamic and metabolic effects respond to most of the vascular alterations present in the transplant recipients. Apart from the reduction of CV events and renal protection clearly demonstrated in the CVOTs, SGLT-2i have shown anti-inflammatory and anti-oxidative effects in animal models^{52,53}. Despite recent evidence suggests that the benefits deriving from the use of SGLT-2i do not arise from their direct effects on beta and alpha cells^{54,55}, the inflammatory, apoptotic and oxidative stress-induced effects of tacrolimus against beta cell and glomerulus appear to be strongly counteracted by SGLT-2i⁵¹. The met-

abolic effects of SGLT-2i consist mainly of an energy switch, using substrates such as ketone bodies, which are particularly efficient in the production of ATP in cardiomyocytes⁵⁶. Considering the high incidence of early diastolic dysfunction in transplant recipients, as recently observed by Pisano et al⁵⁷ on a cohort of liver transplant patients, the use of SGLT-2i seems to be the most appropriate therapeutic choice, given the demonstrated reduction in the progression of heart failure⁵⁸.

Among the potential adverse effects of the treatment with SGLT-2 inhibitors, genitourinary infections are the most common, while only rare cases of euglycemic diabetic ketoacidosis (Eu-DKA) have been reported⁵⁹. Because of the immunosuppressive therapy of transplant recipients, the risk of genitourinary infection is theoretically higher with the use of SGLT-2i. Eu-DKA is a very rare life-threatening emergency condition in T2D, but it would require longer-term studies recruiting considerably more patients to rule out the theoretically increased risk in PTDM characterized by loss of beta-cell function. Nevertheless, all studies in the literature confirm, though in limited number populations, the safe use of SGLT-2i in post-transplant diabetic patients.

Several independent studies have recently evaluated SGLT-2i for the treatment of PTDM in kidney transplant recipients. In small cohorts of kidney transplant recipients, some retrospective studies have shown that SGLT-2 inhibitors are safe and effective in improving glycemic control and weight reduction⁶⁰. More solid data are shown by

two other prospective studies. Strøm Halden et al⁶¹ tested the efficacy and safety of empagliflozin vs. placebo in a randomized double-blind trial with a total of 49 renal transplant recipients with stable PTDM. Of 24 patients receiving empagliflozin, two reduced their daily insulin dose, but no participant discontinued the remaining hypoglycemic therapy. After 24 weeks, patients receiving empagliflozin had better glycemic control and reduced body weight compared to placebo. In a single arm study by Schwaiger et al⁶², empagliflozin, in replacement of previous therapy, was started in 14 PTDM patients who had received a kidney transplant more than 6 months prior. Seven patients with inadequate glycometabolic control under single treatment with empagliflozin restarted insulin therapy after 4 weeks. After one year, all participants lost body weight, no patients developed EDKA, and in only one case genital infection was observed. In both these last two studies, empagliflozin was shown to improve glycemic control, but alone it was not powerful enough to replace insulin therapy, suggesting that it could be used as add-on to the ongoing therapy. Treatment was also well tolerated, with no apparent pharmacokinetic interaction with immunosuppressive therapy or signif-

icant increase of genitourinary infections. Other studies with small cohorts found similar results in kidney recipients with PTDM^{63,64}. Canagliflozin was shown to reduce HbA1c, blood pressure, and body weight with no hypoglycemic episodes or significant adverse events in renal transplant patients, as demonstrated in a pilot study of 24 patients (including only one woman) by Shah et al⁶⁵ and in a case series by Rajasekeran et al⁶⁶.

On the other hand, given the known cardiovascular effects, SGLT-2i could play a primary role not only in the management of post-cardiac transplantation metabolic alterations but, in general, in the prevention of cardiac allograft vasculopathy, with an extended indication to non-diabetic patients⁶⁷. Empagliflozin has been studied in some retrospective studies, and its safety has been confirmed as a long-term therapeutic option^{68,69}. Table 4 summarizes the reported studies on SGLT-2i in PTDM.

CONCLUSIONS

PTDM is a very common metabolic disorder in organ transplant recipients and increases the already high cardiovascular risk in this specific patient population. PTDM also adversely affects the development of renal damage often as a result of immuno-

Table 4. Summary of reported studies on sodium-glucose cotransporter-2 inhibitors use in post-transplant diabetes mellitus

STUDY	TYPE OF STUDY (N PATIENTS)	TREATMENT	ORGAN TRANSPLANTED	SAFETY	GLYCEMIC CONTROL	EFFECT ON WEIGHT	RENAL FUNCTION	OTHER OUTCOMES	FOLLOW-UP
Muir et al (69) 2017	Retrospective (n=19)	Empagliflozin	Heart	Dizziness in 1 patient reported, exacerbation of UTI symptoms in 1 patient; no ketonemia or acid-base disorders	No significant change in HbA1c	Body weight reduction (p<0.05)	No significant change in eGFR	Blood pressure reduction (p=0.03)	9 months (median)
Rajasekeran et al (66) 2017	Retrospective (n=10)	Canagliflozin	Kidney, Pancreas/Kidney	No UTI; no AKI; non-severe hypoglycemia in 1 patient; cellulitis in 1 patient	No significant change in HbA1c (p=0.07)	No significant change in body weight (p=0.07)	No significant change in eGFR	No significant change in blood pressure	80.5 person-months
Cehic et al (68) 2019	Retrospective (n=101)	Empagliflozin (22 patients) or alternative glucose-lowering therapy (79 patients)	Heart	Three adverse events in empagliflozin group (exacerbation of urinary symptoms, dizziness, AKI); no genitourinary infections	No significant change in HbA1c	Body weight reduction (p=0.003)	No significant change in eGFR	No significant change in blood pressure	12 months
Mahling et al (63) 2019	Prospective (n=10)	Empagliflozin	Kidney	UTI in 2 patients; AKI in 1 patient; no decline in renal function was observed; no urosepsis; no ketoacidosis	Trend of HbA1c reduction	Trend of body weight reduction	Stable kidney allograft function	Trend of blood pressure and uric acid reduction	12 months (median)
Schwaiger et al (62) 2019	Prospective (n=14)	Empagliflozin	Kidney	No ketoacidosis; balanitis in 1 patient	No significant change in HbA1c at week 4, reduction at 12 mo (p=0.03)	Body weight reduction (p=0.02) at week 4, no change at 12 mo	eGFR reduction (p=0.01) at week 4, no significant change at 12 mo	No significant change in blood pressure	12 months
Strøm Halden et al (61) 2019	Prospective (n=49)	Empagliflozin vs. placebo	Kidney	No significant differences between the groups in adverse events, immunosuppressive drug levels or eGFR	HbA1c reduction in empagliflozin vs placebo group (p=0.025)	Body weight reduction in empagliflozin vs placebo group (p=0.014)	No significant change in eGFR	No significant change in blood pressure	24 weeks
Alkindi et al (60) 2020	Retrospective (n=8)	Empagliflozin (6 patients) or dapagliflozin (2 patients)	Kidney	Symptomatic hypoglycemia in 1 patient; no documented diabetic ketoacidosis; cystitis in 2 patients, cellulitis in 1 patient, no genital fungal infection or recurrent UTIs	HbA1c reduction (p<0.05)	Body weight reduction (p<0.05)	No significant change in eGFR	No significant change in blood pressure	12 months

AKI, acute kidney injury. BMI, body mass index. eGFR, estimated glomerular filtration rate. HbA1c, hemoglobin A1C. Mo, months. UTI, urinary tract infection.

suppressive therapy and, generally, the survival of the transplanted organ. GLP-1RAs and SGLT-2i have been found to play an important role in T2D for their ability to improve glycometabolic control, with a very low hypoglycemic risk, and for their cardiovascular and renal protection effects. Their mechanism of action and glucose-independent effects seem to fully respond to the changes that PTDM entails. Nevertheless, to date evidence is limited and, though available studies agree on their safety, specific risks for immunosuppressed patients cannot be completely ruled out. Prospective randomized, possibly multicenter, studies including an adequate number of patients and long follow-up are therefore required. New evidence will allow the alignment of the PTDM therapeutic indications with the most up-to-date indications on the management of T2D, which are now moving toward the abandonment of glucocentricity, with a closer focus on micro- and macrovascular complications.

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