**Name of Journal:** *World Journal of Transplantation*

**Manuscript NO:** 62523

**Manuscript Type:** MINIREVIEWS

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

Schwarzenbach M *et al*. SGLT-2 inhibitors in transplantation

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

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

**Author contributions:** Czerlau C and Sidler D designed the study; Schwarzenbach M and Bernhard FE performed the literature search; Schwarzenbach M, Bernhard FE, Czerlau C and Sidler D wrote the paper.

**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

**Received:** January 11, 2021

**Revised:** May 17, 2021

**Accepted:** May 26, 2021

**Published online:**

**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

Schwarzenbach M, Bernhard FE, Czerlau C, Sidler D. Chances and risks of sodium-glucose cotransporter 2 inhibitors in solid organ transplantation: A review of literatures. *World J Transplant* 2021; In press

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

**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 (HbA1c) 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 HbA1c, 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 HbA1c 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-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 normoglycaemic 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 m2 or above, although the CANVAS study included patients with eGFR of 30-45 mL/min/1.73 m2 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 m2 or above[2,50]. They observed a small, yet significant improvement of HbA1c and increased weight loss in the intervention group. Interestingly, the magnitude of glucose reduction was dependent on eGFR and baseline HbA1c. 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 HbA1c 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.

**REFERENCES**

1 **Jenssen T**, Hartmann A. Post-transplant diabetes mellitus in patients with solid organ transplants. *Nat Rev Endocrinol* 2019; **15**: 172-188 [PMID: 30622369 DOI: 10.1038/s41574-018-0137-7]

2 **Ahmed SH**, Biddle K, Augustine T, Azmi S. Post-Transplantation Diabetes Mellitus. *Diabetes Ther* 2020; **11**: 779-801 [PMID: 32095994 DOI: 10.1007/s13300-020-00790-5]

3 **Kwong A**, Kim WR, Lake JR, Smith JM, Schladt DP, Skeans MA, Noreen SM, Foutz J, Miller E, Snyder JJ, Israni AK, Kasiske BL. OPTN/SRTR 2018 Annual Data Report: Liver. *Am J Transplant* 2020; **20 Suppl s1**: 193-299 [PMID: 31898413 DOI: 10.1111/ajt.15674]

4 **Hart A**, Smith JM, Skeans MA, Gustafson SK, Wilk AR, Castro S, Foutz J, Wainright JL, Snyder JJ, Kasiske BL, Israni AK. OPTN/SRTR 2018 Annual Data Report: Kidney. *Am J Transplant* 2020; **20 Suppl s1**: 20-130 [PMID: 31898417 DOI: 10.1111/ajt.15672]

5 **Colvin M**, Smith JM, Hadley N, Skeans MA, Uccellini K, Goff R, Foutz J, Israni AK, Snyder JJ, Kasiske BL. OPTN/SRTR 2018 Annual Data Report: Heart. *Am J Transplant* 2020; **20 Suppl s1**: 340-426 [PMID: 31898418 DOI: 10.1111/ajt.15676]

6 **Guenette A**, Husain S. Infectious Complications Following Solid Organ Transplantation. *Crit Care Clin* 2019; **35**: 151-168 [PMID: 30447777 DOI: 10.1016/j.ccc.2018.08.004]

7 **Sen A**, Callisen H, Libricz S, Patel B. Complications of Solid Organ Transplantation: Cardiovascular, Neurologic, Renal, and Gastrointestinal. *Crit Care Clin* 2019; **35**: 169-186 [PMID: 30447778 DOI: 10.1016/j.ccc.2018.08.011]

8 **American Diabetes Association**. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2021. *Diabetes Care* 2021; **44 (Suppl 1)**: S15-S33 [PMID: 33298413 DOI: 10.2337/dc21-S002]

9 **Sharif A**, Hecking M, de Vries AP, Porrini E, Hornum M, Rasoul-Rockenschaub S, Berlakovich G, Krebs M, Kautzky-Willer A, Schernthaner G, Marchetti P, Pacini G, Ojo A, Takahara S, Larsen JL, Budde K, Eller K, Pascual J, Jardine A, Bakker SJ, Valderhaug TG, Jenssen TG, Cohney S, Säemann MD. Proceedings from an international consensus meeting on posttransplantation diabetes mellitus: recommendations and future directions. *Am J Transplant* 2014; **14**: 1992-2000 [PMID: 25307034 DOI: 10.1111/ajt.12850]

10 **Cehic MG**, Nundall N, Greenfield JR, Macdonald PS. Management Strategies for Posttransplant Diabetes Mellitus after Heart Transplantation: A Review. *J Transplant* 2018; **2018**: 1025893 [PMID: 29623219 DOI: 10.1155/2018/1025893]

11 **Conte C**, Secchi A. Post-transplantation diabetes in kidney transplant recipients: an update on management and prevention. *Acta Diabetol* 2018; **55**: 763-779 [PMID: 29619563 DOI: 10.1007/s00592-018-1137-8]

12 **Hecking M**, Haidinger M, Döller D, Werzowa J, Tura A, Zhang J, Tekoglu H, Pleiner J, Wrba T, Rasoul-Rockenschaub S, Mühlbacher F, Schmaldienst S, Druml W, Hörl WH, Krebs M, Wolzt M, Pacini G, Port FK, Säemann MD. Early basal insulin therapy decreases new-onset diabetes after renal transplantation. *J Am Soc Nephrol* 2012; **23**: 739-749 [PMID: 22343119 DOI: 10.1681/ASN.2011080835]

13 **Lo C**, Jun M, Badve SV, Pilmore H, White SL, Hawley C, Cass A, Perkovic V, Zoungas S. Glucose-lowering agents for treating pre-existing and new-onset diabetes in kidney transplant recipients. *Cochrane Database Syst Rev* 2017; **2**: CD009966 [PMID: 28238223 DOI: 10.1002/14651858.CD009966.pub2]

14 **Hecking M**, Sharif A, Eller K, Jenssen T. Management of post-transplant diabetes: immunosuppression, early prevention, and novel antidiabetics. *Transpl Int* 2021; **34**: 27-48 [PMID: 33135259 DOI: 10.1111/tri.13783]

15 **Ponticelli C**, Favi E, Ferraresso M. New-Onset Diabetes after Kidney Transplantation. *Medicina (Kaunas)* 2021; **57**: 250 [PMID: 33800138 DOI: 10.3390/medicina57030250]

16 **Young BY**, Gill J, Huang E, Takemoto SK, Anastasi B, Shah T, Bunnapradist S. Living donor kidney versus simultaneous pancreas-kidney transplant in type I diabetics: an analysis of the OPTN/UNOS database. *Clin J Am Soc Nephrol* 2009; **4**: 845-852 [PMID: 19201918 DOI: 10.2215/CJN.02250508]

17 **Orsenigo E**, Socci C, Fiorina P, Zuber V, Secchi A, Di Carlo V, Staudacher C. Cardiovascular benefits of simultaneous pancreas-kidney transplant versus kidney alone transplant in diabetic patients. *Transplant Proc* 2005; **37**: 3570-3571 [PMID: 16298664 DOI: 10.1016/j.transproceed.2005.09.059]

18 **Biesenbach G**, Königsrainer A, Gross C, Margreiter R. Progression of macrovascular diseases is reduced in type 1 diabetic patients after more than 5 years successful combined pancreas-kidney transplantation in comparison to kidney transplantation alone. *Transpl Int* 2005; **18**: 1054-1060 [PMID: 16101726 DOI: 10.1111/j.1432-2277.2005.00182.x]

19 **Fiorina P**, Gremizzi C, Maffi P, Caldara R, Tavano D, Monti L, Socci C, Folli F, Fazio F, Astorri E, Del Maschio A, Secchi A. Islet transplantation is associated with an improvement of cardiovascular function in type 1 diabetic kidney transplant patients. *Diabetes Care* 2005; **28**: 1358-1365 [PMID: 15920052 DOI: 10.2337/diacare.28.6.1358]

20 **Jukema JW**, Smets YF, van der Pijl JW, Zwinderman AH, Vliegen HW, Ringers J, Reiber JH, Lemkes HH, van der Wall EE, de Fijter JW. Impact of simultaneous pancreas and kidney transplantation on progression of coronary atherosclerosis in patients with end-stage renal failure due to type 1 diabetes. *Diabetes Care* 2002; **25**: 906-911 [PMID: 11978689 DOI: 10.2337/diacare.25.5.906]

21 **Bajaj HS**, Raz I, Mosenzon O, Murphy SA, Rozenberg A, Yanuv I, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Gause-Nilsson IAM, Sabatine MS, Wiviott SD, Cahn A. Cardiovascular and renal benefits of dapagliflozin in patients with short and long-standing type 2 diabetes: Analysis from the DECLARE-TIMI 58 trial. *Diabetes Obes Metab* 2020; **22**: 1122-1131 [PMID: 32090404 DOI: 10.1111/dom.14011]

22 **Maranta F**, Cianfanelli L, Cianflone D. Glycaemic Control and Vascular Complications in Diabetes Mellitus Type 2. *Adv Exp Med Biol* 2021; **1307**: 129-152 [PMID: 32266607 DOI: 10.1007/5584\_2020\_514]

23 **Zoungas S**, Woodward M, Li Q, Cooper ME, Hamet P, Harrap S, Heller S, Marre M, Patel A, Poulter N, Williams B, Chalmers J; ADVANCE Collaborative group. Impact of age, age at diagnosis and duration of diabetes on the risk of macrovascular and microvascular complications and death in type 2 diabetes. *Diabetologia* 2014; **57**: 2465-2474 [PMID: 25226881 DOI: 10.1007/s00125-014-3369-7]

24 **Beckman JA**, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA* 2002; **287**: 2570-2581 [PMID: 12020339 DOI: 10.1001/jama.287.19.2570]

25 **Emerging Risk Factors Collaboration**, Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, Ingelsson E, Lawlor DA, Selvin E, Stampfer M, Stehouwer CD, Lewington S, Pennells L, Thompson A, Sattar N, White IR, Ray KK, Danesh J. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010; **375**: 2215-2222 [PMID: 20609967 DOI: 10.1016/S0140-6736(10)60484-9]

26 **Low Wang CC**, Hess CN, Hiatt WR, Goldfine AB. Clinical Update: Cardiovascular Disease in Diabetes Mellitus: Atherosclerotic Cardiovascular Disease and Heart Failure in Type 2 Diabetes Mellitus - Mechanisms, Management, and Clinical Considerations. *Circulation* 2016; **133**: 2459-2502 [PMID: 27297342 DOI: 10.1161/CIRCULATIONAHA.116.022194]

27 **Howard BV**, Best LG, Galloway JM, Howard WJ, Jones K, Lee ET, Ratner RE, Resnick HE, Devereux RB. Coronary heart disease risk equivalence in diabetes depends on concomitant risk factors. *Diabetes Care* 2006; **29**: 391-397 [PMID: 16443893 DOI: 10.2337/diacare.29.02.06.dc05-1299]

28 **Fong DS**, Aiello LP, Ferris FL 3rd, Klein R. Diabetic retinopathy. *Diabetes Care* 2004; **27**: 2540-2553 [PMID: 15451934 DOI: 10.2337/diacare.27.10.2540]

29 **Boulton AJ**, Vinik AI, Arezzo JC, Bril V, Feldman EL, Freeman R, Malik RA, Maser RE, Sosenko JM, Ziegler D; American Diabetes Association. Diabetic neuropathies: a statement by the American Diabetes Association. *Diabetes Care* 2005; **28**: 956-962 [PMID: 15793206 DOI: 10.2337/diacare.28.4.956]

30 **Tsai HI**, Liu FC, Lee CW, Kuo CF, See LC, Chung TT, Yu HP. Cardiovascular disease risk in patients receiving organ transplantation: a national cohort study. *Transpl Int* 2017; **30**: 1161-1171 [PMID: 28691253 DOI: 10.1111/tri.13010]

31 **Gillis KA**, Patel RK, Jardine AG. Cardiovascular complications after transplantation: treatment options in solid organ recipients. *Transplant Rev (Orlando)* 2014; **28**: 47-55 [PMID: 24412041 DOI: 10.1016/j.trre.2013.12.001]

32 **Szymczak M**, Kluz J, Małecki R, Wątorek E, Obremska M, Głuszek M, Klinger M, Boratyńska M. Effect of Immunosuppressive Treatment on Carotid Atherosclerosis in Renal Transplant Recipients. *Transplant Proc* 2016; **48**: 1626-1629 [PMID: 27496459 DOI: 10.1016/j.transproceed.2016.03.005]

33 **Zeier M**, Van Der Giet M. Calcineurin inhibitor sparing regimens using m-target of rapamycin inhibitors: an opportunity to improve cardiovascular risk following kidney transplantation? *Transpl Int* 2011; **24**: 30-42 [PMID: 20642495 DOI: 10.1111/j.1432-2277.2010.01140.x]

34 **Launay-Vacher V**, Izzedine H, Deray G. Statins' dosage in patients with renal failure and cyclosporine drug-drug interactions in transplant recipient patients. *Int J Cardiol* 2005; **101**: 9-17 [PMID: 15860377 DOI: 10.1016/j.ijcard.2004.04.005]

35 **Boerner BP**, Shivaswamy V, Desouza CV, Larsen JL. Diabetes and cardiovascular disease following kidney transplantation. *Curr Diabetes Rev* 2011; **7**: 221-234 [PMID: 21644915 DOI: 10.2174/157339911796397857]

36 **Munagala MR**, Phancao A. Managing Cardiovascular Risk in the Post Solid Organ Transplant Recipient. *Med Clin North Am* 2016; **100**: 519-533 [PMID: 27095643 DOI: 10.1016/j.mcna.2016.01.004]

37 **Schnuelle P**, Lorenz D, Trede M, Van Der Woude FJ. Impact of renal cadaveric transplantation on survival in end-stage renal failure: evidence for reduced mortality risk compared with hemodialysis during long-term follow-up. *J Am Soc Nephrol* 1998; **9**: 2135-2141 [PMID: 9808102 DOI: 10.1681/ASN.V9112135]

38 **Jardine MJ**, Mahaffey KW, Neal B, Agarwal R, Bakris GL, Brenner BM, Bull S, Cannon CP, Charytan DM, de Zeeuw D, Edwards R, Greene T, Heerspink HJL, Levin A, Pollock C, Wheeler DC, Xie J, Zhang H, Zinman B, Desai M, Perkovic V; CREDENCE study investigators. The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) Study Rationale, Design, and Baseline Characteristics. *Am J Nephrol* 2017; **46**: 462-472 [PMID: 29253846 DOI: 10.1159/000484633]

39 **Vasilakou D**, Karagiannis T, Athanasiadou E, Mainou M, Liakos A, Bekiari E, Sarigianni M, Matthews DR, Tsapas A. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med* 2013; **159**: 262-274 [PMID: 24026259 DOI: 10.7326/0003-4819-159-4-201308200-00007]

40 **Inzucchi SE**, Zinman B, Wanner C, Ferrari R, Fitchett D, Hantel S, Espadero RM, Woerle HJ, Broedl UC, Johansen OE. SGLT-2 inhibitors and cardiovascular risk: proposed pathways and review of ongoing outcome trials. *Diab Vasc Dis Res* 2015; **12**: 90-100 [PMID: 25589482 DOI: 10.1177/147916411455985]

41 **Vaduganathan M**, Januzzi JL Jr. Preventing and Treating Heart Failure with Sodium-Glucose Co-Transporter 2 Inhibitors. *Am J Cardiol* 2019; **124 Suppl 1**: S20-S27 [PMID: 31741436 DOI: 10.1016/j.amjcard.2019.10.026]

42 **Toyama T**, Neuen BL, Jun M, Ohkuma T, Neal B, Jardine MJ, Heerspink HL, Wong MG, Ninomiya T, Wada T, Perkovic V. Effect of SGLT2 inhibitors on cardiovascular, renal and safety outcomes in patients with type 2 diabetes mellitus and chronic kidney disease: A systematic review and meta-analysis. *Diabetes Obes Metab* 2019; **21**: 1237-1250 [PMID: 30697905 DOI: 10.1111/dom.13648]

43 **Jenssen T**, Hartmann A. Emerging treatments for post-transplantation diabetes mellitus. *Nat Rev Nephrol* 2015; **11**: 465-477 [PMID: 25917553 DOI: 10.1038/nrneph.2015.59]

44 **Wanner C**. EMPA-REG OUTCOME: The Nephrologist's Point of View. *Am J Cardiol* 2017; **120**: S59-S67 [PMID: 28606346 DOI: 10.1016/j.amjcard.2017.05.012]

45 **Neal B**, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR; CANVAS Program Collaborative Group. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med* 2017; **377**: 644-657 [PMID: 28605608 DOI: 10.1056/NEJMoa1611925]

46 **Wu JH**, Foote C, Blomster J, Toyama T, Perkovic V, Sundström J, Neal B. Effects of sodium-glucose cotransporter-2 inhibitors on cardiovascular events, death, and major safety outcomes in adults with type 2 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 2016; **4**: 411-419 [PMID: 27009625 DOI: 10.1016/S2213-8587(16)00052-8]

47 **Jin J**, Jin L, Luo K, Lim SW, Chung BH, Yang CW. Effect of Empagliflozin on Tacrolimus-Induced Pancreas Islet Dysfunction and Renal Injury. *Am J Transplant* 2017; **17**: 2601-2616 [PMID: 28422431 DOI: 10.1111/ajt.14316]

48 **Halimi S**, Vergès B. Adverse effects and safety of SGLT-2 inhibitors. *Diabetes Metab* 2014; **40**: S28-S34 [PMID: 25554069 DOI: 10.1016/S1262-3636(14)72693-X]

49 **Rosenstock J**, Ferrannini E. Euglycemic Diabetic Ketoacidosis: A Predictable, Detectable, and Preventable Safety Concern With SGLT2 Inhibitors. *Diabetes Care* 2015; **38**: 1638-1642 [PMID: 26294774 DOI: 10.2337/dc15-1380]

50 **Halden TAS**, Kvitne KE, Midtvedt K, Rajakumar L, Robertsen I, Brox J, Bollerslev J, Hartmann A, Åsberg A, Jenssen T. Efficacy and Safety of Empagliflozin in Renal Transplant Recipients With Posttransplant Diabetes Mellitus. *Diabetes Care* 2019; **42**: 1067-1074 [PMID: 30862658 DOI: 10.2337/dc19-009]

51 **Schwaiger E**, Burghart L, Signorini L, Ristl R, Kopecky C, Tura A, Pacini G, Wrba T, Antlanger M, Schmaldienst S, Werzowa J, Säemann MD, Hecking M. Empagliflozin in posttransplantation diabetes mellitus: A prospective, interventional pilot study on glucose metabolism, fluid volume, and patient safety. *Am J Transplant* 2019; **19**: 907-919 [PMID: 30585690 DOI: 10.1111/ajt.15223]

52 **Cehic MG**, Muir CA, Greenfield JR, Hayward C, Jabbour A, Keogh A, Kotlyar E, Muthiah K, Macdonald PS. Efficacy and Safety of Empagliflozin in the Management of Diabetes Mellitus in Heart Transplant Recipients. *Transplant Direct* 2019; **5**: e450 [PMID: 31165085 DOI: 10.1097/TXD.0000000000000885]

53 **AlKindi F**, Al-Omary HL, Hussain Q, Al Hakim M, Chaaban A, Boobes Y. Outcomes of SGLT2 Inhibitors Use in Diabetic Renal Transplant Patients. *Transplant Proc* 2020; **52**: 175-178 [PMID: 31924404 DOI: 10.1016/j.transproceed.2019.11.007]

54 **Rajasekeran H**, Kim SJ, Cardella CJ, Schiff J, Cattral M, Cherney DZI, Singh SKS. Use of Canagliflozin in Kidney Transplant Recipients for the Treatment of Type 2 Diabetes: A Case Series. *Diabetes Care* 2017; **40**: e75-e76 [PMID: 28416475 DOI: 10.2337/dc17-0237]

55 **Peláez-Jaramillo MJ**, Cárdenas-Mojica AA, Gaete PV, Mendivil CO. Post-Liver Transplantation Diabetes Mellitus: A Review of Relevance and Approach to Treatment. *Diabetes Ther* 2018; **9**: 521-543 [PMID: 29411291 DOI: 10.1007/s13300-018-0374-8]

56 **Cigrovski Berkovic M**, Virovic-Jukic L, Bilic-Curcic I, Mrzljak A. Post-transplant diabetes mellitus and preexisting liver disease - a bidirectional relationship affecting treatment and management. *World J Gastroenterol* 2020; **26**: 2740-2757 [PMID: 32550751 DOI: 10.3748/wjg.v26.i21.2740]

57 **Attallah N**, Yassine L. Use of Empagliflozin in Recipients of Kidney Transplant: A Report of 8 Cases. *Transplant Proc* 2019; **51**: 3275-3280 [PMID: 31732204 DOI: 10.1016/j.transproceed.2019.05.023]

58 **Beshyah SA,** Beshyah AS, Beshyah WS, Yaghi S. Use of SGLT2 Inhibitors in Diabetic Renal Transplant Recipients: A Mixed Method Exploratory Exercise. *Int J Diabetes Metab* 2018; **21**: 16-21 [DOI: 10.1159/000492758]

**Footnotes**

**Conflict-of-interest statement:** The authors declare no conflict of interest.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Unsolicited manuscript

**Peer-review started:** January 11, 2021

**First decision:** May 5, 2021

**Article in press:**

**Specialty type:** Transplantation

**Country/Territory of origin:** Switzerland

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Shalaby S **S-Editor:** Zhang H **L-Editor:** Filipodia **P-Editor:**

**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 |
| HbA1c | ≥ 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; HbA1c: Haemoglobin A1c; OGTT: Oral glucose tolerance test.

**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; HbA1c was reduced in the empagliflozin group, during patients in the control group experienced a mean increase in HbA1c; although the reduction in HbA1c 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 HbA1c, 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, surveys of physicians’ opinions, and a review of the literature | KTRs | Case report: Off-label use of dapagliflozin in a patient with diabetes mellitus and renal transplantation | The index case suggests the safe use of SGLT2 inhibitors by renal transplant recipients. It seemed that physicians are willing to use SGLT2 inhibitors in such patients if the renal function is satisfactory.  |

BMI: Body mass index; HbA1c: 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.