Transplantation Reviews 29 (2015) 145–153

Contents lists available at ScienceDirect

Transplantation Reviews

journal homepage: www.elsevier.com/locate/trre

Antidiabetic therapy in post kidney transplantation diabetes mellitus

Johannes Werzowa [a,*], Marcus Säemann [a], Michael Haidinger [a], Michael Krebs [b], Manfred Hecking [a]

[a] Department of Medicine 3, Division of Nephrology and Dialysis, Medical University of Vienna, Austria
[b] Department of Medicine 3, Division of Endocrinology and Metabolism, Medical University of Vienna, Austria

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-

* Corresponding author at: Medical University of Vienna, Department of Medicine 3, Division of Nephrology and Dialysis, Währinger Gürtel 18-20, A-1090 Vienna, Austria. Tel.: +43 1 40400 43910; fax: +43 1 40400 43920.
E-mail address: Johannes.werzowa@meduniwien.ac.at (J. Werzowa).

http://dx.doi.org/10.1016/j.trre.2015.01.001
0955-470X/

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