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Antidiabetic therapy in post kidney transplantation diabetes mellitus

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A B S T R A C T

Post-transplantation diabetes mellitus (PTDM) is a common complication after kidney transplantation that affects up to 40% of kidney transplant recipients. By pathogenesis, PTDM is a diabetes form of its own, and may be characterised by a sudden, drug-induced deficiency in insulin secretion rather than worsening of insulin resistance over time. In the context of deteriorating allograft function leading to a re-occurrence of chronic kidney disease after transplantation, pharmacological interventions in PTDM patients deserve special attention. In the present review, we aim at presenting the current evidence regarding efficacy and safety of the modern antidiabetic armamentarium. Specifically, we focus on incretin-based therapies and insulin treatment, besides metformin and glitazones, and discuss their respective advantages and pitfalls. Although recent pilot trials are available in both prediabetes and PTDM, further studies are warranted to elucidate the ideal timing of various antidiabetics as well as its long-term impact on safety, glucose metabolism and cardiovascular outcomes in kidney transplant recipients.

1. Introduction

In the last decade increased emphasis on the integrated management of care for patients with type 2 diabetes was followed by steady improvements in self-management behaviours and risk-factor control. In combination with the adoption of new, effective pharmacological approaches, these strategies were associated with large reductions in the rates of acute myocardial infarction, stroke, amputation, and end-stage renal disease among adults with diabetes between 1990 and 2010 [1]. Moreover, patients with diabetes have experienced a disproportionate reduction in in-hospital mortality and a complete reversal in risk of mortality relative to patients without diabetes [2]. Severe hypoglycaemia, however, is still the most common adverse effect of glucose-lowering therapies and associates with poor outcomes especially in vulnerable patients with multiple comorbidities [3]. Hospital admission rates for hypoglycaemia among older patients have now even surpassed hospitalisations for hyperglycaemia [4]. Thus, the efforts to improve metabolic control in patients with diabetes – although generally successful – have still been linked with unacceptably high rates of hypoglycaemia. New pharmacologic strategies including incretin-based therapies as a component of multimodal individualised diabetes management might help to increase the safety of lowering glucose.

PTDM has previously been suggested to be just a form of type 2 diabetes [5,6]. However, although PTDM is not mentioned in the American Diabetes Association (ADA) position statement [7], it most reasonably classifies in the category of "other specific types" of diabetes mellitus rather than in the type 2 diabetes category. According to the ADA experts, it is less important to label the particular type of diabetes than to understand the pathogenesis of hyperglycaemia in order to treat it effectively. We have previously pointed out that hyperglycaemia after kidney transplantation appears rapidly, and that the appearance of overt PTDM is steeper in kidney transplant patients than the development of type 2 diabetes in the general population [8,9], due to a variety of transplant-specific mechanisms [10]. Adding to this pathomechanistic difference, evidence generated by us and others suggests that β cell dysfunction rather than insulin resistance is the principal factor contributing to PTDM development [11–15], mainly as a consequence of calcineurin inhibitor action on β cells [16–20]. Previous consensus guidelines have emphasised the individualisation of immunosuppressive therapy as a hallmark of PTDM management [6]. However, a large international group of clinicians and scientists most recently recommended using strategies for prevention and treatment of PTDM beyond modification of immunosuppression [21]. Therefore, we here aim at reviewing and discussing pharmacological antihyperglycaemic therapy after kidney transplantation.

Our review focusses on antidiabetic substances for which at least some evidence regarding their use in PTDM is available or for which – at least theoretically – a positive impact on PTDM can be expected. This holds true for insulin, incretin-based therapies (in particular DPP-4 inhibitors), glitazones and metformin, as will be discussed below. From our point of view there is little rationale for the use of sulfonylureas and glinides in PTDM patients because of the negative cardiovascular profile of at least some of these compounds in the non-transplanted population [22]. In addition sulfonylureas failed to produce a sustained antihyperglycaemic effect in type 2 diabetes and appear to have a negative impact on β cell function, being particularly undesirable in the context of PTDM [23]. α-Glucosidase inhibitors show limited glucose-

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lowering efficacy in general combined with high rates of gastrointestinal side-effects making their use in transplant recipients less attractive [24]. Furthermore, their use in CKD stages 3 and higher is not recommended [25]. SGLT2 inhibitors will also not be discussed here, due to the lack of available data in kidney transplant recipients.

2. Insulin

Insulin treatment in patients with type 2 diabetes is typically introduced late during disease development [26], and this strategy has previously also been advocated for patients after renal transplantation in the previous PTDM consensus guidelines dating back to 2003 [6]. However, there are several potential advantages for earlier insulin administration in type 2 diabetes [27], most importantly protection of β cells by aggressive lowering of hyperglycaemia. An intermittent insulin therapy of only three weeks has shown promise in inducing remission of newly diagnosed type 2 diabetes mellitus in the general population [28]. We adopted this approach for kidney transplant patients and were able to show that early correction of postoperative hyperglycaemia using basal insulin reduces the risk of developing diabetes, most probably through β cell protection [29]. Specifically, in our proof-of-concept randomised controlled trial, we administered 17 IU basal insulin per patient and day during the immediate postoperative period and observed 73% lower odds of NODAT throughout the 1 year follow-up, compared with standard-of-care management. In treatment group patients who had undergone the early insulin intervention, β cell function derived from an oral glucose tolerance test was superior at 3 months in comparison to control patients, and remained superior at 6 months and 12 months. Insulin sensitivity, however, was strikingly similar between the intervention and the control group.

Metabolic changes from before to after transplantation may explain why insulin treatment is effective in this early post-operative phase. Before transplantation, renal gluconeogenesis is impaired in CKD patients and the kidneys clear markedly less insulin once the GFR drops below 20 ml/min [30,31]. Impaired insulin degradation in the failing kidneys [32] as well as in the periphery (muscle and liver) plays an additional role in causing hyperinsulinaemia in CKD patients and may be due to the accumulation of renal toxins [31]. In a 25-year old review article on hypoglycaemia associated with kidney failure, the author speculated that spontaneous hypoglycaemia may occur as a consequence of the patient's inability to sufficiently account for the surplus of insulin by augmented peripheral insulin resistance [33].

After successful kidney transplantation the metabolic situation is likely reversed very rapidly. Nam et al. performed oral glucose tolerance tests as well as short insulin tolerance tests 1 week before and 9–12 months after living-related renal transplantation [12]. They recruited 114 patients who all had normal glucose tolerance during the pre-transplant OGTT and found that only 31.6% of them had normal glucose tolerance during the post-transplant OGTT, while 45.7% had impaired glucose tolerance and 23.7% had PTDM. Importantly, the insulin sensitivity index measured by short insulin tolerance test increased in all 3 OGTT-derived subgroups from before to after renal transplantation. Insulin levels, proinsulin levels, and proinsulin:insulin ratios decreased from before to after renal transplantation (Table 2 in [12]), indicating a decline not only in total insulin concentration, but also in β cell secretory capacity. This study has been challenged by results from Hornum et al., who observed exactly the opposite, namely an increase in insulin secretion and a decline in insulin sensitivity [34]. However, this latter analysis did not follow the same study design as the study by Nam et al. and did not analyse insulin sensitivity separately within subgroups of patients with normal glucose tolerance, impaired glucose tolerance, and diabetes. Using an entirely different approach, our recent comparison of stable renal transplanted patients with OGTT-derived data from a large general population cohort has shown that insulin sensitivity is higher and insulin secretion lower in renal transplant recipients, as compared with the general population [14] as shown in Fig. 1.

The kidney transplant community is well familiar with metabolic syndrome components [35] and many of us may righteously favour risk reduction strategies to prevent PTDM. In an attempt to raise awareness for the possibility of biased views (including our own), we have previously cited the popular metaphor that "to a man with a hammer, everything looks like a nail", which has been attributed to Mark Twain [36]. Using a hammer for everything applies perfectly well to antidiabetic treatment. Considering the pathomechanism outlined above, as well as our positive experience thus far [10,29], we may be guilty of perceiving predominantly the advantages of insulin treatment. Insulin treatment, however, may not be suitable for all patients, especially not for those who exhibit only moderately elevated daily glucose profiles, or may be reluctant to inject insulin. Concerns for weight gain may also be carried over from the general population. Whether the risk of hypoglycaemia in future remains as low as in our previous proof-of-concept study, will be clarified with further clinical experience as well as in an ongoing multicentric study conducted in Europe and the United States (NCT01683331 [10]). Nevertheless, the previously mentioned group of international PTDM experts agreed that, while lifestyle modification → oral anti-diabetic therapy → insulin may be an appropriate stepwise approach for management of late-PTDM, the reverse might be the most appropriate for immediate post-transplant hyperglycaemia [21]. Our long term hopes are that insulin may prove beneficial, not only in the context of high glucocorticoid doses and acute illness, but also in the long term prevention of PTDM and its associated complications (Fig. 2).

3. Incretin-based therapies

The first incretin was identified in the 1970s and was given the name glucose-dependent insulinotropic peptide (GIP) followed by the discovery of the even more potent incretin Glucagon-like peptide-1 (GLP-1) 1in the 1980s [37]. Among the plethora of physiologic reactions to GLP-1 are increased insulin biosynthesis and β cell proliferation with decreased glucagon secretion, delayed gastric emptying, and an increase in insulin sensitivity in muscle cells along with appetite down-regulation (Fig. 3). Besides the possibility to directly administer GLP-1 analogues to ameliorate blood glucose excursions, the action of GLP-1 and GIP can be augmented by inhibiting the key enzyme dipeptidyl peptidase-4 (DPP-4 or CD26) that inactivates these two incretins [38]. DPP-4 is widely expressed in many tissues including liver, lung, kidney, intestines, and also on lymphocytes as well as endothelial cells and its enzymatic function is not restricted to inactivation of incretins since many diverse peptides and chemokines are cleaved by DPP-4 [39]. The clinical relevance of these "off-target" actions of DPP-4 – and thereby its pharmacological inhibition by DPP-4 inhibitors – is still unclear as will be briefly discussed below.

Before the introduction of DPP-4 inhibitors, direct GLP-1 agonists such as exenatide and liraglutide appeared in the armamentarium of antihyperglycaemic agents by virtue of their direct incretin stimulating potency. GLP-1 agonists appear to be more effective in reducing HbA1c levels than DPP-4 inhibitors [40]. However, there are only few data on GLP-1 agonists in patients with kidney failure and large studies with GLP-1 agonists in kidney transplant recipients have not been published to date. Exenatide and the recently approved drug lixisenatide are mainly excreted via glomerular filtration making their use in moderate to severe renal impairment difficult [41,42]. GLP-1 agonists have been shown to be less well tolerated than DPP-4 inhibitors, mainly due to gastrointestinal upset and nausea [43] and are therefore less attractive in kidney transplant recipients who generally display increased rates of gastrointestinal side-effects by their immunosuppressants [44]. Liraglutide seems to be most suitable for the use in patients with renal impairment, because only a small fraction of liraglutide is excreted via the kidneys [45]. A small case-series in kidney transplant recipients with mildly impaired renal function demonstrated that administration of liraglutide did not influence tacrolimus trough levels [46], although

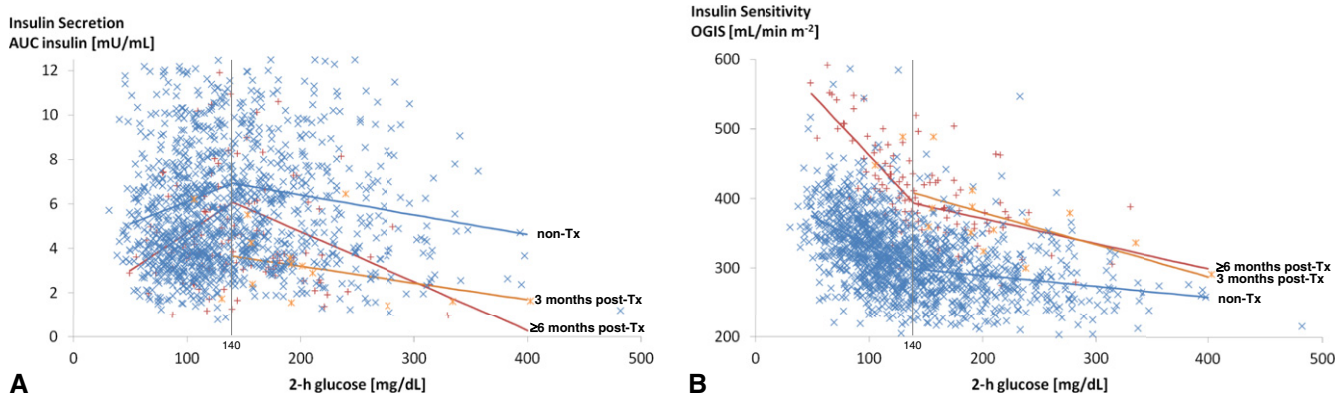

Fig. 1. Glucose metabolism after kidney transplantation. OGTT-derived measures of insulin secretion and insulin sensitivity are shown from subjects at 3 (red line) and 6 (orange line) months post-transplant (post-Tx) in comparison to the general population (non-Tx, blue line). (A) Insulin secretion by 2-h glucose (left) and (B) insulin sensitivity by 2-h glucose (right). Model shows ordinary least-squares regression analysis of 2-h glucose (independent variable) against (A) insulin AUC and (B) OGIS (dependent variables). 2-h glucose was modelled using a linear spline function with a single knot at 140 mg/dL showing significant differences in insulin secretion as well as insulin sensitivity between Tx and non-Tx patients ($p < 0.001$) (Adapted from [14]).

the delay of gastric emptying especially with short acting GLP-1 agonists may reduce the rate of absorption of orally administered medication. Furthermore, a significant number of overtly diabetic kidney transplant candidates suffer from diabetic gastroparesis making GLP-1 receptor stimulation with consecutively delayed gastric emptying less attractive. Although an ongoing study is assessing the safety of liraglutide in patients with end-stage renal disease [47], recommendations for the use of GLP-1 agonists in patients with moderate to severe renal impairment cannot be made at the moment, limiting their usability in kidney transplant recipients.

In contrast to GLP-1 agonists, DPP-4 inhibitors are generally not associated with a deceleration of gastric emptying or weight loss, perhaps due to the modest stabilisation of postprandial levels of intact biologically active plasma GLP-1 [48]. Most DPP-4 inhibitors can be safely used in patients with mildly to severely reduced renal function: Linagliptin e.g. can be prescribed without dose reduction [49]; saxagliptin, vildagliptin and sitagliptin can also be used in severe renal impairment but following dose reduction [50–53]. A summary of the current DPP-4 dosage for Europe and the United States, by glomerular filtration rate, is depicted in Table 1. DPP-4 inhibitors may even exhibit renoprotective properties in animal models of diabetic nephropathy [54] and ameliorate kidney fibrosis in diabetic mice [55]. They also

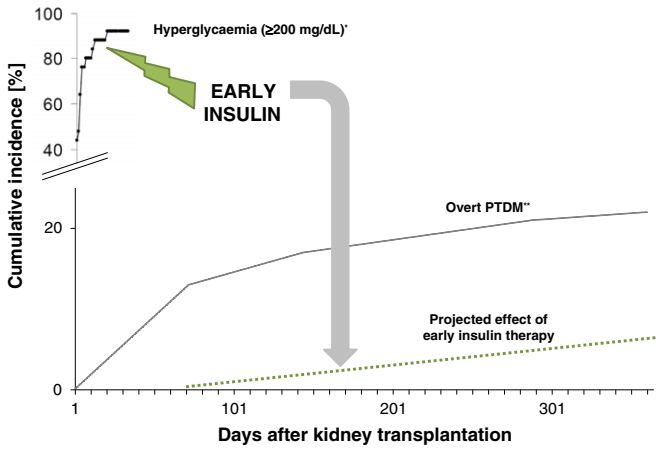

Fig. 2. Hyperglycaemia and PTDM incidence after kidney transplantation and possible consequences of early intervention. * Hyperglycaemia incidence in the early post-operative phase observed at our centre during the TIP (Treat-to-target Trial of Basal Insulin in Posttransplant Hyperglycaemia) study [29]. ** PTDM incidence over time as reported in the literature (grey line) [9]. The green dashed line shows the projected PTDM incidence based on the data of the TIP-study (Adapted from [10]).

have a favorable drug-interaction profile as none of the available DPP-4 inhibitors have shown relevant influences on trough levels of calcineurin inhibitors [56]. In general, DPP-4 inhibitors show good safety profiles although there are some areas where caution is warranted:

3.1. Hypoglycaemia

DPP-4 inhibitors carry a low risk for the development of hypoglycaemia. This is due to their mode of action stimulating only glucose-dependent insulin secretion [39], and severe hypoglycaemic events caused by mono-therapy with a DPP-4 inhibitor are extremely rare [57]. Mild hypoglycaemic events occur in 0%–4% of patients and appear to be more common in patients with liver disease, female sex and after alcohol consumption [58]. GLP-1 agonists confer a higher risk for hypoglycaemia compared to DPP-4 inhibitors [40]. As mentioned above, one of the major goals in modern diabetes medicine must be to reduce the number of therapy-induced hypoglycaemic events [4], and DPP-4 inhibitors hold promise in helping to reach this goal. Linagliptin e.g. added to existing glucose-lowering drugs was well tolerated and improved glycaemic control in patients with type 2 at high risk for hypoglycaemia (aged 70 years or older with long-standing diabetes, renal impairment, use of combination therapies) [59]. Transplant recipients become increasingly older and show a high number of comorbidities making the use of DPP-4 inhibitors in these patients even more attractive, because they carry a high risk for developing hypoglycaemic events.

3.2. Acute pancreatitis

Pancreatitis and pancreatic cancer caused by GLP-1-based therapies have been extensively discussed in the literature during the past years, since Elashoff et al. have published a report indicating that sitagliptin and exenatide increased the odds-ratio for the development of pancreatitis and pancreatic cancer [60]. A subsequent histopathological study of the same research group reported that in human organ donors, incretin therapy was associated with a marked expansion of the exocrine and endocrine pancreatic compartments with increased proliferation and dysplasia and α cell hyperplasia [61].

These analyses were initially triggered by case-reports about acute pancreatitis in patients receiving exenatide treatment [62,63]. In 2009 the United States Food and Drug Administration issued a safety alert on acute pancreatitis in patients treated with sitagliptin [64]. Subsequent experimental data in animal models confirmed a potential causal link between use of GLP-1 agonists and pancreatic acinar inflammation [65], although these negative effects were not confirmed by other

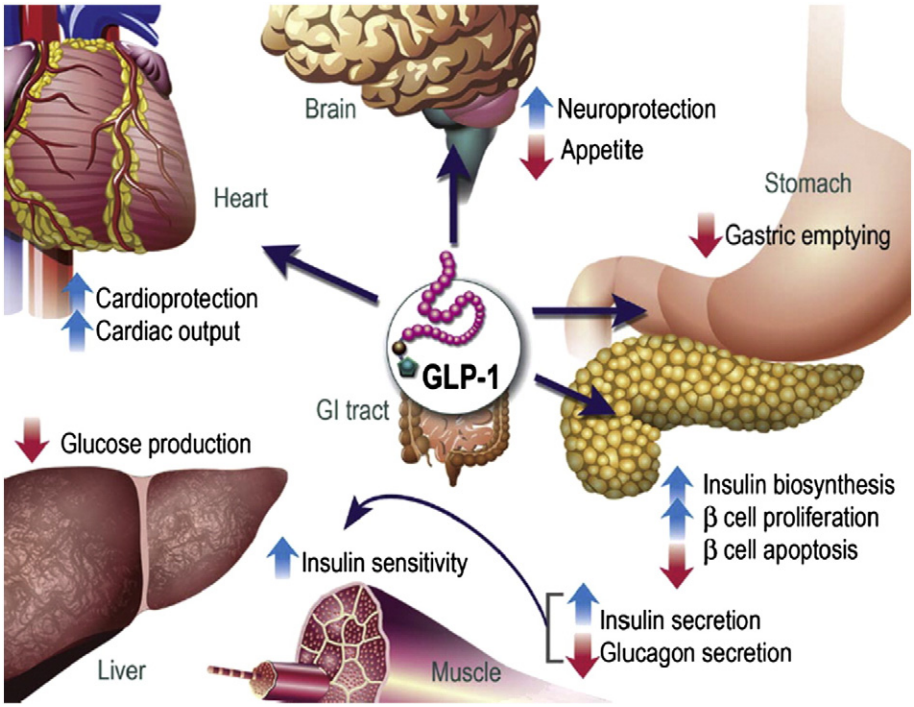

Fig. 3. Actions of GLP-1 (Reprinted from [48] with permission from Elsevier).

studies in rodents, dogs and monkeys [66]. Furthermore, in a large study based on 138 nonhuman primates, no histopathological changes were observed in the pancreas associated with liraglutide or semaglutide, two structurally different GLP-1 receptor agonists [67]. Analyses of health insurance databases showed no increased pancreatitis risk in patients treated with sitagliptin or exenatide compared to patients treated with metformin or glyburide [68], given the fact that patients with type 2 diabetes show an increased pancreatitis risk in general [69]. Recent large meta-analyses did not show an increased pancreatitis risk for patients on DPP-4 inhibitors [70,71]. In summary, DPP-4 inhibitors are now seen as safe with regard to acute pancreatitis although physicians should be aware of this potential complication.

However, uncertainty remains regarding the question of the pancreatic and thyroid cancer risk conferred by incretin-based therapies since sufficient long-term data on these complications are not available, yet, especially not for patients under immunosuppressive therapy [72,73].

3.3. Cardiovascular events

Cardiovascular mortality is the major threat to the lives of patients with type 2 diabetes, and this threat is even augmented in patients with PTDM [74–76], moving the cardiovascular effects of anti-diabetic drugs increasingly into the centre of attention. Ideally, an anti-diabetic drug used in renal transplant recipients, who represent a cardiovascular high-risk population *per se*, should offer not only good glycaemic control but also favorable cardiovascular effects. In animal models GLP-1 has shown positive pleiotropic effects on myocardial remodelling and myocardial cytoprotection [77]. In addition, DPP-4 inhibitors have several non-incretin substrates and therefore have an immunomodulatory activity that holds promise for cardiovascular protection [78]. *In vitro* and *in vivo* experiments showed that DPP-4 inhibition plays a pivotal role in endothelial growth and may have a potential role in the recovery of local circulation following diabetic vascular complications [79]. There is, however, also experimental evidence that suggests negative cardiovascular effects of DPP-4 inhibition. Ayaori et al. showed that DPP-4 inhibition attenuated endothelial function as evaluated by flow-mediated vasodilatation in T2DM patients [80]. Whether these properties translate into relevant clinical effects is not clear, yet. Two recent large clinical trials examined the cardiovascular outcomes in type 2 diabetes patients treated with the DPP-4 inhibitors saxagliptin (SAVOR-TIMI 53 trial) and alogliptin (EXAMINE trial) [81,82]. Taken together both studies did not find a significant effect of DPP-4 inhibitors on cardiovascular outcomes, indicating that these compounds at least do not have negative effects on macrovascular endpoints but positive effects could also not be shown. In the SAVOR-TIMI 53 trial there were significantly more hospital admissions for heart failure in the saxagliptin arm compared to placebo. A subsequent meta-analysis suggested that DPP-4 inhibitors in general could be associated with an increased risk for heart failure but it was not clear which group of patients was at risk in particular [85].

In contrast, it has recently been shown that intravenous GLP-1 treatment (exenatide) during acute ST-segment elevation myocardial infarction resulted in an increased salvage index both among patients with normoglycaemia and hyperglycaemia, indicating that cardioprotection by exenatide treatment might be independent of glucose levels [86]. In direct comparison with sulfonylureas, a meta-analysis of randomised clinical trials showed that DPP-4 inhibitors were associated with 21% less total adverse events and even 47% less cardiovascular events but worse glycaemic control compared to sulfonylureas [85]. Results from two large studies testing linagliptin (CAROLINA trial) and sitagliptin (TECOS trial) with primary cardiovascular endpoints are awaited in the near future which will hopefully shed more light on the cardiovascular effects of DPP-4 inhibitors.

Table 1
Daily dosage of dipeptidyl peptidase-4 inhibitors, by glomerular filtration rate.

	European Medical Association			*US Food & Drug Administration*
	GFR ≥ 30	GFR < 30	Dialysis	
Alogliptin	25 mg	12.5 mg	6.25 mg	Dosage as in Europe
Linagliptin	5 mg	5 mg	5 mg	Dosage as in Europe
Saxagliptin	5 mg	2.5 mg	2.5 mg	Dosage as in Europe
Sitagliptin	100 mg	25–50 mg	25 mg	Dosage as in Europe
Vildagliptin	100 mg	50 mg	50 mg	Not approved

Abbreviations: GFR = glomerular filtration rate (in ml/min/m^2); US = United States; mg = milligram.
Sources: http://www.ema.europe.eu/, www.drugs.com.

3.4. Immune-mediated adverse reactions

DPP-4 inhibitors display several immunomodulatory functions such as interference with T-cell responses, activation of regulatory T-cells, changes in lymphocyte subpopulations and inhibition of IL-17 production [86,87]. Treatment with DPP-4 inhibitors increased the risk for distinct infections, especially nasopharyngitis and urinary tract infections [57]. Although the risk is low, these side-effects may be relevant in renal transplant recipients who are already at an increased risk for infections. Urinary tract infections, viral infections and respiratory tract infections are common after renal transplantation and factors that further increase this risk should therefore be avoided [88].

Skin reactions, some of them severe, have been shown to occur in patients treated with DPP-4 inhibitors [89], most probably because the enzyme DPP-4 is also expressed in the skin. Decreased levels of DPP-4 have been shown to correlate with disease severity of autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematodes, inflammatory bowel disease and ANCA-associated vasculitides [90]. Several cases of bullous pemphigoid in patients receiving DPP-4 inhibitors have been described, perhaps explained by enhanced activation of eosinophils by DPP-4 inhibitors [91]. Although these events are rare they may indicate that there are still many effects of DPP-4 inhibitors that are poorly understood and could still posit a safety risk.

There are several reasons why DPP-4 inhibitors are promising candidates for the treatment of PTDM, such as their (*in vitro*) ability to improve β cell function, possibly by blocking apoptosis or activation-induced cell death caused by high doses of immunosuppressants, their low risk for causing hypoglycaemia and their low potential for interactions with immunosuppressive therapies. This may explain why most of the few studies on the efficacy of antidiabetics after renal transplantation have been conducted using DPP-4 inhibitors. There are two prospective studies using vildagliptin in renal transplant recipients. One study compared pioglitazone vs. vildagliptin vs. placebo in patients with impaired glucose tolerance after transplantation and showed an improvement in HbA1c for pioglitazone and vildagliptin after three months of treatment, compared to placebo [92]. The other study compared vildagliptin vs. placebo in patients with overt PTDM and found a significant reduction in 2-h glucose and HbA1c after 3 months compared to placebo even after a wash-out period of 4 weeks indicating the robustness of the antidiabetic effect [93]. Both studies were of short duration and small sample-size, but can serve as proof-of principle that DPP-4 inhibition leads to a reduction in HbA1c in renal transplant recipients. Three studies assessed the efficacy of sitagliptin in PTDM patients. Boerner et al. retrospectively analysed 22 PTDM patients who received sitagliptin and found no adverse effects of sitagliptin after treatment durations beyond one year [94]. HbA1c improved in most sitagliptin treated patients but no comparator was used. Two studies prospectively examined sitagliptin: Lane et al. treated 15 PTDM patients for three months (no comparator) with the primary aim to demonstrate safety of sitagliptin in PTDM patients [95]. No influences on immunosuppressive drug levels were observed, and no negative effects on renal function, while HbA1c was reduced compared to baseline. Strøm Halden et al. treated 19 PTDM patients for 4 weeks with sitagliptin and compared the treatment phase to a treatment-free period using a cross-over design. Sitagliptin treatment improved insulin secretion, 2-h glucose and microvascular endothelial function [96]. However, the available trials using sitagliptin showed even smaller sample sizes, were very short in duration and were not placebo-controlled making the evaluation of its efficacy difficult. Linagliptin was assessed in one retrospective study with 12 PTDM patients and the follow-up time was 24 weeks [97]. HbA1c levels decreased and tacrolimus levels were not influenced, however, no comparator was used.

Taken together, the evidence from randomised controlled trials testing the efficacy of DPP-4 inhibition in PTDM is limited but several pilot studies suggest that DPP-4 inhibitors are safe and show positive short-term effects on HbA1c and other measures of glucose control quality.

4. Metformin

Chemically, metformin belongs to the group of biguanides that are derived from the plant *Galega officinalis* (French lilac). Metformin has been in clinical use since the late 1950s although approval by the Food and Drug Administration (FDA) was granted as late as 1994. It is now the most widely prescribed antidiabetic drug in the world serving as first-line agent in patients with type 2 diabetes mellitus who did not reach their HbA1c target with life-style modifications alone [98,99]. Metformin has been shown to reduce macrovascular complications in type 2 diabetes mellitus without leading to weight gain or hypoglycaemia [100]. In addition, metformin has anti-neoplastic properties, at least *in vitro*, is cost-effective and can help to attenuate the metabolic syndrome [101–103]. In addition, metformin carries a low risk for pharmacological interactions with other drugs such as calcineurin inhibitors. All these features would make it the perfect drug also for the treatment of PTDM but the use of metformin is counter-indicated in kidney disease, despite country-specific differences regarding the threshold of acceptable kidney function. In the US metformin is not recommended with serum creatinine levels ≥ 1.5 mg/dL in males and ≥ 1.4 mg/dL in females. In Canada and many European countries metformin use is not recommended below a creatinine clearance of 60 ml/min. Impaired kidney function is a risk factor for the most-feared complication of metformin therapy: lactic acidosis (LA). LA is a rare but serious complication with a fatal outcome in approximately 25% of cases [104]. However, the role of metformin in the development of LA has been debated during the last years and there might even be a protective effect of metformin against LA as long as metformin is not overdosed [30]. In a large Cochrane systematic review analysing 347 trials with >70,000 patient-years of metformin treatment, no cases of LA were identified. There were also no significant differences in blood lactate levels in metformin treated patients compared to placebo or non-biguanide treatments [105]. Diabetes *per se* represents a risk factor for LA and lactate levels in patients taking metformin may be no greater than in the general diabetic population [106]. Bodmer et al. showed a higher incidence of LA in patients taking sulfonylureas than in patients on metformin (4.8 vs 3.3 cases per 100,000 person-years) [107]. No increased LA incidence was observed in patients with elevated serum creatinine levels in the range from 1.5 to 2.5 mg/dL [108]. In a large Korean analysis of almost 2000 patients with type 2 diabetes mellitus, conditions of tissue hypoxia such as sepsis, major bleeding or shock were associated with hyperlactataemia or LA, but not with metformin therapy [109]. Clinical practice shows that many physicians prescribe metformin despite impaired kidney function. 4.5% of patients in a primary care setting in the US received metformin despite serum creatinine levels above 1.5 mg/dl (in men) or 1.4 mg/dL (in women). 18% of females and 13% of males had eGFR levels below 60 ml/min/1.73 m^{-2} [110]. Similar results came from the National Health and Nutrition Examination Survey (NHANES) 1999–2006 showing that 15% of metformin treated patients had an eGFR <60 ml/min/1.73 m^{-2}; some even had eGFRs well below 50 ml/min/1.73 m^{-2} [111].

However, metformin clearance significantly drops at an eGFR <30 ml/min/1.73 m^{-2} and metformin should not be used in this setting due to the risk of overdosing [112]. Although some small studies reported that metformin has also been safely used in dialysis patients [113,114] the available evidence does not allow for a general recommendation of metformin in patients with end-stage renal disease. Kurian et al. retrospectively analysed 32 kidney transplant recipients with PTDM (n = 21) or pre-existing DM (n = 11) who were treated with metformin for a mean duration of 16 months [115]. Treatment appeared safe, but there was a significant reduction in GFR in metformin treated patients with pre-existing diabetes mellitus during follow-up.

In light of the above mentioned evidence Lipska et al. proposed to modify the traditional dosing recommendations in mild-to-moderate renal insufficiency [116]: according to this proposal metformin should be prescribed with caution in those patients who are at risk of sudden

deterioration of kidney function and at risk of an estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2. These recommendations are summarised in Table 2. The recommendation also stresses the importance to exhibit caution in patients at risk for acute kidney injury or with anticipated fluctuations in renal status based on previous history, other comorbidities or potentially interacting medications. These additional recommendations are of particular importance for kidney transplant recipients since these patients show stronger fluctuations in kidney function and usually have a large number of comorbidities and thus a high level of caution is warranted in general. The increased rate of infectious complications in kidney transplant recipients also adds the to risk of acute kidney injury [88]. Probably due to these concerns no randomised trials have been conducted to date using metformin in patients with PTDM. Such trials would, however, be highly desirable since use of metformin is associated with reduced mortality in patients with an eGFR of 30 to 60 ml/min/1.73 m^{-2} [117] and therefore many kidney transplant recipients with PTDM could potentially benefit from metformin treatment if used with caution.

5. Glitazones

Glitazones or thiazolidinediones including rosiglitazone and pioglitazone can be used in patients with glomerular filtration rates below 30 ml/min. They act via modulation of the peroxisome proliferator-activated receptor γ (PPAR- γ) thereby improving glucose metabolism by acting as insulin sensitisers [118]. PPAR-γ activation increases insulin sensitivity in several tissues including muscle, fat and liver and leads to reduced levels of free fatty acids. In type 2 diabetes mellitus glitazones have been shown to produce a more durable glucose-lowering effect as sulfonyl ureas [23], still they are probably the most debated class of oral antihyperglycaemic agents at the moment. This is due to several unwanted side-effects which came to attention during the last years. For rosiglitazone there were doubts regarding its cardiovascular safety and rosiglitazone was therefore withdrawn from sale in Europe in 2010 but is still on the market in the US. The remaining thiazolidinedione pioglitazone can cause weight gain, congestive heart failure, bone fractures, macular edema, and possibly bladder cancer [119]. On the other hand pioglitazone carries a low risk for causing hypoglycaemia and has even shown to exhibit cardio-protective effects and may protect against cancers of the gastrointestinal tract [120]. Its use in type 2 diabetes mellitus has declined due to the above mentioned safety concerns but glitazones are still the only drugs on the market that exhibit an insulin-sensitising effect which is desirable in patients who show a high degree of insulin resistance.

Glitazone use is associated with a significant reduction of albuminuria in diabetic nephropathy and can help to ameliorate GFR decline in diabetic patients [121,122]. In the Diabetes Reduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial 5269 type 2 diabetic patients were treated with either ramipril or rosiglitazone with a composite cardio-renal and CVD endpoint after three years of treatment. While both compounds were not able to affect the primary outcome, rosiglitazone, but not ramipril, improved the renal outcome, but also increased the risk of heart failure [123]. In a *post hoc* analysis of data from the PROactive study, on the other hand, no positive effect of pioglitazone on GFR was detected making a clear statement on the renal effects of glitazones difficult [124]. There is further no clear role for glitazones in end-stage renal disease (ESRD), because there are conflicting results regarding their cardiovascular safety in dialysis patients, especially when using rosiglitazone [125,126]. The increased bone fracture risk under glitazone therapy is also relevant in CKD patients because this group of patients regularly suffers from severe osteodystrophy that, although distinct from classical osteoporosis, is also associated with increased bone fracture rates. Thereby, glitazones might pose an additional risk for bone fractures in patients who are already at an elevated risk for this complication. Interestingly, glitazone treatment doubles the risk for fractures in women with type 2 diabetes mellitus but not in men, arguing against the use of glitazones in women with pre-existing bone disorders [127].

Glitazones exhibit favorable pharmacokinetic profiles for the treatment of kidney transplant recipients, because they show no significant liver toxicity and they do not interact with CYP3A4 which is responsible for calcineurin inhibitor metabolism. There is, however, a case-report on a potential interaction between rosiglitazone and mycophenolate mofetil (MPA) resulting in significantly elevated MPA levels [128]. For pioglitazone no such interactions have been described.

There are several small studies assessing the effectiveness of glitazones in KTRs. Baldwin et al. analysed 11 kidney transplant recipients with pre-existing type 2 diabetes and 7 recipients with PTDM who were treated with rosiglitazone for a duration of up to 2 years [129]. No negative effects on renal function or calcineurin inhibitor levels were observed and HbA1c was significantly improved after rosiglitazone therapy in all 18 patients. In insulin-dependent patients the addition of rosiglitazone therapy allowed for a significant reduction of insulin doses. As a consequence of these findings Villanueva and Baldwin prospectively treated 40 PTDM patients (32 liver, 8 kidney transplanted) with rosiglitazone for 12 months. Rosiglitazone was safe and effective allowing for discontinuation of insulin therapy in more than 90% of patients [130]. This study, however, had no control-population and consisted of a combination of liver and kidney transplant recipients who usually have different immunosuppressive regimens. Han et al. assigned 83 kidney transplant recipients without diabetes to either pioglitazone or no treatment and could show that after 1 year of treatment carotid intima–media thickness and insulin sensitivity were significantly improved in the pioglitazone group [131]. Although this study did not assess PTDM it still points out positive metabolic effects of pioglitazone in KTRs. Similar results were obtained by Voytovich et al. who treated 10 glucose intolerant kidney transplant recipients with rosiglitazone for only 4 weeks resulting in an improved glucose disposal rate and improved endothelial function [132]. In another uncontrolled observational study Pietruck et al. analysed 22 kidney transplant recipients with PTDM who had been treated with rosiglitazone and followed for at least 44 days [133]. 16 of the 22 patients showed positive results of the rosiglitazone treatment with improvements in fasting plasma glucose. Six patients did not show significant improvements after treatment and one patient stopped the medication after 5 days due to edema. No negative influences on kidney function or CNI levels were observed. Kurian et al. retrospectively followed 46 KTRs (33 PTDM, 13 pre-existing type 2 diabetes) who received glitazone therapy for a mean duration of 37 months [115]. No effect on HbA1c levels was observed but also no concerns regarding safety were raised, especially no cardiovascular events were recorded. We performed a randomised controlled trial assessing the efficacy of pioglitazone in stable KTRs with impaired glucose tolerance [92] showing that pioglitazone was effective in reducing HbA1c levels compared to placebo. In a rat renal transplantation model glitazone treatment showed anti-fibrotic and anti-inflammatory effects and thereby inhibited chronic allograft damage [134].

Table 2
Dosing recommendations for metformin based on eGFR.

eGFR level (mL/min/1.73 m^2)	Action
≥60	no renal contraindication to metformin
<60 and ≥ 45	continue use increase monitoring of renal function
<45 and ≥ 30	prescribe metformin with caution use lower dose (e.g. half-maximal dose) closely monitor renal function do not start new patients on metformin
<30	stop metformin

Additional caution is required in patients at risk for acute kidney injury or with anticipated fluctuations in renal status. Since this holds true for kidney transplant recipients in general a high level of caution is warranted. (adapted from [116]).

Taken together, pioglitazone is still an attractive oral antidiabetic agent but also carries its specific risks as all other antidiabetic agents do, too. Results from the PROactive study show that pioglitazone may even have positive cardiovascular effects in patients with CKD [135] and cardiovascular events are still the main reason for death after kidney transplantation. Its calculated use in PTDM may help to prolong patient and graft survival.

6. Conclusion

Improving long-term outcomes of kidney transplantation is the major challenge of transplantation medicine today and reducing the rate of cardiovascular events in this particularly vulnerable population represents a major goal. PTDM is an important contributor to mortality in kidney transplanted patients, and effective management of this comorbidity could therefore lead to a profound improvement in long-term outcomes after kidney transplantation. Although evidence from prospective trials for the treatment of PTDM is still very limited, some basic recommendations can be given at this point. Insulin therapy in the early post-operative phase might have a beneficial effect on long-term PTDM development through β cell protection [29]. Beyond the early post-operative phase oral antihyperglycaemic agents might be preferable (except for patients with very high glucose levels). DPP-4 inhibitors are highly attractive for use in PTDM due to their unique molecular mode of action directly targeting the β cell. Several members of this class such as linagliptin and vildagliptin can be used even in severely impaired renal function, they have shown clinical efficacy in small studies and no safety concerns have been raised in kidney transplant recipients so far, although the increased pancreatitis risk should be borne in mind.

Glitazones, especially pioglitazone, also hold some promise for treatment of PTDM in selected patients. Their unique insulin-sensitising mechanism can help to counteract the metabolic syndrome present in some patients with PTDM and pioglitazone may even have cardioprotective properties. The main drawback is their suboptimal side effect profile including the increased risk of bone fractures in elderly women and the increased bladder cancer risk. Metformin is considered as first-line therapy in type 2 diabetes mellitus but its use in PTDM has been regarded as unsafe by many due to the alleged risk of lactic acidosis. Newer evidence suggests that this risk has been overestimated in the past and tissue hypoxia rather than metformin is the primary cause of lactic acidosis. Still, any overdosing of metformin in patients with impaired renal function has to be strictly avoided leading to the suggestion that metformin can be safely used until an eGFR of 45 ml/min/1.73 m^2. Between 30 and 45 ml/min/1.73 m^2 a dose reduction is necessary and metformin should not be used below an eGFR of 30 ml/min/1.73 m^2. In addition patients have to be educated to pause metformin therapy in situations with increased risk of sudden deterioration of kidney function such as infection probably reserving metformin therapy for patients with stable graft function and a high level of compliance. Besides this safety issue, metformin could be of great value in PTDM due to its cardioprotective and anti-neoplastic properties.

Taken together there are several promising approaches for the pharmacological therapy of PTDM taking the pathophysiological characteristics of PTDM into account. Future research should focus on long-term cardiovascular and safety outcomes of these strategies in order to be able to make definitive recommendations for clinical practice.

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