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Thiazolidinediones in the treatment of patients with Post-Transplant-Hyperglycemia or new-onset diabetes mellitus after renal transplantation (NODAT) – A new therapeutic option?

Background

Metabolic derangements including new-onset diabetes after transplantation (NODAT) or transplant-associated hyperglycemia (TAH) are common after solid organ transplantation. In the fist year after kidney transplantation the incidence of diabetes is increased by two- to three-fold and disturbed glucose metabolism is observed in the vast majority of patients in the fist week after transplantation [1, 2]. While advances in the quality and quantity of immunosuppressive drugs have been made over the recent decades, no specific therapeutic regimens have been developed for the treatment of TAH/NODAT. Diabetes after transplantation constitutes a major risk factor for cardiovascular disease and is strongly associated not only with excessive morbidity and mortality but also with inferior graft survival [3]. While graft survival rates have steadily improved over time mainly through advancements of immunosuppressive therapy, further progress in the fields of solid organ transplantation can only be expected, if modifiable risk factors can be positively influenced. As the majority of registry data indicate that TAH/NODAT is a relevant and common condition in a significant proportion of transplant patients, it seems prudent to suggest that prevention and/or adequate treatment of this metabolic disorder holds the promise to further improve the success of transplantation as both graft and patient survival might be positively affected by such measures.

The selection of antihyperglycemic agents can be based on their effectiveness in lowering glucose, extraglycemic effects that may reduce long-term complications, safety profiles, tolerability, ease of use, and expense. Unfortunately, even in the field of type 2 diabetes the lack of clinical trials that directly compare different treatment regimens makes it difficult to recommend one class of drugs over another [4]. Because of the increased risks of side-effects including hypoglycemia secondary to drug accumulation and lactate acidosis in the case of metformin most glucose lowering drugs are contraindicated in patients with impaired renal function. Thiazolidinediones (TZDs or glitazones) belong to the few orally available drugs that are approved for patients with glomerular filtration rates below 30 ml/min. Therefore, the current perspective is intended to review the current data on this class of antihyperglycemic agents and to discuss the potential roles of TZDs in the treatment of TAH/NODAT after renal transplantation.

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Mechanisms of action

TZD are peroxisome proliferator–activated receptor (PPAR-gamma) – modulators. PPAR gamma activation triggers adipocyte differentiation and adipose tissue remodeling. TZDs improve glucose metabolism by acting as insulin sensitizers [5]. PPAR gamma activation increases the sensitivity of insulin sensitive tissues including muscle, fat, and liver to endogenous and exogenous insulin likely by changes in circulating concentrations of adipocyte-derived non-esterified fatty acids and peptide hormones. A redistribution of toxic lipid metabolites from peripheral organs to adipose tissue has been observed [6]. This is associated with an increase in largely subcutaneous adiposity. Additionally TZDs might improve glucose homeostasis independently from adipose tissue actions by the direct interaction with muscle and liver [7].

Clinical experiences in the treatment of patients with type 2 diabetes

When used as monotherapy TZDs have demonstrated an effectiveness in glucose lowering of ~1% point decrease in HbA1c [4]. Especially when compared with sulfonylureas, TZDs have been shown to have a more durable effect on glycemia by maintaining long-term glycemic control over 4 years of follow-up [8]. The most common adverse effects with TZDs are weight gain and fluid retention leading to peripheral edema and a twofold increased risk for congestive heart failure [9]. Currently pioglitazone and rosiglitazone are approved for the treatment of type 2 diabetes. Beyond mere antihyperglycemic actions, several putative beneficial effects have been proposed to be exerted by TZDs such as nephroprotective effects (see below) [10]. The PROactive-study demonstrated no significant effects of pioglitazone compared with placebo on the primary cardiovascular disease outcome. However, after 3 years of

follow-up pioglitazone reduced the composite secondary end point of all-cause mortality, non-fatal myocardial infarction, and stroke in patients with type 2 diabetes that had a high risk of macrovascular events by 16% [11]. Furthermore, based on data from the PROactive study Schneider et al. indicated that pioglitazone significantly lowered cardiovascular events also in patients with reduced eGFR [12]. In contrast to a previously published meta-analysis that suggested an increased incidence of myocardial infarction associated with rosiglitazone [13] the randomized RECORD study has demonstrated no increased risk of overall cardiovascular morbidity or mortality compared with standard glucose-lowering drugs [14]. A continuous concern is an ~30% increased incidence in predominantly peripheral fractures in women and perhaps men [15]. Women more than 65 years of age appear to be at greatest risk for fracture with a ~70% increased risk [16].

TZDs in chronic kidney disease (CKD): experimental data

Several experimental and small clinical studies indicated possible beneficial effects of TZDs on various forms of chronic renal insufficiency apart from their anti-hyperglycemic effects [17]. In the Zucker obese rat fed with high-protein diet, an experimental model of the human metabolic syndrome, pioglitazone was able to foster the antihypertensive as well as the antiproteinuric effects of candesartan [18]. Interestingly, histological analysis revealed less interstitial fibrosis in the affected kidneys in TZD-treated animals. Several preliminary studies indicated that TZDs may be especially effective against diabetic nephropathy by reducing microalbuminuria. When appropriate mouse models were employed, TZDs were not only effective in preventing the gradual rise in albuminuria observed in control mice, but e.g. rosiglitazone while not affecting glucose metabolism, prevented the typical podocyte loss and protein oxidation products and glomerular fibronectin accumulation seen after several weeks of disease initiation [19]. Interestingly, Ohtomo et al. demonstrated that one of the pleiotropic effects of TZDs that may account for its beneficial effects in models of diabetic nephropathy may reside in its capability to suppress TGF-beta expression as main driving force of fibrogenesis [20]. Raphael et al. recently demonstrated that pioglitazone exerted remarkable effects in a genetic model of polycystic kidney disease (PCKD), where TZD treatment was associated with a better survival of the affected animals, while direct effects on cyst formation could not be observed [21]. Specifically, PCKD mice treated with pioglitazone displayed a better arterial blood pressure indicating unique antihypertensive effects in polycystic kidney disease. These data indicate that indeed TZD may have direct effects on the distinct renal tissue components possibly associated with amelioration of renal disease.

Studies in animals suggest that TZDs might ameliorate toxic effects of immunosuppressants. A fascinating molecular mode to explain the efficiency of TZDs in post-transplant diabetes beyond affecting insulin resistance was very recently proposed by Kim et al. who could demonstrate that rosiglitazone was also able to affect the direct beta-cell toxic effects of CsA by altering typical cellular stress markers and finally beta-cell apoptosis [22]. Furthermore, the use of rosiglitazone antagonized the sirolimus-induced tubular wasting of magnesium and potassium in a murine model implicating the clinical use of TZDs when attenuating one of the typical side-effects of rapamycin as an immunosuppressant is considered [23]. These data further reinforce the potent effects of TZD on the renal tubular system also apart from its effects on sodium handling in both the proximal and distal tubuli. The combined use of both substances might further be conceivable, as mTOR-inhibitors like sirolimus are associated with an increased incidence of PTDM/NODAT possibly by decreasing insulin sensitivity [24].

TZDs in diabetic patients with advanced renal disease: registry data and clinical studies

When it comes to effects in renal insufficiency patients, several registry data and subgroup analyses from larger studies and also the various stages of renal insufficiency have to be considered. A recent meta-analysis addressed the relevance of TZD in affecting albuminuria in diabetic nephropathy [25]. Retrieving over 15 studies comprising 2860 patients it was concluded that TZD use was associated with a significant decrease in proteinuria in patients with diabetes. A recent prospective trial in Korea studying the effect of rosiglitazone on the GFR decline in type 2 diabetic patients found a significant amelioration in the decline in GFR by the TZD [26]. Similarly, Trivedi et al. observed such effects in a cohort of 114 diabetic patients treated with rosiglitazone [27]. The Diabetes Reduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial assessed 5269 patients in type 2 diabetic patients treated with either ramipril or rosiglitazone on a composite cardiorenal and CVD outcome after three years of treatment [28]. While both compounds were not able to affect the primary outcome, rosiglitazone, but not ramipril, reduced the risk of renal disease independent of its hyperglycemic effect.

In contrast, a very recent retrospective cohort study in type 2 diabetics analyzing 5666 patients found an association between an accelerated decline of renal function and rosiglitazone use (67.7 ml/min/1.73 m^2 *vs.* 73.8 ml/min/1.73 m^2) [29]. In a recent analysis of the PROactive study Schneider et al. found a more rapid decline in GFR (1.8 ml/min/yr *vs.* 0.9 ml/min/yr) in the TZD-treated group, which was significant, although the overall GFR decline was modest [12]. Furthermore, no difference between the urinary albumin excretion rates between both groups could be observed. This observation is in contrast to several smaller studies suggesting potent renoprotection by TZDs. Hence these smaller studies were ambiguous or the cohort in this study behaved differently in some other way. Also pioglitazone might also have caused a true deterioration of renal function, although compensating the cardiovascular risk by some other distinct mechanisms.

Given its anti-inflammatory potential, efficiency against glucose metabolic disturbances and its favorable pharma-

cokinetic advantages, TZD could an interesting option in patients with CKD stage V. However, data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) calculated for a follow-up period of 1.1 years from 2393 long-term hemodialysis patients with type 2 diabetes revealed that the prescription of rosiglitazone was associated with a significantly higher all-cause (hazard ratio 1.38) and cardiovascular mortality (hazard ratio 1.59) [30]. Especially concerning was a 3.5-fold increase of hospitalizations due to myocardial infarction. Further analysis of this specific registry with pioglitazone in hemodialysis patients is eagerly awaited. In contrast, Brunelli et al. studied the effect of TZD use on overall survival among chronic dialysis patients in a national cohort of 5290 incident dialysis patients with type-2 diabetes and observed a lower incidence of all-cause mortality in subjects not on insulin versus insulin-requiring diabetic patients [31].

The data obtained from these large registries of hemodialysis patients are hypothesis generating and obviously need further study within carefully controlled prospective trials with TZDs in this unique population. As mortality in these patients is the consequence of a conundrum of competing causes and the overall prognosis still remains poor, such trials will have to incorporate a large number of patients to avoid under-powering of the results. Nevertheless, the visibility of data as those retrieved from the DOPPS registry should remind us that we should be cautious in the imprudent use of TZDs in patients with CKD stage V.

Finally, those patients regularly suffer from severe osteodystrophy that is distinct from classical osteoporosis but also associated with increased fracture rates. Furthermore, diabetics at this stage of disease regularly display microangiopathy also affecting bone tissue. These mechanisms together with the dialysis-inherent dysregulation of PTH, phosphorus and calcium metabolism often culminates in a dangerous low-turnover osteodystrophy. As TZDs are at least associated with a significantly increased risk of fractures in diabetic patients, further caution should be emphasized regarding the use of TZD in diabetics with severe renal insufficiency.

Effectiveness of TZDs in PTDM/NODAT

Regarding the treatment of renal transplant patients, both newer TZDs may seem suited with regard to their pharmacokinetic profile, since they do not exhibit significant liver toxicity, both are metabolized via CYP-2C8 and there is no known induction of CYP3A4 minimizing the possibility to interact with calcineurin inhibitor metabolism. However, results from the Bergamo group indicated that there might exist a relevant pharmacokinetic and pharmacodynamic interaction between rosiglitazone and mycophenolate mofetil (MPA), as significantly higher levels of MPA were observed under concomitant TZD use that may also have resulted in profound anemia in a renal transplant patient [32].

Initial small studies with TZDs in renal transplant patients by Baldwin and Duffin patients with pre-existing diabetes ($n=11$) and PTDM ($n=7$) were primarily treated with rosiglitazone in addition to insulin or glyburide from 133 to 718 days [33]. In principal, TZD use was safe in this small cohort as no effects on calcineurin inhibitor (CNI) levels and serum-creatinine was observed. Moreover TZDs were effective, since the mean HbA1c improved from 8.1% to 6.9%. Overall, a remarkable reduction of the exogenous insulin dose was observed and all patients were relatively well-controlled regarding their glucose homeostasis independent of their antidiabetic comedication. As a follow-up investigation, Villanueva and Baldwin prospectively assessed rosiglitazone in a cohort of PTDM patients during a 12-month period of time in both liver and renal transplant patients [34]. PTDM was diagnosed according to ADA standard criteria and 40 patients were included at a rather early time point after transplantation (inpatient and up to 4 weeks post transplantation). Initial treatment was done with insulin and/or sulfonylurea and rosiglitazone was added on top- and insulin was tapered when possible. Again the overall HbA1c could be significantly reduced reflecting antihyperglycemic potency in the patient cohort. Again no significant influence on CNI levels was observed, however, in most patients as a part of the centre-specific strategy CNI levels were minimized as possible and steroids were completely tapered off (39%). Also a significant percentage of patients were still on sulfonylureas and only about 30% of patients could be managed by a rosiglitazone monotherapy. Nevertheless, in about 91% of insulin-dependent patients exogenous insulin could be completely withdrawn upon up-titration of rosiglitazone. A major limitation of this study was the lack of any control group and the mixture of renal and liver transplant patients requiring different amounts of immunosuppression; this is important to recognize, because PTDM/NODAT is well-known to behave in a reversible manner, hence a substantial portion of patients especially as they were selected after a very early phase after transplantation might have returned to a normal glucose homeostasis especially as a pronounced reduction of general immunosuppression including steroid withdrawal was enforced in this cohort. Luther and Baldwin also reported a retrospective analysis on their experience with pioglitazone in patients with PTDM [35]. While similar to the safety data obtained with rosiglitazone, pioglitazone use was not associated with any interference with immunosuppressant levels and also no direct toxicity. In this small series of patients also a decrease in insulin requirement along with a reduction of HbA1c was observed by pioglitazone (8.3% *vs.* 7.08%). As most patients received a therapy with statins a possible effect of TZDs on the lipid profile was not discernible. The main conclusion obtained from these studies as also stated by the authors, was the potential to achieve euglycemia with an oral antidiabetic therapy mostly consisting of a TZD combined with a sulfonylurea.

Formally, renal transplant patients with disturbed glucose metabolism, who were administered rosiglitazone for a period of only 4 weeks were studied with a hyperinsulinaemic euglycaemic glucose clamp leading to a significantly increased insulin sensitivity [36]. Of note, the patients had a markedly improved endothelial function even after this short treatment period. Further, Han et al.

randomized 83 patients without overt diabetes to a pioglitazone versus a placebo control group and assessed carotid intima-media thickness as marker of subclinical atherosclerosis along with insulin secretory function and insulin resistance for 12 months [37]. The pioglitazone group showed a drastic reduction in the phenotypical atherosclerosis indices along with an increase of insulin sensitivity corroborating the data by Voytovich et al. [36]. Interestingly, the authors also found an increase of the insulin secretory reserve after a relatively long follow-up period of 12 months indicating a robust and solid effect of TZD treatment on glucose homeostasis in transplant patients.

Summary and outlook

At present TZDs have an established role in the therapy of type 2 diabetic patients, especially after failure of metformin monotherapy. Results from recent large trials indicated that TZD at least do not significantly increase the overall cardiovascular mortality. As the PROactive study was able to provide evidence of a reduction of the cardiovascular outcome along with an efficient antihyperglycemic effect, glitazones are still worthy to be further studied in the various settings of diabetes mellitus. With regard to patients with CKD also the PROactive study presented data as the composite endpoint in this particular high-risk population was also significantly ameliorated by TZD use. This is in contrast to registry data in hemodialysis patients, where the use of rosiglitazone was associated with increased cardiovascular and overall mortality. Whether, pioglitazone may be preferable over rosiglitazone in patients with CKD in general remains unanswered. However, the intersection of diabetes, CKD and cardiovascular disease is dangerous and cautious prescribing of potent drugs such as TZD will be mandatory. Two eminent drug-related side effects, i.e. osteoporosis and heart failure due to water/sodium retention are especially troublesome in this regard and further pleiotropic effects of TZDs potentially negatively affecting diabetic CKD patients must be weighed consistently against the current available evidence. Renal transplant recipients may be regarded as at least CKD stage II–IV patients.

Hence many of the mortality risks found in the hemodialysis population such as inflammation, nutrient wasting, increased oxidation, dyslipidemia, etc. are reverted to some degree when the patient is transplanted, a significantly increased cardiovascular risk, however still remains. This might be the reason, why pharmacological intervention strategies known to be potent in the renal healthy population and that are ineffective in the hemodialysis population, yield at least conflicting results in renal transplant patients such as is the case with statins or ACE-I/ARBs. As the transplant community seldom can rely on large prospective, controlled trials but instead on smaller, often uncontrolled studies, further answering of an effect of TZDs on hard clinical outcomes in the renal transplant population is not to be expected.

It is our belief that novel diagnostic criteria and consequently appropriate treatment strategies have to be envisaged in this peculiar patient setting. For example, several recent data indicate that renal transplant recipients display an atypical form insulin resistance frequently peeking pre-lunch thereby precluding an accurate diabetes diagnosis by typical assessment of fasting glucose that is often normal in those patients that regularly exhibit an impaired glucose homeostasis. Finally, a substantial portion of patients will develop typical type-2 diabetes as a consequence of declining beta cell function and might be treated as if they were non-transplant patients. Hence, as is the case for non-transplanted type 2 diabetics, solid data obtained from larger studies that indicate that a particular therapeutic regimen is able to prevent the progressive decline in beta cell function is also needed for the transplant community. Currently, several smaller studies are away to address central issue in renal transplant patients also testing newer antidiabetic drugs such as DPP-4 inhibitors in comparison to TZDs in a controlled, prospective manner. It will be the task of future studies to discriminate typical type 2 diabetic patients from PTDM/NODAT patients in order to allow an individualized anti-diabetic regimen. As long as we do not have such measures, a calculated use of TZDs as one of the available tools to treat hyperglycemia in the renal transplant population can be recommended giving special attendance to potential hazardous side-effects that might be more prominent in this population, while also paying attention to possible benefits for the transplanted CKD patient including positive influences on atherosclerosis and latent inflammation and thereby possibly patient and graft survival.

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Conflict of interest

The authors declare no conflict of interest.

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