REVIEW

Management of post-transplant diabetes: immunosuppression, early prevention, and novel antidiabetics

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SUMMARY

Post-transplant diabetes mellitus (PTDM) shows a relationship with risk factors including obesity and tacrolimus-based immunosuppression, which decreases pancreatic insulin secretion. Several of the sodium–glucose-linked transporter 2 inhibitors (SGLT2is) and glucagon-like peptide 1 receptor agonists (GLP1-RAs) dramatically improve outcomes of individuals with type 2 diabetes with and without chronic kidney disease, which is, as heart failure and atherosclerotic cardiovascular disease, differentially affected by both drug *classes* (presumably). Here, we discuss SGLT2is and GLP1-RAs in context with other PTDM management strategies, including modification of immunosuppression, active lifestyle intervention, and early postoperative insulin administration. We also review recent studies with SGLT2is in PTDM, reporting their safety and antihyperglycemic efficacy, which is moderate to low, depending on kidney function. Finally, we reference retrospective case reports with GLP1-RAs that have not brought forth major concerns, likely indicating that GLP1-RAs are ideal for PTDM patients suffering from obesity. Although our article encompasses PTDM after solid organ transplantation in general, data from kidney transplant recipients constitute the largest proportion. The PTDM research community still requires data that treating and preventing PTDM will improve clinical conditions beyond hyperglycemia. We therefore suggest that it is time to collaborate, in testing novel antidiabetics among patients of all transplant disciplines.

Introduction

PTDM incidence; major controversies embedded in previous consensus recommendations; outcomes associated with PTDM, as they relate to diagnosis

Post-transplant diabetes mellitus (PTDM) [1,2] is a common and important complication after solid organ transplantation. Although the majority of PTDM data are derived from kidney transplant recipients, PTDM incidence has been reported as being higher in other solid organs. Compared to kidney transplant recipients, whose PTDM incidence ranges between 10% and 20% [3-5], PTDM occurs in 20% to 30% of heart transplant recipients [6], 20% to 40% of liver transplant recipients [7-11], and 20% to 40% of lung transplant recipients [12,13] (as reviewed in [14] and shown in Fig. 2). It may seem that PTDM is more common among liver rather than kidney transplant recipients, as one center, which reported virtually the same immunosuppressant use in both types of solid transplant recipients, found that the incidence of PTDM was much higher in individuals receiving a liver rather than those receiving a kidney transplant (30% vs. 19%, respectively [9]). Risk factors for development of PTDM in liver transplant recipients are most often reported to be age [8], higher BMI [8,10,11], and especially hepatitis C virus (HCV) infection [7,8,10,11] as well as use of tacrolimus [7,8,15,16]. In one study, the incidence of PTDM was 42% in HCV-positive patients compared to 19% in HCV-negative patients, and the risk was particularly enhanced in patients using tacrolimus instead of cyclosporine [11].

The pathophysiology of PTDM is of intrinsic interest. Rather than being simply another form of type 2 diabetes, PTDM is a pathophysiological entity in its own right [17-20]. The American Diabetes Association (ADA) previously classified PTDM in the category of "other specific types" of diabetes [21], but has recently described it as "diabetes after organ transplantation" [22]. At an expert meeting hosted in Vienna in 2013 [23], the objectives were to update previous consensus statements [17,24], and secondly to debate deficiencies in the PTDM clinical evidence base. Discussions that ensued led to 7 recommendations (box):

1. Change terminology from New-Onset Diabetes After Transplantation (NODAT) back to post-transplantation diabetes mellitus (PTDM).

2. Exclude transient post-transplantation hyperglycemia from PTDM diagnosis.
3. Expand screening tests for PTDM to incorporate postprandial (and evening) glucose monitoring and HbA1c to raise suspicion, while oral glucose tolerance tests remain the gold standard.
4. Identify patients at risk for PTDM.
5. Choose immunosuppression regimens so as to achieve the best outcome for patient and graft survival, irrespective of PTDM risk.
6. Adopt strategies for prevention and treatment beyond modification of immunosuppressive regimens.
7. Expand basic, translational, and clinical research in PTDM to address the areas of remaining controversy and speculation.

The previous recommendations 1, 2, and 7, in our understanding, have been well received and are widely accepted. The term PTDM, rather than *"New-Onset"* Diabetes After Transplantation (NODAT), is an acknowledgment of the heterogeneity of dysglycemia within the group, with some patients having undiagnosed diabetes pretransplant and others destined to develop diabetes regardless of any effects associated with transplantation. Although not specifically mentioned in the paper [23], pretransplant identification of glucose disorders in patients on the transplant waitlist was also encouraged. Such screening efforts would ideally include an oral glucose tolerance test (OGTT) [25], but even an HbA1c measurement at time of transplantation, despite the well-known pitfalls of the HbA1c arising, for example, from (changes in) erythropoiesis-stimulating agents and the uremic state of patients with kidney disease [26], might be helpful for differentiating between PTDM and true NODAT, and also to clinically judge the course of hyperglycemia post-transplantation.

However, there is still significant insecurity with respect to all other recommendations. Recommendations 3 and 4 deal with *post-transplant* screening, diagnosis, and PTDM risk, and respective to these issues, it again has to be emphasized that PTDM and type 2 diabetes are not "one and the same." Glycemic thresholds for diagnosis of type 2 diabetes have been thoroughly validated for the general population, based on microvascular complications (retinopathy) [27]. Only one study, from a single center, however, has specifically addressed retinopathy in transplanted individuals [28]. Therefore, it is currently unclear whether glycemic thresholds from

the general population can be used in transplanted patients, due to their different pathophysiology for developing hyperglycemia. In the general population, diabetic complications may take years to manifest (for diabetic retinopathy, please refer to reference [29]), suggesting that studies in transplanted populations may require similarly long periods of time to be able to present diabetic secondary manifestations. Consistent with this assumption, an earlier registry study found only 8.3% ophthalmic complications among 4,105 patients with "new-onset" diabetes over their 3-year follow-up (out of a total population of 21,489 primary kidney transplant recipients identified through the USRDS, 1995-2001 [30]).

Based on the available evidence, the major concern with PTDM is not the risk of developing microvascular disease such as retinopathy (although data are scarce), but rather the increased risk of cardiovascular disease and death. For example, a study from the Oslo transplant center showed for the 10-week post-transplant time point that repeatedly elevated fasting plasma glucose $\geq$ 126 mg/dL and OGTT-derived hyperglycemia at thresholds $\geq$ 200 mg/dL (diabetes) as well as $\geq$ 140 mg/dL (impaired glucose tolerance) were all associated with mortality in kidney transplant recipients, while HbA1c levels $\geq$ 6.5% were not associated with mortality [4]. In an earlier analysis, the same group has also shown a very similar mortality association for PTDM ("manifest" and diagnosed by OGTT-derived 2-hour plasma glucose) and impaired glucose tolerance [3]. The fact that the risk associated with hyperglycemia extends from PTDM to prediabetes was reaffirmed in a study from Spain where impaired glucose tolerance plus impaired fasting glucose, as well as PTDM itself, diagnosed at 12-months post-transplant, were associated with cardiovascular events in kidney transplanted patients [31]. How and when to screen for hyperglycemia during the unstable post-transplant phase [32,33], and the best way to identify patients at risk (previous recommendations 3 and 4) are therefore not trivial issues. However, the fact that there truly is an increased risk of mortality in kidney transplant recipients [34], especially if they have treated PTDM [35,36], and that this mortality risk is most likely due to cardiovascular causes [3-5,31,37,38], is by now well established.

Among solid organ transplant recipients other than kidney, analyzed together, PTDM based on HbA1c at 3 months post-transplantation was recently reported to be prognostically relevant [39]. One study which involved nearly 1.000 liver transplant recipients found that PTDM persisting over 5-10 years was associated with increased number of cardiovascular events [40], whereas 12-yr survival was not affected in another study [15]. In a very detailed review from the year 2016 which also addressed this particular question, Shivaswamy et al. arrived at the conclusion that PTDM may only reduce short-term survival after liver transplant, while the impact of PTDM on survival after lung transplant is unclear and PTDM after heart transplantation does not affect survival [1].

Understanding and further addressing the relationship between PTDM and outcomes will be important, as PTDM stands out as a potentially modifiable complication [41-43], but to date, there are no studies showing that treatment of PTDM actually positively modifies outcomes, other than glycemia [38]. One of the central debates in PTDM research related to this issue is the relative importance of the metabolic syndrome [20], and the question has been asked whether patients with morbid obesity should be transplanted at all, or whether the metabolic syndrome should come into control before transplant. Metabolic syndrome is prevalent among dialysis patients and, in the complex post-transplant interplay between weight gain, exacerbation of underlying metabolic syndrome and increased diabetogenicity from immunosuppression can lead to increased risk for PTDM [44]. Pretransplantation weight is a risk factor for PTDM [45] and weight loss before kidney transplantation can successfully reduce the odds of developing PTDM [46]. This raises the question whether modifiable pretransplantation risk factors such as obesity should be targeted to reduce post-transplant complications like PTDM. While no study has explored pharmacological interventions to target obesity pretransplantation, the strategy of surgical interventions has some limited evidence base. For example, in one published report bariatric surgery was shown to improve access to kidney transplantation while achieving measurable improvements in pretransplantation cardio-metabolic profiles including weight loss and reduction in diabetes rates (albeit defined inadequately by need for glucose-lowering therapy) [47]. In another small preliminary report, bariatric surgery was shown to improve pretransplant diabetes rates and PTDM was not observed in the 9/25 kidney transplant patients without pretransplant diabetes [48]. However, more definitive data are required concerning attenuation of post-transplant cardio-metabolic risks and long-term safety profiles before surgical intervention can be advocated for eligible obese candidates.

The present review will not answer the specific question of obesity, but addresses the issue of tackling obesity and PTDM by lifestyle modification and using novel antidiabetic drugs. Our work to a large extent represents the experience and reading of all co-authors, which encompasses the limitation that a predefined literature search was not formally performed. The text was inspired by the realization that *management of PTDM*, as would be embedded in the previous consensus recommendations 5 and 6, is still among the most controversial issues, as of today, and that the reason is lack of evidence. Thus, we believe that there is a pressing need to discuss here and subsequently collaborate on PTDM management.

Management of PTDM: immunosuppression

Immunosuppression remains the major modifiable risk factor for development of PTDM [49]. The transplant community by now has a common understanding of the diabetogenicity of commonly used immunosuppressants, and again most studies have been conducted after kidney transplantation rather than other solid organs. Calcineurin inhibitors are the mainstay of immunosuppression and decrease insulin release from pancreatic beta cells [50-54]. A randomized controlled study ("DIRECT") [55] confirmed an earlier meta-analysis on the increased diabetogenicity of tacrolimus compared to cyclosporine post kidney transplantation [56]. However, this study had limitations including short follow-up (6 months) and tacrolimus trough levels above those now targeted by many transplant centers. Indeed, strategies to minimize or avoid calcineurin inhibitor exposure have been shown to reduce the odds of developing PTDM in a meta-analysis of 56 randomized controlled trials (with concomitant superior overall graft survival) [57]. Torres et al. randomized de novo kidney transplant recipients without previous diabetes history but high PTDM risk into a tacrolimus versus a cyclosporine group (with and without early corticosteroid withdrawal in the tacrolimus group). Participants in the cyclosporine group had a lower 1-year PTDM incidence that failed to reach statistical significance, but also an increased probability of acute rejection [58].

Conversion of tacrolimus to cyclosporine for improvement of the glucose metabolism in stable kidney transplant recipients has been suggested, both from previous literature [59] and one randomized controlled trial [60], where replacement of tacrolimus by cyclosporine in patients with PTDM resulted in diabetes reversal. In this trial [60], concomitant changes in

insulin secretion and/or sensitivity were unfortunately not reported, but a study from Vienna suggested that the *balance* between these two entities might be deranged in kidney transplant recipients, compared with general population subjects as controls [61]. Recently, Müller et al. analyzed belatacept-treated kidney transplant recipients as yet another control group, in comparison to tacrolimus-treated kidney transplant recipients [62]. The tacrolimus-treated kidney transplant recipients had lower insulin release in the presence of higher insulin sensitivity, when compared to belatacept-treated kidney transplant recipients. The study also confirmed a lower PTDM rate with belatacept, compared to tacrolimus [62], which has recently been observed in another retrospective study [63]. The tacrolimus-belatacept comparison represents new information, as the available literature had previously only suggested superiority of belatacept, in terms of a reduced PTDM incidence [64,65], when this immunosuppressive agent was compared to cyclosporine. Additional insight is provided by a study showing that patients receiving tacrolimus, but not those receiving cyclosporine after kidney transplantation had a higher risk of developing PTDM, if they also had high triglycerides levels (i.e., metabolic syndrome) pretransplant [66]. Furthermore, from a mechanistic point of view, tacrolimus seems to interact with free fatty acids to impair beta cell function [67]. The recent re-classification of individuals from the general population with type 1 diabetes, type 2 diabetes, and late autoimmune diabetes in adults into 5 novel categories (clusters), by their degree of insulin deficiency, respective to insulin resistance [68] may help the PTDM community in solving the conflict whether it is impaired insulin secretion [61,62,69] or higher insulin resistance that dominates the pathophysiology of PTDM patients [70]. As in the general population, there may be individual differences in PTDM patients, which are further modified by the type of immunosuppression that these individuals are receiving after solid organ transplantation.

Present knowledge indicates that mammalian target of rapamycin (mTOR) inhibitors can no longer be considered inert for development of PTDM. For example, registry data demonstrated an increased risk of PTDM in association with use of sirolimus [71], though patients in this study may have been exposed to levels higher than currently used in some centers. In the Symphony study where target levels of sirolimus were 3 to 7 ng/mL, sirolimus-treated patients developed PTDM at a rate in-between cyclosporine and tacrolimus [72]. While at least one report has reported no increase in

PTDM in patients converted to an mTOR inhibitor [73], and a retrospective study suggested potential benefit for patients with established PTDM converting to an mTOR inhibitor [74], there are insufficient data to recommend this practice, especially in view of increased noncancer mortality risk associated with sirolimus [75,76]. Mechanistically, Teutonico et al. have shown that both a decrease in beta cell function and a decrease in insulin sensitivity occurs when patients are switched from either cyclosporine A or tacrolimus to sirolimus, suggesting that mTOR inhibitors actually do not ameliorate the glycometabolic profile of kidney transplant recipients [77].

In contrast to calcineurin inhibitors and mTOR inhibitors, no link has been established between use of antiproliferative agents such as mycophenolate mofetil or azathioprine and the risk of PTDM. However, controversy remains within the transplant community with regards to corticosteroid avoidance (defined as complete avoidance or withdrawal within the first days kidney transplantation [78]) or corticosteroid withdrawal (defined as discontinuation at a certain time point in the later post-transplant phase [78]), as potential strategies to attenuate the risk of PTDM. Despite the known contribution of corticosteroids to hyperglycemia and diabetes in general [79], a clear long-term benefit from corticosteroid-sparing strategies has not been demonstrated [80]. A meta-analysis of corticosteroid withdrawal between 3 and 6 months after transplantation found no meaningful effect on PTDM incidence [81]. Early corticosteroid withdrawal within the first-week post-transplant has shown decreased PTDM incidence, but only in the context of cyclosporine use [82]. The caveat to this approach is the higher risk of acute rejection, which may counteract the beneficial glycemic effects [81]. Withdrawal of corticosteroids to prevent PTDM is not supported in the study by Woodle et al. [80]. Furthermore, when insulin sensitivity was assessed by a state-of-the-art euglycemic, hyperglycemic clamp technique in kidney transplant recipients, insulin action did not improve when prednisolone was withdrawn from a 5 mg daily dose [83]. In the most recent Cochrane review on the use of prednisolone in kidney transplanted patients, published in 2016, no significant difference in PTDM risk was found comparing corticosteroid withdrawal versus maintenance (relative risk = 0.77, 95% confidence interval 0.49 to 1.21), and there was also no evidence to suggest a difference in patient mortality or graft loss up to five years after transplantation [78], while the risk of acute rejection was significantly increased [78]. However, in the more

recently published HARMONY trial (which was not included in the Cochrane review [78]), rapid corticosteroid withdrawal, again, was associated with reduced PTDM incidence, which in this study was defined as a secondary endpoint [84]. As a side note, with high doses of prednisolone (20 mg per day), split dosing can reduce glycemic variability and peak hyperglycemia [85], and may be an interesting, but understudied option to potentially reduce PTDM risk.

Finally, with respect to induction therapy, one study reported a reduction in PTDM incidence with alemtuzumab compared to IL2 receptor antagonists [86], which was suggested to be related to a reduction in calcineurin inhibitor and corticosteroid dosing with alemtuzumab use. Another single-center retrospective study of 264 renal transplant recipients suggested that basiliximab provides an intrinsic diabetogenic risk [87], with PTDM occurring at 10-week post-transplantation in 51.5% of patients receiving basiliximab versus 36.9% who did not receive induction, $P = 0.017$) [87]. In the absence of other studies, the significance of these results remains unclear.

In summary, 6 years after the consensus recommendations [23], there is no clear evidence that risk of PTDM can be decreased (e.g., by use of cyclosporine instead of tacrolimus or steroid avoidance/withdrawal), without increasing the risk of rejection. Therefore, the previous recommendation, which the immunosuppressive regimen should maximize patient and allograft survival, regardless of whether this increases the risk of PTDM [23], still appears sensible. Importantly, this view still acknowledges a generally recognized reduction in cardiovascular mortality [88], primarily due to the restoration of renal function. The long-term success of the graft is of paramount importance for the outcome, which is assured by effective immunosuppression. As a consequence, tacrolimus has been the recommended calcineurin inhibitor since the 2009 KDIGO guidelines [89], and it seems reasonable that immunosuppression should be given primarily according to recommended guidelines [89].

Management of PTDM: early prevention—lifestyle and early insulin

While some debate may continue with respect to immunosuppressant modification, there appears to be agreement that prevention strategies to reduce risk for PTDM should be more actively encouraged. Lifestyle modification (dietary advice, physical activity, and weight loss encouragement) in kidney allograft

recipients was reported to facilitate reversal of impaired glucose tolerance to normal glucose tolerance within 6-months in a nonrandomized study [90]. In support of this concept, central obesity rather than body mass index is associated with development of PTDM [91]. A randomized controlled trial (CAVIAR) comparing active versus passive lifestyle intervention postkidney transplantation [92] demonstrated improvements in secondary clinical endpoints including weight loss, reduced fat mass, and a suggestion of reduced PTDM incidence (7.6% versus 15.6% respectively, $P = 0.123$). A multi-center study with reduction in PTDM as the primary outcome is being planned, powered by the empirical data obtained from the CAVIAR study.

A step-wise approach to management of established PTDM has much earlier been advocated [17], but with hyperglycemia arising in the immediate post-transplant period, the *reverse* was subsequently recommended [23]. Insulin is the safest, most effective agent in the early post-transplant period with possibly enduring benefits: In a randomized controlled proof-of-concept study, institution of basal insulin following detection of early post-transplant hyperglycemia (<3 weeks) reduced subsequent odds of persistent PTDM in the first-year post-transplantation by 73% [41]. The results of a larger randomized controlled clinical trial (ITP-NODAT, NCT03507829) have recently been submitted. Although PTDM incidence in the subsequent trial was dramatically smaller than in the previous proof-of-concept study, early intervention against post-transplant hyperglycaemia by capillary blood glucose monitoring and basal insulin treatment, again, was safe and prevented overt PTDM onset. However, the primary endpoint (incidence of PTDM at 1 year) was only reached in the per-protocol analysis which excluded some severe protocol violations resulting in diabetes misclassification [93], and additional analyses showed that the results depend on protocol adherence [94]. Of note, data from the previous proof-of-concept trial showed that this strategy, albeit decreasing the incidence of PTDM, may not improve cardiovascular complications [38].

If management of post-transplant hyperglycemia is placed in context with treatment of postoperative hyperglycemia, then insulin will remain first choice [95,96]. However, there are also advantages for postoperative initiation of antihyperglycemic therapy other than insulin, especially if postoperative hyperglycemia is mild. Recently issued guidelines on the Detection and Management of Diabetes post-Solid Organ Transplantation by the Association of British Clinical Diabetologists (ABCD) and by the British Renal Association (RA) aimed to stratify a hierarchy of pharmacological therapy and encouraged metformin as first-line oral therapy for suitable kidney transplant recipients, defined as eGFR of ≥ 30 ml/min/1.73m^2 and BMI ≥ 25 kg/m^2 [97]. The writing group, however, emphasized additional ABCD/RA guidance, clearly suggesting the use of metformin "sick day rules" whereby metformin therapy should be temporarily stopped when there is a risk of hypovolemia [98]. Among oral agents, some therapies like sulfonylureas, meglitinides, and thiazolidinediones were suggested with significant caveats in mind due to lack of evidence regarding efficacy and potential for significant side effects [97]. Therefore, the use of novel antidiabetics for management of PTDM is of increased interest, while glucose-lowering therapies in the context of PTDM treatment also include dipeptidylpeptidase-4 inhibitors and have been summarized in several reviews prior to the year 2018, by us and others [1,99-101].

Management of PTDM: novel antidiabetics

The landscape of diabetes therapy in the general population has changed dramatically since the success of novel antidiabetic agents inhibiting sodium–glucose linked transporter 2 (SGLT2i), and acting as agonists of the glucagon-like peptide 1 receptor (GLP1-RA). Among several medical societies that have by now endorsed the SGLT2is and GLP1-RAs in their guidelines are the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Specifically, an ADA/EASD Consensus Report from the year 2018 recommended GLP1-RAs or SGLT2is for type 2 diabetics with established atherosclerotic cardiovascular disease (ASCVD) or chronic kidney disease (CKD), if their glycated hemoglobin (HbA1c) levels under therapy with metformin and lifestyle modification were above 7%, the recommended target for nonpregnant adults [102]. The choice of using either SGLT2i or a GLP1-RA should depend on the predominance of CKD, ASCVD, or heart failure: Patients with a predominance of ASCVD should receive a GLP1-RA, while patients with a predominance of heart failure patients or CKD should receive an SGLT2i with proven benefit in the respective conditions.

Only a few months after the publication of the ADA/EASD recommendations, the European Renal Association—European Dialysis and Transplant Association (ERA-EDTA) working groups "DIABESITY" and "EUropean REnal and CArdiovascular Medicine" (EUR-ECA-m) published their consensus statement on nephroprotection and cardioprotection with SGLT2is and GLP1-RAs in patients with diabetes mellitus and

CKD [103]. An important update to the ADA/EASD Consensus Report [104] rendered the treatment less glucose-centered, as was also stated in the most recent ADA document [105]: "Among patients with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit is recommended *as part of the glucose-lowering regimen independent of A1C and in consideration of patient-specific factors*." Thus, metformin is still first choice when the patient does not have ASCVD, heart failure, or CKD. However, if one or more of the two comorbidities are present, metformin, and an SGLT2i, alternatively a GLP-1RA (always with proven benefit) should be started together with metformin. And if a patient is on metformin and develops one such comorbidity, an SGLT2i or GLP-1RA should be started regardless of HbA1c.

Recapitulating the highlights of the previous ADA/EASD guidelines [102,104] and of the subsequent consensus statement by DIABESITY and EURECA-m [103] is beyond the scope of this review, as they both focus on the general population with type 2 diabetes. However, we have summarized the results of the recent, major trials using SGLT2is and GLP1-RAs in Table 1 (in the first row and third row, for the general population with T2DM). One trial that is not mentioned in Table 1 is Vertis (studying the SLGT2i ertugliflozin), which was presented at the ADA in June 2020. This trial found no significant superiority of the treatment versus placebo group, with respect to the primary outcome, although the numerical signal was in the same favorable direction as seen for the other SGLT2is. Among the explanations for this puzzling result, seemingly subtle differences in eligibility criteria have been put forth, as Vertis, when compared to EMPA-REG-OUTCOME, recruited patients above 40 years (versus any age in EMPA-REG-OUTCOME) [106]. Vertis moreover included only 6.4% and 8.4% participants of Asian and South American origin, respectively (versus 19% and 15% in EMPA-REG-OUTCOME, respectively) [106]. Despite the fact that both study populations had established cardiovascular disease, the existence of a class effect among the SGLT2is might not have to be questioned altogether.

Besides Vertis, the most recent developments (DAPA-heart failure; DAPA-CKD and EMPEROR) were also beyond the scope of this review. However, it is worth mentioning here that the 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease by the Kidney Disease: Improving Global Outcomes (KDIGO) initiative provides perhaps the most detailed overview for the general population, now emphasizing comprehensive care with risk factor management and antihyperglycemic therapy individualization in individuals with CKD and diabetes mellitus [107]. We strongly recommend this excellent and timely KDIGO publication as an important source of information and guidance, acknowledging, however, that the guideline is not specific in the setting of solid organ transplantation, where the target population does not consist 100% of individuals with CKD, and where patients also receive immunosuppressive therapy.

Mechanistic considerations

Although the mechanisms of action differ completely between SGLT2is that lead to excretion of glucose into the urine [108] and GLP1-RAs which enhance the incretin effect [109], their effects on the primary endpoint (usually cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) shown in most trials seem amazingly similar between both drug classes (Table 1). However, when both drug classes are considered at detail, their impact on the kidney and heart is meaningfully different (e.g., GLP1-RAs affect proteinuria but do not slow CKD progression and do not improve heart failure [110]). Some of the postulated mechanisms known form the general population are summarized with respective references in Table 2. These mechanisms of nephroprotection and cardioprotection have been thoroughly discussed and reviewed in the EURECA-m and DIABESITY consensus statements [103].

SGLT2is

Metabolic and cardiovascular effects of empagliflozin shown in published PTDM studies

Based on the rationale that novel antidiabetic agents have been shown to be immensely beneficial in the general population with T2DM, the SGLT2i empagliflozin was used at the Vienna transplant center in patients with PTDM after kidney transplantation, in a study which resulted in the formally first publication on this subject (the EMpagliflozin in Post-TRAnsplant Diabetes Mellitus [EMPTRA-DM] pilot study [111]). Only a few months later, the transplant center in Oslo also published a randomized controlled study on empagliflozin

Table 1. Recent studies with novel antidiabeticss in the general population with type 2 diabetes (T2DM) and in solid organ transplant patients with post-transplant diabetes mellitus (PTDM)

Drug Class	Population	Study/Author	Agent	N patients	Organ	Result	Endpoint
SGLT2is	T2DM	EMPA-REG OUTCOME [148]	Empagliflozin	*n* = 4687 versus *n* = 2333 (placebo)		HR = 0.86 (0.74–0.99)	Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. [Primary Endpoint.]
		EMPA-REG OUTCOME [149]	Empagliflozin	*n* = 4687 versus *n* = 2333 (placebo)		HR = 0.61 (0.53–0.70)	Incident or worsening nephropathy (progression to macroalbuminuria, doubling of serum creatinine, initiation of renal replacement therapy, or death from renal disease). [Prespecified renal endpoint.]
		CANVAS [150]	Canagliflozin	*n* = 5795 versus *n* = 4347 (placebo)		HR = 0.86 (0.75–0.97)	Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. [Primary Endpoint.]
		DECLARE-TIMI [151]	Dapagliflozin	*n* = 8582 versus *n* = 8578 (placebo)		HR = 0.93 (0.84–1.03)	Major adverse cardiovascular events, defined as cardiovascular death, myocardial infarction, or ischemic stroke. [Primary Endpoint.]
		DECLARE-TIMI [151]	Dapagliflozin	*n* = 8582 versus *n* = 8578 (placebo)		HR = 0.83 (0.73–0.95)	Composite of cardiovascular death or hospitalization for heart failure. [Primary Endpoint.]
		CREDENCE [152]	Canagliflozin	*n* = 2202 versus *n* = 2199 (placebo)		HR = 0.70 (0.59–0.82)	End-stage kidney disease (dialysis, transplantation, and sustained eGFR < 15 ml/min/ 1.73 m2), doubling of serum creatinine, or death from renal or cardiovascular causes. [Primary Endpoint.]
	PTDM	Schwaiger et al. [111]	Empagliflozin	*n* = 14	Kidney	no sign.	OGTT-derived 2-hour plasma glucose before versus

Table 1. Continued.

Drug Class	Population	Study/Author	Agent	N patients	Organ	Result	Endpoint
		Halden et al. [112]	Empagliflozin	n = 22 versus n = 22 (placebo)	Kidney	not possible to report	4 weeks after therapy initiation (replacement). Change in weighted mean glucose by cont gluc monitoring, baseline to week 24 compared with placebo.
		Mahling et al. [113]	Empagliflozin	n = 10	Kidney	n.a.	Case series.
		Shah et al. [114]	Canagliflozin	n = 24	Kidney	n.a.	Not prespecified.
		Attallah et al. [115]	Empagliflozin	n = 8	Kidney	n.a.	Case series.
		Cehic et al. [116]	Empagliflozin	n = 22	Heart	n.a.	Retrospective study.
		Muir et al. [117]	Empagliflozin	n = 19	Heart	n.a.	Retrospective study.
GLP1-RAs	T2DM	ELIXA [153]	Lixisenatide	n = 3034 versus n = 3034 (placebo)		HR = 1.02 (0.89-1.17)	Cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina. [Primary Endpoint.]
		LEADER [154]	Liraglutide	n = 4668 versus n = 4672 (placebo)		**HR = 0.87 (0.78-0.97)**	**First occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. [Primary Endpoint.]**
		LEADER [155]	Liraglutide	n = 4668 versus n = 4672 (placebo)		**HR = 0.78 (0.67-0.92)**	New-onset persistent macroalbuminuria, persistent doubling of serum creatinine, end-stage kidney disease, or death due to renal disease. [Prespecified secondary renal outcomes.]
		SUSTAIN-6 [135]	Semaglutide	n = 1648 versus n = 1649 (placebo)		**HR = 0.74 (0.58-0.95)**	**First occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. [Primary Endpoint.]**
		EXSCEL [156]	Exenatide	n = 7356 versus n = 7396 (placebo)		HR = 0.91 (0.83-1.00)	First occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. [Primary Endpoint.]

Table 1. Continued.

Drug Class	Population	Study/Author	Agent	N patients	Organ	Result	Endpoint
		Harmony [157]	**Albiglutide**	**n = 4731 versus n = 4732 (placebo)**		**HR = 0.78 (0.68-0.90)**	**First occurrence of cardiovascular death, myocardial infarction, or stroke. [Primary Endpoint.]**
		REWIND [134]	**Dulaglutide**	**n = 4949 versus n = 4952 (placebo)**		**HR = 0.88 (0.79-0.99)**	**First occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. [Primary Endpoint.]**
	PTDM	Halden et al. [130]	GLP-1	n = 12 (PTDM) vs n = 12 (no-PTDM)	Kidney	Sign. lower in PTDM	Sample size calculation was based on GLP-1 induced suppression of glucagon.
		Pinelli et al. [124]	Liraglutide	n = 5	Kidney	n.a.	Case series.
		Liou et al. [125]	Liraglutide	n = 7	Kidney	n.a.	Retrospective study.
		Singh et al. [126]	Dulaglutide	n = 63	Kidney, liver, heart	n.a.	Retrospective study.
		Singh et al. [127]	Dulaglutide., Liraglutide	n = 63, n = 25, respectively	Kidney, liver, heart	n.a.	Retrospective study.
		Kukla et al. [128]	Lira, Exena, Dulaglutide	n = 17	Kidney	n.a.	Retrospective study.
		Thangavelu et al. [129]	Exena, Lira, Dula, Semaglutide	n = 19	Kidney, liver, heart	n.a.	Retrospective study.

Table 2. Potential mechanisms of nephroprotection and cardioprotection exerted by novel antidiabetics (data from the general population)

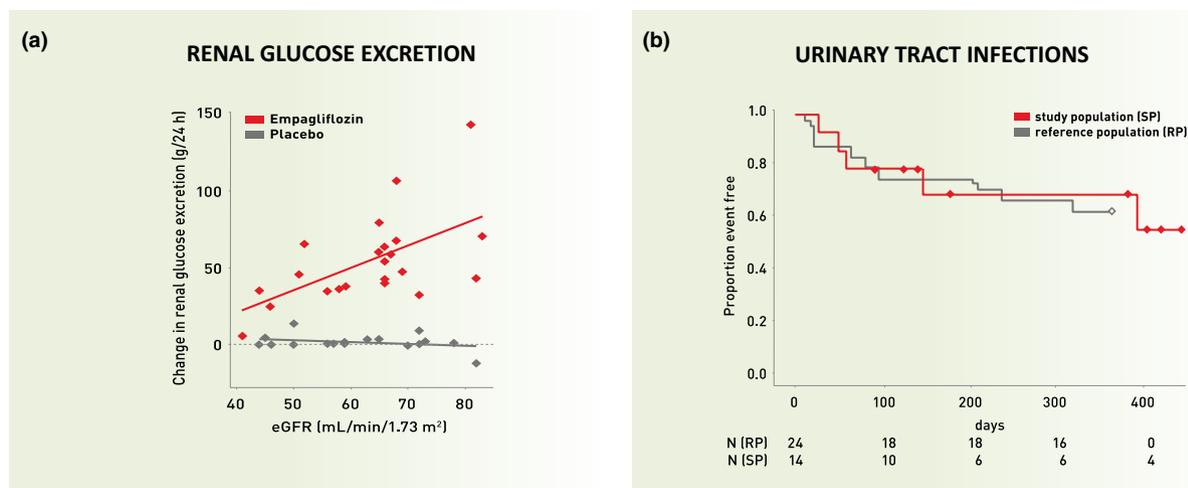| Drug Class	Benefit	Observations	First shown for … in	Mechanism	Details
SGLT2is	Nephroprotection	Estimated GFR dropped but then stabilized; Patients were less likely to double their serum creatinine and to start kidney replacement therapy.	Empagliflozin, EMPA-REG OUTCOME[149,158]	Hemodynamic effect	Amelioration of hyperfiltration in animal models of diabetic nephropathy [159–161]; according to a study measuring GFR and effective renal plasma flow in type 1 diabetics [162]: in hyperfiltration, empagliflozin attenuated GFR (hyperglycemia> euglycemia) by reducing increased Na and gluc reabsorption in proximal tubule, leading to more Na reaching lumen of distal tubule, being measured in macula densa, restoring tubuloglomerular feedback, increasing resistance in the vas afferens, reducing vasodilation (hallmark of the hyperfiltrating, and diabetic kidney).
		Progression to macroalbuminuria was less frequent.	Empagliflozin, EMPA-REG OUTCOME [149]	A consequence of the hemodynamic effect	Reduction in vascular rigidity [163,164]; decrease in serum uric acid [165,166]; natriuresis [167]; role of glucagon [168]; activation of HIF-1 (hypoxia-inducible factor) [169].
	Cardioprotection	CV events were reduced and hospitalization due to heart failure was less frequent.	Empagliflozin, EMPA-REG OUTCOME [148]	Unknown; Could be several mechanisms [103,170]	Reduction in SBP and DBP [171] (per se benefits diabetics [172]); diuretic effect [173,174]); reduction of interstitial volume [175]; reduction in waist circumference [148] and vascular stiffness [164,170]; changes in hematocrit mediating 50% of CV benefit [176]; reduction in renal blood flow leading to heart relief [103]; increased glucagon levels and associated ketone body formation may be beneficial [103,120,177].
GLP1-RAs	Nephroprotection	Estimated GFR decreased (a small decrease of 2%).	Liraglutide, LEADER [155]	Complex	Mediated directly by GLP1; mediated by nitrogen monoxide (NO); various indirect effects, involving tubuloglomerular feedback, RAS, and (reviewed in [139] and [140]); intestine–kidney axis may be involved; GLP1RAs trigger natriuresis and diuresis [178,179].
		New onset of persistent macroalbuminuria was	Liraglutide, LEADER [155]	Anti-inflammatory	Anti-inflammatory in the kidney (animal model [180]); inhibition of T-cell proliferation in experimental glomerulonephritis animal

Table 2. Continued.

Drug Class	Benefit	Observations	First shown for ... in	Mechanism	Details
		reduced; Albuminuria was reduced.			model [143]; lower inflammatory biomarkers in RCT [181]; suggested benefit for a variety of inflammatory diseases (reviewed in [144]).
	Cardioprotection	CV events including MCIs were reduced.	Liraglutide, LEADER [154]; simultaneously for Semaglutide, SUSTAIN-6 [135]	General improvement in CV risk profile	Reduction of body weight and blood lipids [182,183]; even for albiglutide (unlikely to cross the blood-brain barrier), a reduction in CV events has been shown [157], suggesting that GLP1-RAs exert important peripheral effects on the cardiovascular system (summarized here: [184]).
				Anti-atherosclerotic	Shown in ApoE deficient mice [185]; reduced intake of oxidized LDL cholesterol into foam cells [186]; GLP1-RAs were shown to be anti-inflammatory [186,187].

administration after kidney transplantation (EMPA-Renal Tx [112]), and several other studies have followed on kidney [113-115] and heart [116,117] transplant patients.

EMPTRA-DM: The Vienna study [111] aimed at obtaining data on glycemic control in post-transplant diabetics under empagliflozin. Therefore, participants with pre-existing insulin therapy were initially given empagliflozin (10 mg) as monotherapy over a period of 4 weeks. Oral glucose tolerance tests (OGTTs) before and after the 4-week empagliflozin monotherapy, as well as the evaluated glucose profiles showed that empagliflozin monotherapy yielded inferior glucose control, in comparison to the pre-existing insulin therapy [111]. The average 2-hour plasma glucose value from the OGTT (primary endpoint), however, barely missed the limit of significance to show inferiority of empagliflozin, compared to previous insulin therapy ($P = 0.06$) [111]. To include the relatively small number of participants studied in EMPTRA-DM ($n = 14$, per prespecified sample size calculation), markedly more patients had to be screened from 1120 outpatients. After the 4-week empagliflozin monotherapy, the EMPTRA-DM study was continued for 11 months further, but 6 participants withdrew, due to poor glycemic control, urinary tract infections, and worsened eGFR. Of the 8 participants remaining in the study, 3 had to be placed back on insulin therapy.

EMPA-Renal Tx: The study in Oslo by Halden et al. was a randomized controlled double-blind study [112]. Only patients with stable PTDM and transplant duration of at least 1 year were included. These patients were identified during their extensive post-transplant visit at year 1, where all patients receive an OGTT. The EMPA-Renal Tx study examined the efficacy and safety of empagliflozin (10 mg) as monotherapy or add-on therapy in a total of 24 patients, against 25 placebo patients. Two participants did not complete the entire 24-week study period. Two participants were able to reduce their pre-existing insulin therapy, but no patient was able to completely omit the pre-existing antidiabetic medication. An OGTT, a 24-hour blood pressure measurement, and a body composition measurement (dual X-ray) were also carried out at the beginning of the study and after 24 weeks. In addition, the study included a 24-hour urine collection to evaluate glucosuria.

Considering the hierarchy inherent in the different study designs, the randomized, placebo-controlled study from Oslo is clearly to be preferred over the Vienna study, which had only one study arm, so that each

Figure 1 Messages derived from two prospective SGLT2 inhibitor studies in PTDM patients. EMPA-Renal Tx study (Oslo, a = left panel [112]) and EMPTRA-DM study (Vienna, b = right panel [111]). Abbreviations: LDL = low-density lipoprotein, SMBG = self-monitored blood glucose

study participant served as his own control. Despite these differences in design, both studies arrived at remarkably similar conclusions:

i) Weak antihyperglycemic action of empagliflozin: The antihyperglycemic effect of empagliflozin was weak in both studies (HbA1c decrease of 0.2% at week 24 in Oslo compared to a slight HbA1c increase [+ 0.1%] in the placebo group; HbA1c increase of 0.4% in Vienna at the end of the study [with fewer cases]). The Oslo results also showed that HbA1c decrease depended on kidney function, based on the fact that the increase in renal glucose excretion by SGLT2 inhibition is strongly GFR-dependent: at an eGFR < 50 mL/min/1.73m^2 empagliflozin-induced glucosuria and HbA1c reduction were virtually absent (Fig. 1a) [112].

ii) Kidney function under empagliflozin: In both studies (from Vienna and Oslo), the eGFR initially dropped, but then stabilized, indicating perhaps that one of the principal mechanisms of action of the SGLT2is (the hemodynamic effect [see Table 2]) took place in the study patients.

iii) Decrease in body weight but unaltered body composition: Empagliflozin led to a decrease in body

weight in the Oslo study (3.5 kg compared to placebo in week 24; −5 kg in Vienna in month 12), but neither study noted a significant change in body composition (examined by bioimpedance spectroscopy [Vienna] or DXA [Oslo]) at study termination.

iv) Metabolism: Empagliflozin led to a decrease in uric acid concentration in both studies. In Oslo, the OGTTs (in contrast to Vienna, where glucose control became significantly worse) showed no group difference in insulin secretion or insulin sensitivity.

v) Urinary tract infections: Symptomatic bacterial urinary tract infections (UTIs) occurred in 2 dropouts and in 3 participants who completed the EMPTRA-DM study [111]. UTIs were initially perceived as an important side effect of the empagliflozin therapy. However, the analysis of a suitable reference population (*n* = 24), matched at a 2:1 ratio to the EMPTRA-DM participants over the same treatment period showed that 9 matched patients also suffered from a symptomatic UTI (*P = 0.81*, compared to empagliflozin patients, Fig. 1b). Not only 5 study participants in Vienna, but also 3 patients from the Oslo empagliflozin group and 3 patients from the

POTENTIAL BENEFITS OF SGLT2 INHIBITORS AND GLP1-RAs IN SOLID ORGAN TRANSPLANT PATIENTS

		DIRECT EFFECTS ON ORGANS		INDIRECT EFFECTS ON ORGANS	
		SGLT2 inhibitors	GLP1R agonists	SGLT2 inhibitors	GLP1R agonists
KIDNEY TRANSPLANT RECIPIENTS		KIDNEY			
	PTDM risk: 10-20% [REFs 3-5]. Increased risk of mortality. Graft loss is a challenge. **Opinion:** Use SGLT2i as add-on, monitor glucosuria ketonuria, UTI by urinary dipstick tests. GLP1-RA for ↑BMI patients, ideal in poor glycemic control. Study monotherapy!	↑ natriuresis → restoration of TGF → intraglomerular pressure ↓ → albuminuria ↓	↑ natriuresis (potentially similar as with SGLT2i, but less potent, [renal endpoints in studies all driven by albuminuria]) ↓ glomerular pressure ↓ inflammation ↓ albuminuria	↓ glucose ↑ ketones (↑ glucagon) ↓ vascular rigidity ↓ uric acid ↑ HIF-1	↑ utilization of glucose (and potentially of other macronutrients, prandially)
HEART TRANSPLANT RECIPIENTS		HEART & CV-SYSTEM			
	PTDM risk: 20-30% [REF 6]. Increased risk of mortality. **Opinion:** Safety suggested from retrospective studies. SGLT2is and GLP1-RAs could be even more attractive than for kidney transplant recipients (better eGFR; UTIs no major concern, potential CV risk reduction). ↑BMI patients: GLP1-RAs first. Study prospectively!	Speculative. (SGLT2 is not expressed in the heart [only SGLT1.]) However, direct effects of SGLT2is on the heart have been described [REF 123]	↑ heart rate (but does not appear to increase cardiovascular risk [REF 141])	↓ glucose ↑ ketones (↑ glucagon) ↓ insulin resistance ↓ uric acid ↓ weight & BP ↓ visceral fat ↓ arterial stiffness ↓ plasma volume	↑ utilization of glucose (and potentially of other macronutrients, prandially) ↓ weight ↓ blood pressure ↑ cardiac output ↑ vasodilation ↓ fatty acid metabolism
LIVER TRANSPLANT RECIPIENTS		LIVER			
	PTDM risk: 20-40% [REFs 7-11]. Increased risk of mortality. **Opinion:** No data available for SGLT2is, but SGLT2is & GLP1-RAs very attractive. Study prospectively!	Speculative. (SGLT2 is not expressed in the liver; direct effects of SGLT2is have not been described.)	↓ steatosis ↓ VLDL (ApoB100) ↓ glucose production ↓ inflammation Direct benefit? [REF 144]	↓ glucose ↑ glucagon ↑ hepatic glucose production (↑ SNS)	↑ utilization of glucose (and potentially of other macronutrients, prandially)
LUNG TRANSPLANT RECIPIENTS		LUNG			
	PTDM risk: 20-40% [REFs 12, 13]. Increased risk of mortality. **Opinion:** Attractive, study prospectively! (no data)	Speculative. (SGLT2 is not expressed in the lung. See also above.)	↓ inflammation Direct benefit? [REF 144]	↓ glucose ↑ ketones (↑ glucagon)	↑ utilization of glucose (and potentially of other macronutrients, prandially)

Figure 2 Potential benefits of SGLT2 inhibitors and GLP1R agonists in solid organ transplant patients. Abbreviations: PTDM = post-transplantation diabetes mellitus, SGLT2i = sodium–glucose-linked transporter 2 inhibitor, GLP1-RA = glucagon-like 1 receptor agonist, LDL = low-density lipoprotein, TGF = tubuloglomerular feedback, SNS = sympathetic nervous system

Oslo placebo group suffered from urinary tract infections during the course of the respective studies. However, 2 participants of the Oslo empagliflozin group with urinary tract infections had to prematurely drop out of the EMPA-Renal Tx study (due to urosepsis and recurrent UTI, which was already known in the latter case [112]).

Mechanistic considerations

The high number of dropouts in the EMPTRA-DM study [111] and also the need for close monitoring, which was a primary finding from both the EMPTRA-DM and the EMPA-Renal Tx studies [112], demonstrate clearly that the antidiabetic agent empagliflozin and presumably also other SGLT2is can only be given with caution in PTDM patients. Mechanistically, kidney function is the primary limiting obstacle for glucose lowering. As the drug loses its glucose-lowering effects [112,118,119], it might be reasonable to argue that prescribing SGLT2is in PTDM should be limited by eGFR, at least as long as a long-term protective effect on the kidney graft (or cardiovascular outcomes) has not been

proven for PTDM patients (in contrast to the general population with type 2 diabetes).

Another mechanistic aspect with SGLT2i that may often be overlooked (which is positive) and therefore deserves mentioning is the indirect organ protection (including cardioprotection), mediated by a mild increase of ketones observed under SGLT2 inhibition. With excess glucose leaving the human body through the urine, the ketone β-hydroxybutyrate is freely taken up by various organs and oxidized to fatty acids. Such a fuel selection improves the transduction of oxygen into work efficiency at the mitochondrial level, through increased energy supply, and may thus also improve the metabolic status and function of heart, kidney, and possibly also other organs [120] (Fig. 2). Furthermore, this change in metabolism might also directly influence immune cells since these cells especially T-cell subpopulations have a different metabolic profile [121,122]. Thereby, ketosis might limit immune activation, which stops the development of fibrosis. Still, these effects could not only have a beneficial effect in CKD, but also in the post-transplant situation. An additional, fascinating question is whether

SGLT2is may exert a direct effect on the human heart (reviewed in [123]).

In summary, these data from Vienna and Oslo suggest that empagliflozin should primarily be used as add-on therapy in PTDM due to its weak antihyperglycemic effect. Patients receiving empagliflozin should be closely monitored for kidney function, ketoacidosis, and urinary tract infections [111,112]. Urinary dipstick tests, preferably performed by the patients themselves, while taking empagliflozin, may be particularly advisable. In support of these data from Vienna and Oslo, 5 additional publications, all case series and retrospective studies [113-117], have been subsequently published for the SGLT2is so far (summarized in Table 1, second row). Two of these publications reported on empagliflozin in heart transplant patients [116,117].

GLP1-RAs

Metabolic and cardiovascular effects of GLP1-RAs shown in published studies

Compared to SGLT2is, the clinical experience of GLP1-RAs in PTDM is entirely limited to case series and retrospective studies [124-129]. The largest study, from Singh and colleagues, investigated the use of dulaglutide in 63 solid organ transplant recipients with diabetes (of whom 20 had PTDM compared to 43 with pre-existing type 2 diabetes) [126]. At 12 months, a significant decrease was observed in weight and insulin requirement but not in HbA1c or survival outcome measures. Due to the retrospective nature of this and all other studies on GLP1-RAs, changes in HbA1c could be a consequence of concomitant adoptions of the additional antihypergylcemic therapy (mostly insulin dosage). HbA1c reduction with GLP1-RAs, when compared to the SGLT2is, does not depend on kidney function and has been clinically meaningful (from 10.0% to 8.1% in average) in 7 diabetic patients with poor glycemic control [125] (this study unfortunately did not explicitly state that these were PTDM patients, as opposed to T2DM patients after kidney transplantation). However, weight reduction was observed in all of these studies [124-129] (Kukla et al. reporting a nonsignificant P-value of 0.2 [128]).

Mechanistic considerations

From a mechanistic perspective, Halden and colleagues, using the hyperglycemic clamp, have shown PTDM patients in general have impaired insulin release and high glucagon levels which could partly be normalized with GLP-1 infusion [130]. This study demonstrating the potential benefit of GLP1-RAs in correcting pathophysiological defects in glucose metabolism suggests that further investigation of the benefits of GLP1-RAs for PTDM is warranted.

Among GLP1-RAs, the dosing of liraglutide does not require to be adjusted to impaired kidney function. However, liraglutide administration bares the risk of gastrointestinal side effects with reduced volume intake and consequently worsening eGFR [131]. Liraglutide should therefore no longer be used for the indication "weight regulation," if the eGFR < 30 mL/min/1.73m^2. For the indication diabetes mellitus, the only contraindication exists for actual end-stage kidney failure [131], although liraglutide has been safely used in hemodialysis patients without increments in plasma levels of the drug [132]. Dulaglutide and semaglutide need to be injected only once weekly and can also be used in patients with impaired kidney function, down to an eGFR of 15 mL/min/1.73m^2 (dulaglutide), and without contraindication except terminal kidney failure (semaglutide) [133]. The positive results from REWIND [134] and SUSTAIN-6 [135] with regard to the primary endpoint (see Table 1) render dulaglutide and semaglutide attractive agents for patients with diabetes after kidney transplantation. The significant HbA1c reduction observed with dulaglutide [136] argues in favor of its use in patients with "derailed" type 2 diabetes after kidney transplantation and patients with "severe" PTDM, especially if obese [137]. Due to the gastrointestinal side effects, it may be necessary to monitor the calcineurin inhibitor trough levels (tacrolimus and cyclosporine). Although a recently published retrospective analysis on the use of dulaglutide after solid organ transplantation does not provide details about calcineurin inhibitor levels [126], a very recent study showed that endogenous incretin levels vary according to the type of calcineurin inhibitor used [138]. One of the primary tasks while performing outcome studies with GLP1-RAs would therefore be to confirm the data on immunosuppressant blood levels, for example, tacrolimus area under the curve, during its use, which were previously published for a case series [124].

Several mechanisms have been proposed how GLP1-RAs exert their cardio- but also nephroprotective effects (partly summarized in Table 2, illustrated in Fig. 2 and reviewed in [139] and [140]). Direct effects of GLP1-RAs on the heart may to our knowledge not play a major role and include a small but significant rise in heart rate [141]. Indirect effects might be more

important. Specifically, vasodilation through mechanisms that include blockade of atrial natriuretic peptide, endothelin-1, the renin–angiotensin–aldosterone system, and sodium reabsorption in the proximal tubular system may play a central role [139]. Interestingly, a gut–renal axis may also be of note and involves both neural and non-neural pathways [140]. One hypothesis that may not be well known is that by reducing prandial intraglomerular pressure, macronutrient loss into the glomerular filtrate may be prohibited [140]. Reduction in intraglomerular pressure and a subsequent antiproteinuric affect in the diabetic kidney, however, are also a consequence of GLP1-RA induced natriuresis and subsequent increase in tubuloglomerular feedback, which most likely originates from GLP1-RA-induced inhibition of the sodium hydrogen exchanger 3 [140]. Besides inhibition of reactive oxygen species, GLP1-RAs have also been shown to exert immunomodulatory properties [142]. The latter seem to be of utmost interest in the setting of organ transplantation, since recent murine data point toward a T-cell anti-proliferative capacity of GLP1-RAs by changing glucose metabolism in T cells [143]. Based on previous literature, an earlier review also suggested a role for GLP1-RAs in diseases of liver and lung, such as nonalcoholic steatohepatitis, asthma, and psoriasis [144]. Future studies, especially in humans, are needed to evaluate the effect of GLP1-RAs on T-cell proliferation and their potential role in the transplantation of these solid organs.

Summary and outlook

Management of PTDM remains the most controversial issue since the 2013 consensus recommendations [23]. In the most recent ADA document [105] following the 2018 ADA/EASD consensus report [102] and its update [104] on management of hyperglycemia in type 2 diabetes, an SGLT2i or GLP1-RA was recommended for individuals with type 2 diabetes and established ASCVD, CKD, or heart failure as part of the glucose-lowering regimen. The choice of using either SGLT2i or a GLP1-RA should depend on the predominance of CKD, ASCVD, or heart failure: Patients with a predominance of ASCVD should receive a GLP1-RA, while patients with a predominance of heart failure patients or CKD should receive an SGLT2i with proven benefit in the respective conditions. The mechanisms by which these novel antidiabetics may protect the kidney and the cardiovascular system are both complex and interesting, and they are currently being researched intensively. Individuals with PTDM after kidney and other solid organ transplantation, and even more so those with type 2 diabetes who have a known pretransplant history of hyperglycemia, are particularly affected by CKD and ASCVD. In consequence, it is sensible to implement recommendations for novel antidiabetics in the solid organ post-transplant setting, as has already been proposed for liver [145] and heart transplant patients [146]. To date, there are, however, no studies showing that treatment of PTDM actually positively modifies outcomes, other than glycemia. It would therefore be trend-setting to be able to demonstrate for SGLT2is and/or GLP1-RAs in PTDM patients after solid organ transplantation that they modify progression of kidney disease, cardiovascular disease, and heart failure, perhaps translating into improved clinical outcomes, including mortality. In the case of the SGLT2is, several small studies have been conducted after transplantation, two of them prospective [111-117]. These studies show that SGLT2is can potentially be used in post-transplant diabetes, but the patients should undergo close monitoring. In the case of the GLP1-RAs, only retrospective case reports for PTDM patients are available [124-128,130], wherein no serious safety concerns have arisen so far. Eight years after the initial call for clinical trials on PTDM treatment, it is therefore once again "time to collaborate" [147].

Author contribution

Author roles for each author: MH, AS, KE, and TJ wrote the paper.

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