POST TRANSPLANT DIABETES MELLITUS IN SOLID ORGAN TRANSPLANTED PATIENTS

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Abstract

Solid organ transplantation (SOT) is an established treatment for patients with end-organ disease. SOT is also a life-saving procedure although kidney failure patients may survive with dialysis treatment. However, transplantation is accompanied by associated cardiovascular risk factors, and post-transplant diabetes mellitus (PTDM) is one of the most important ones. PTDM develops in 10-20% of kidney transplanted patients and in some 20-40% of other SOT patients. PTDM patients have twice as high mortality as other SOT patients at least in kidney and heart transplanted patients. PTDM is elicited both by predisposing factors as in type2 diabetes but also by specific post-transplant risk factors. Even though PTDM has many characteristics in common with type 2 diabetes, prevention and treatment is often different. SOT patients have improved their life-span over the last twenty years, and PTDM accumulates over time in these patients. Accordingly PTDM becomes and important condition not only to be aware of, but also to handle. The aim of this review is to present current knowledge on PTDM in kidney, heart, liver and lung transplant recipients, not only for transplant health providers, but also for endocrinologists and others who will meet these patients in their clinic.

Introduction

Solid organ transplantation (SOT) has become a successful treatment for organ end-stage failure. The introduction of calcineurin inhibitor (CNI) treatment and further refinement of immunosuppressive therapy have been crucial for this success along with advancements in surgical techniques and medical care. Recent registry data show that the 5-yr graft survival has reached 80 % for renal transplants (1), 70 % for liver transplants (2), up to 67 % for lung transplants (3), and 78 % for heart transplants (4). A major problem however, is that solid organ recipients are still at substantial risk for cardiovascular disease and premature death. This is partly due to a pre-transplant history of long term chronic disease, but probably also due to side effects of the immunosuppressive medication. These adverse effects include hypertension, hyperlipidemia and diabetes mellitus. Diabetes mellitus occurring after organ transplantation is an important risk factor for patient survival and occurs in 10-40 % of solid organ recipients depending on type of organ, heredity and age (5).

Diabetes mellitus diagnosed after organ transplantation was previously called New Onset Diabetes After Organ Transplantation (NODAT), but this may be a misnomer since as many as 10% have undiagnosed diabetes prior to transplantation, as found in kidney transplant recipients (6). The term post-transplant diabetes mellitus (PTDM) was consequently adopted in a recent consensus report (7). The expression PTDM refers to time of diagnosis rather than time of occurrence. We will consistently use the term PTDM in this review. PTDM is associated with premature cardiovascular disease and death in renal transplant recipients (8, 9), increased comorbidity (10, 11) and premature death in heart transplant recipients (12), and in lung transplant recipients hyperglycemia is also associated with impaired survival (13). Furthermore, cardiovascular events are more frequent in liver

transplant recipients with the metabolic syndrome (14), and cardiovascular death is increased in liver transplant patients with PTDM (15). The patients are primarily seen by nephrologists, cardiologists, gastroenterologists and lung specialists in their respective units. However, given the substantial incidence of PTDM among organ transplant recipients and the significance of the disease, at least some of the transplant physicians taking care of the patients should have some expertise in diabetes.

Prevention and treatment of PTDM depends essentially on understanding the pathogenesis and evolution of the disease. In this context it is important also to understand the role of immunosuppressive drugs which facilitate development of PTDM, and important drug-drug interactions in these patients who are typically treated with multiple pharmaceutical agents beyond immunosuppression. This review will further discuss these issues.

Diagnosis of PTDM

Studies published 15-20 years ago often used inappropriate diagnostic measures for PTDM. PTDM was diagnosed by, e.g., need of insulin treatment, introduction of any hypoglycemic agent, or at best measurement of fasting glucose. Thus, PTDM was to a large extent underdiagnosed with these measures. An international consensus report from 2003 decided to diagnose post-transplant diabetes by an oral glucose tolerance test (OGTT) performed twice according to the WHO criteria (16), and this was reinforced in a second consensus report from 2005 (17). In 2012 ADA and WHO decided that HbA1c should serve as the primary criterion to diagnose type 2 diabetes (18). However, this may not be uniformly applied for the diagnosis of PTDM (19). A quite recent consensus report agreed that HbA1c thresholds should not be used as the sole criterion for diagnosis of PTDM (7). Limitations in

using HbA1c to diagnose PTDM are due to 1) The diagnostic threshold for HbA1c in type 2 diabetes mellitus (≥6,5%, 48 mmol/mol) relates to the risk of developing diabetic retinopathy (18), which obviously is not the major concern in organ transplanted patients. 2) Mechanisms beyond hyperglycemia may compromise HbA1c assessment in the early post-transplant period. These include change in red cell turnover rate and bone marrow suppression due to immunosuppressant drugs (20). A recent meta-analysis among renal transplant patients showed that the sensitivity for diagnosing PTDM with HbA1c (OGTT being the reference) is 50% and 75%, respectively, when HbA1c threshold is set at 6,5% (48 mmol/mol) and 6,2% (44 mmol/mol), respectively (21), while specificities are 96% and 89%. The mortality risk is increased more than 2-fold among kidney transplant patients when PTDM is diagnosed by an OGTT (22) but not by HbA1c (8). Furthermore, impaired glucose tolerance (IGT) is associated with premature death to almost the same degree as PTDM in these patients (22), and IGT can only be diagnosed by an OGTT. However, the observations above are primarily made in patients two-three months after transplantation, and at a time when variations in HbA1c both within and between subjects are larger than in the general population (23). Thus, it remains to be seen whether HbA1c could be an adequate diagnostic tool in a stable phase, e.g., more than one year after transplantation. At present we recommend using glucose criteria with an OGGT to diagnose PTDM after SOT, unless fasting glucose is diagnostic. An OGTT should however not be performed before 2 months posttransplant or before doses of immunosuppressant drugs are stabilized. At our center all renal transplant patients undergo an OGTT at this time-point. However, with limited resources an OGTT could be selected for those patients who have metabolic syndrome and hypertriglyceridemia (24). Alternatively one may consider to reserve and OGTT for patients with HbA1c above 5.7% (39 mmol/mol). An OGTT in these patients will detect 90% of all

cases with PTDM by testing only half of the patients with an OGTT. This has been shown in a renal transplant Caucasian population 10 weeks after renal transplantation (25).

Pathogenesis

PTDM has over the years been considered a diagnostic entity on its own (16, 17, 26). It is evident that it shares many characteristics with type 2 diabetes, e.g., insulin resistance and decompensated insulin release, hypertriglyceridemia, obesity, hypertension and low-grade inflammation (5, 27) . Even if these characteristics are in common for PTDM and type 2 diabetes, the underlying mechanisms may be different. Impaired insulin-mediated glucose uptake in peripheral tissue in type 2 diabetes patients was shown already in the late 1980-ies (28) and is also later documented in PTDM patients (29, 30). Furthermore, impaired insulin-mediated suppression of hepatic glucose output in type 2 diabetes patients (28) was recently also confirmed in PTDM patients (30). Dysfunctional insulin release is an early sign leading to dysglycemia and type 2 diabetes (31), and is certainly also present in PTDM (26). Dysfunction in the incretin axis between gut and pancreas, which reinforces impaired beta cell function and enhances glucagon activity is an early sign in type 2 diabetes (32), and was recently also demonstrated in PTDM patients (33). Increased renal gluconeogenesis as well as increased proximal tubular sodium-glucose reabsorption is present in type 2 diabetes (34), but is not yet demonstrated in PTDM. Finally, it has for some years been known that there is a cross-talk between the brain and the systemic metabolism also regulating appetite, white fat mass and hepatic glucose output (35), which possibly may be operative also in PTDM. Side effects of immunosuppressive drugs, hypomagnesemia and viral infections are particular features in organ transplant recipients, all of these may promote glucose intolerance and PTDM. Contributing pathways that may lead to PTDM are summarized in figure 1. In the following

we present risk factors that may be relevant in the clinical evaluation of the organ transplanted patients.

Predisposing factors common with type 2 diabetes

Central obesity. The database of the European Group for the study of Insulin Resistance (EGIR), which used hyperinsulinemic, euglycemic clamp measurements in altogether 1.146 non-diabetic subjects, reported that as many as 40% of those with BMI >35 kg/m^2 were not insulin resistant (36). It seems that the localization of the fat rather than the fat mass itself is more important (37). Recent reports indicate that PTDM is strongly associated with central obesity (38, 39). Central obesity is the clinical equivalent of ectopic fat deposition, and is associated with hypertriglyceridemia, adipocyte-derived cytokine release and low-grade inflammation, all inducing insulin resistance (40). Low levels of adiponectin are associated with insulin resistance and PTDM independently of sex, age and immunosuppressive therapy (41). The less active low-molecular weight adiponectin fraction, which is associated with cardiovascular risk in Japanese patients, is also associated with PTDM (42), while beta cell function is hampered by increased levels of free fatty acids (43). Unfortunately, only one uncontrolled pilot study on life-style intervention has so far been undertaken, but it signals that such intervention including weight loss can be efficient to treat PTDM (44).

Age. The risk of developing PTDM increases substantially in renal transplant recipients older than 40 years (45). It is of interest to note that incidence of PTDM after renal transplantation shows a biphasic curve with the first peak occurring the first few months after transplantation, followed by a second surge over the next 2-3 years (fig. 2) (46). It is

tempting to speculate that the first peak relates to surgery and introduction of immunosuppressive therapy, while the second surge partly depends on age and evolution of classical diabetic risk factors on top of transplant-related risk factors.

Susceptibility genes. Genetic predisposition has over the last two decades been reported to increase the risk of type 2 diabetes, although the risk imposed by each gene itself is rather small (47). Several studies have recently reported a risk association between PTDM in kidney transplant recipients and some common SNPs, of which some are associated with beta cell apoptosis (48), ATP-sensitive potassium channels (49), adiponectin and leptin gene polymorphisms (50) and also pathways involving inflammation (51-53) and the innate immune system (54). Their relative importance for development of PTDM is however not yet settled. In any case, genetic factors in general do play a role. A family history of diabetes was already acknowledged as a risk factor for PTDM in a cohort study 20 years ago (55). Furthermore, a recent meta-analysis of patients with autosomal dominant polycystic kidney disease (ADPKD) showed that patients with this genetic defect are at significantly higher risk of PTDM after kidney transplantation than others (56). Although the incidence of PTDM among renal transplant recipients in Japan is reported to be in the same range as in Caucacians (57), ethnical predisposition may be present. In a comparative case-control study from a center in the UK it was shown that South Asians had increased risk for development of PTDM compared to Caucasian controls (58).

Inflammation. Type 2 diabetes is associated with proinflammatory pathways that may both aggravate metabolic dysfunction and facilitate long-term complications (59). It is not surprising that proinflammatory pathways seem to be upregulated also in PTDM (51-54).

TNFα mRNA expression is higher in renal transplant patients who develop PTDM, and adiponectin mRNA is lower (60). In a recent study on inflammation related biomarkers in 852 renal transplant recipients, a proinflammatory pattern involving activation of tumor necrosis factor, macrophages and endothelial cells was associated with hyperglycemia and PTDM (27).

Magnesium. Magnesium supplementation improves insulin sensitivity (61) and glycemia (61, 62) in type 2 diabetes. Hypomagnesemia associated with cyclosporine treatment was described in renal transplant recipients many years ago and is due to excess urinary excretion (63). SOT patients receiving calcineurin inhibitors (cyclosporine and tacrolimus) tend to have low plasma magnesium and particularly in renal transplant patients, where hypomagnesemia is clearly associated with PTDM (64, 65). However, oral administration of magnesium has so far not been effective in treatment of these patients (66, 67).

Who should be considered at risk pre-transplant and perform an OGTT? HbA1c measurement can be considered to replace an OGTT in patients without advanced renal failure. At our center an OGTT is routinely performed in all patients entering the waiting list for kidney transplantation to disclose glucose intolerance or pre-transplant diabetes. However, we acknowledge that this is not often feasible at different centers. As a minimum we would suggest to perform an OGGT prior to transplantation in a subset of patients with advanced renal failure: Family history of diabetes, African American (45) or South Asian (58) race , elevated fasting glucose 5.1-6.9 mmol/l (6), age >45 years (45), metabolic syndrome with hypertriglyceridemia (24), or hepatitis C infection (68, 69).

Predisposing factors specific to PTDM.

Glucocorticosteroids. Solid organ transplant recipients are exposed to large intravenous doses of methylprednisolone at surgery, followed by oral glucocorticosteroid treatment in tapering doses. Insulin release is severely reduced in experimental models with transgenic mice and beta cells sensitized for glucocorticoid action (70) but the significance of this finding is less certain in humans receiving small doses of prednisolone. However, glucocorticosteroids induce peripheral insulin resistance in the clinical setting (71), and probably also hepatic insulin resistance due to increased transcription of gluconeogenic enzymes (72). Insulin sensitivity indices as measured from an intravenous glucose tolerance test improved after withdrawal of prednisolone (at a dose of 10 mg/ day) (73). This finding is further explained by another study measuring insulin sensitivity with a state-of-the art hyperinsulinemic-euglycemic clamp technique (74). In that study insulin sensitivity improved by tapering prednisolone from 10 mg to 5 mg/day, but without any further improvement in insulin sensitivity when prednisolone was withdrawn.

CNIs (calcineurin inhibitors). Cyclosporine A (CsA) came into clinical use in 1983, and this drug expanded organ transplant programs beyond kidney transplantations into additional programs involving heart, liver, lung and intestinal transplantation (75). Tacrolimus was the second CNI that was introduced for clinical use a decade later and has gradually become the most commonly used immunosuppressive drug world-wide in solid organ transplantation. The CNIs are usually part of a triple immunosuppressive regimen involving prednisolone and a proliferation inhibitor, e.g., mycophenolate in addition to CNI.

Clinical relevant concentrations of CsA and tacrolimus inhibit insulin release after prolonged exposure in an insulin-secreting (INS-1) cell line (76). Tacrolimus is most often used in modern immunosuppressive protocols since it seems superior to prevent acute rejections (77). On the other hand, the incidence of PTDM was reported higher with use of tacrolimus compared with CsA in a randomized control trial (78), but the circulating trough levels of tacrolimus were much higher in that study than what is used today. A meta-analysis has indicated that the diabetogenic effect of tacrolimus may be dose-dependent (79), and the diabetogenic effect seems especially pronounced in predisposed patients with hypertriglyceridemia and insulin resistance (24). Calcineurin inhibitors inhibit calcineurin phosphatase activity, which prevents dephosphorylation of the cytoplasmatic calcineurin/NFAT subunit which usually translocates into the cell nucleus to start transcription of cytokines in the T-cell, and transcription of insulin and cell proliferation genes inside the beta cell (80, 81). Intraperitoneal injections of tacrolimus in rats induced diabetes by strongly inhibiting transcription of insulin genes, a finding that was reversible when treatment was stopped after 2 weeks (82). Pancreatic glucagon and α-cell number was on the other not altered in an experimental mice model with deletion of the pathway (81). A special synergism between tacrolimus and fatty acid-mediated lipotoxic effects inside the β cells may be operative, since the toxic effect in INS-1 cell is primarily seen with tacrolimus in combination with high glucose and palmitate, and less so when CsA is tested (83). To what extent CNIs may cause insulin resistance in vivo is at present uncertain.

mTorinhibitors. mTOR- inhibitors (sirolimus and everolimus) are antiproliferative drugs that also have been associated with impaired glucose metabolism. They are sometimes used as an alternative to mycophenolate or CNIs in immunosuppressive protocols. In a study from

the USRDS registry the incidence of PTDM was higher with sirolimus either combined with mycophenolate or CNIs, and especially high when combined with CNIs (84). Another study with a historical cohort consisting of renal transplant recipients switching CNIs to high-dose sirolimus (target trough levels 8-12 ng/dl) resulted in a decrease in insulin sensitivity and impaired compensatory insulin response assessed by glucose tolerance tests (85). Part of this could be explained by increase in serum triglycerides (85). Ex vivo studies indicate that mTOR inhibition may be associated with apoptosis of beta cells (86) and it also impairs beta cell proliferation (87). Sirolimus also seems to impair insulin signal transduction (88). In an experimental model with the fat sand rat P.obesus mTor inhibition with rapamycin severely inhibited insulin transcription and induced beta cell apoptosis in diabetic animals, but not in their non-diabetic littermates (89). Furthermore, insulin signaling in the liver, muscle and fat tissue was severely reduced with rapamycin in the diabetic animals because of suppressed Akt phosphorylation (89), one of the major nodes downstream of insulin receptor substrate 1 (IRS1) (90).

Figure 3 depicts pathways which may cause beta-cell dysfunction and insulin resistance with the major types of immunosuppressive agents. The combination of the different drugs adds up the risk of developing of PTDM the individual patient.

Other immunosuppressive agents. Mycophenolate acid is an antiproliferative agent, and is used as part of the commonly used triple immunosuppressive regimen together with prednisolone and a CNI. It is not reported to increase risk of PTDM. Belatacept is a more recently approved intravenous immunosuppressive drug given as intravenous monthly infusion and blocks T-cell activation by inhibiting the co-stimulatory signal. Belatacept-based

regimens do not appear to have any adverse effect on glucose metabolism and may not cause particular risk of PTDM as compared to CNI-based regimens (91).

Virus. Association between viral infections and PTDM relates primarily to hepatitis C virus (HCV) and cytomegalovirus (CMV) infections in liver and kidney transplantation. There is a 2-4 fold-fold increase in PTDM incidence among HCV infected liver recipients (68, 69) which is not easily explained. One study found an association between HCV and calculated insulin resistance based on fasting glucose and insulin measurements (HOMA index) (92). In kidney transplant recipients both HCV (93) and CMV infection (94) are associated with development of PTDM. Although reports are conflicting, the association has been confirmed in a meta-analysis (95). One may speculate whether a common denominator of the associations of virus infection and PTDM may be stimulation of a pro-inflammatory milieu (22). Unfortunately no study has been undertaken to assess a potential protective effect of increased use of antiviral treatment on the development of PTDM, but such a study would certainly be of interest in the future.

Incidence and outcomes of PTDM in SOT patients

Kidney transplantation.

Incidence of PTDM. The incidence of PTDM in kidney recipients is reported to range 10-40 % in several cohort studies, but with variable diagnostic criteria and at different point estimates after transplantation (5). In a Caucasian population using WHO based OGTT criteria the incidence of PTDM 8-10 weeks after transplantation was 20% in 1997 (55), 13% in 2006 (96) and 12% in 2011 (19), fig.4. The reason for the declining incidence is probably due to less rejection episodes, less use of methylprednisolone to reverse rejections (96) and

lower doses of CNIs. The incidence of PTDM clearly increases with age and time after transplantation (45). A 1-yr incidence of PTDM varies partly in relation to ethnicity (19, 57, 58). It is probably fair to estimate that the 1-year incidence by today is in the range of 10-20% in kidney transplant patients. Evolution of PTDM in kidney transplant recipients may have a bimodal profile before and after the first year post-transplant, which has been demonstrated a Spanish population (46).

Outcomes with PTDM. PTDM was strongly associated both with patient death and graft loss in renal transplant recipients in the US Renal Data System (97), but the database did not allow for correction of graft loss due to rejections. The high mortality risk in PTDM patients has later been confirmed in other cohorts (fig. 5a) (8, 22, 98), but graft loss is not increased in the survivors (99). Patients with post-transplant impaired glucose tolerance (IGT) seem to have the same mortality risk as patients with PTDM (22).

Heart transplantation.

Incidence of PTDM. *In a recent cohort study* of several hundred heart recipients from Korea the cumulative incidence of PTDM was 25-28% after 5 years. Fasting glucose supplied with OGTT was used for diagnosis in this study (10, 12). In a similar study from the Netherlands the incidence of PTDM after 5 years was 20% (100) and the same incidence rate was reported in a study from Spain (11). An Australian study found slightly lower incidence using only random glucose measurements for diagnosis (101). Finally, registry data from the OPTN/UNOS database reported an overall incidence of 33% (102). Also in pediatric transplantation PTDM occur at an incidence above 10% (103).

It is probably fair to estimate that the accumulated incidence of PTDM is about 20-30% in heart transplant recipients (Table 1).

Outcomes with PTDM. Obviously many factors beyond PTDM are important for survival after heart transplantation as recently reviewed (104). Several observational studies have found that recipients with a diagnosis of diabetes have a hazard ratio ranging from 1.15 to 1.62 for death within a year, but none of these studies specifically included PTDM in their analyses (104). Data from the International Society for Heart and Lung Transplantation (ISHLT) Registry revealed similar data in more than 50.000 patients (105). In the recent South-Korean study with 390 heart transplant patients PTDM was determined by OGTT (12). The risk of death was the same in patients with PTDM and pre-transplant diabetes and was 2-fold higher compared to those without diabetes (Fig. 5b) (12).

Liver transplantation.

Incidence of PTDM. Several cohort studies have reported incidence of PTDM, but none with OGTT as the diagnostic criterion. Two retrospective studies from the US reported an accumulated incidence rate of about 40% after 5 years (106, 107). In addition 14% reversed their diabetes within 6 months in one study (107) resembling the biphasic incidence pattern over time as reported by Porrini et al. for renal transplant patients (fig. 2) (46). Similar incidence rates of PTDM were reported in two large cohort studies from China , PTDM was diagnosed in 33% after one year and up to 43% after 5 years (108, 109). Interestingly donor liver steatosis in implant biopsies was clearly associated with a higher incidence of PTDM (109).

A study from the UK Scientific Registry of Transplant Recipients also found higher incidence of PTDM in NASH patients, 40% had PTDM after 5 years versus 27% in non-NASH

recipients and the difference remained significant in multivariate analysis (110). Data from the China Liver Transplant Registry found a 24% accumulated incidence of PTDM after 3 years (111). They also found that CMV and HCV infections were independently associated with PTDM.

It is probably fair to estimate that the accumulated incidence of PTDM is about 30-40% in liver transplant recipients although somewhat lower incidence rates may occur in Asian cohorts (111-113), Table 1.

Outcomes with PTDM. An early single center study from the US found that PTDM patients had a significantly lower 10-yr survival rate of 69% compared to 78% in those without diabetes (107). Infections, but not cardiovascular outcomes, were major explanatory variables. However, two other single center studies, one from the US (114) and one from China (115) were not able to confirm a higher mortality rate in PTDM patients. .

Registry data indicate that PTDM significantly increases mortality risk in liver transplanted patients. A study from Taiwan used the National Insurance Research Database reported on more than 2000 patients who were liver transplanted between 1998 and 2013 (113). Patients with PTDM had a 5-yr cumulative mortality similar to patients with pre-transplant diabetes and higher than those without diabetes. However, a multivariate analysis was not carried out. Also a study from The China Liver Transplant Registry showed that patients with PTDM had a 10% lower long-term survival (111). Finally, a recent single center study from Pennsylvania using the OPTN/UNOS dataset and data from the Penn Data Store Registry reported 5-yr follow-up data from 1000 liver transplant recipients between 2003 and 2014. Sustained PTDM was associated with increased mortality and a doubling of major cardiovascular events (15). This is the first study to demonstrate a role for PTDM with

regards to cardiovascular risk and associated premature death in liver transplant recipients, and data concerning rate of major cardiovascular events are shown in figure 5c.

Lung transplantation.

Incidence of PTDM. In a recent prospective cohort study from Melbourne 156 lung transplant patients were examined with OGTTs after transplantation (116). One third had PTDM after 3 months, 30% after 1 year, and 24% after 2 years. The decline in PTDM could however represent a competing risk estimate, since more patients with PTDM died during the first year. In this cohort cystic fibrosis, bronchiectasis and restrictive lung disease were overrepresented among PTDM patients. In fact, with cystic fibrosis diabetes may be present in 50% of the patients already prior to lung transplantation, and half of the remaining patients develop PTDM after transplantation (117). Retrospective cohort studies from Germany showed an PTDM incidence of 35% over 3 years (118) and 20% in a smaller Italian study (119). The patients who developed PTDM were older, more obese and had more often CMV infections and rejection episodes (118).

Recent data from the ISHLT Registry reported that PTDM occurred in about 30% of those who survived 5 years (120) and the incidence was highest in patients with cystic fibrosis. The OPTN/UNOS Registry reported data from more than 10.000 lung transplant recipients transplanted in the period 2004-2011 showed that 40% of those who survived the first year developed PTDM within 5 years (121). It is probably fair to conclude that the accumulated incidence of PTDM is about 20-40% in lung transplant recipients, see also Table 1.

Outcomes after lung transplantation. PTDM-related outcomes after lung transplantation have not been well studied until recently. However, a recent cohort study from Melbourne analyzed 210 lung transplanted patients from the last decade (13). The mortality was high

since as many as 25% of the patients died during an average follow-up of 3 years. Measures of hyperglycemia, FPG, RPG or HbA1c, were all related to increased risk of death, with an HR varying between 1.2 and 1.5. A caveat of the study was that pretransplant diabetes and PTDM were examined as a mixed group. A previous study from the same center followed 400 patients for 5 years and reported that half of the patients died during follow-up (122). Both PTDM and pre-transplant diabetes were associated with a 4-fold increased risk of death (fig. 5d).

Table 1 summarizes incidence and outcomes of PTDM in the different organ transplanted patients including organ diagnoses at particular risk of PTDM. The incidence of PTDM appears to be highest in lung and liver transplanted patients, intermediate in heart transplant recipients and lowest in kidney transplant recipients that have been most studied. Interestingly PTDM appears to associate with increased mortality risk regardless of organ transplanted (fig. 5).

Prevention and treatment goals

Ideally PTDM could be prevented, and therefore a reasonable first step is to assess the risk of PTDM prior to transplantation. We have experience with performing an OGTT immediately prior to wait listing for renal transplantation, since 2-hr plasma glucose is the most important predictor of post-transplant hyperglycemia, at least in renal transplant patients (123). However, this may not be feasible at some transplantation centers. Another approach is to consider other risk factors before transplantation. These comprise family history of diabetes, age (>40 years), central obesity, impaired fasting glucose (IFG, 5.6-6.9 mmol/l) and HCV infection (especially in liver transplant candidates). At the time of

transplantation tailoring of the immunosuppressive agents is probably the primary tool to prevent or postpone diabetes posttransplant in high-risk persons. However, two important issues must guide clinical decisions: 1) Tapering or tailoring of the immunosuppressive drug regimen should never put the patient at risk for rejection of the transplanted organ. 2) Glycemia is always aggravated in susceptible persons during the first 1-2 months after transplantation and does not necessarily imply a manifest PTDM long-term. HbA1c is a poor monitoring tool during the early post-transplant period (7, 19), partly because of bleeding and increased turnover rate of erythrocytes, or use of erythropoietin in case of renal failure (20). In the early post-transplant period we therefore advocate that fasting plasma glucose should be kept <7 mmol/l and post-prandial glucose <10 mmol/l (5). HbA1c may be a useful tool in monitoring glycemia in renal transplant recipients 6-12 months after surgery and further (8). Severe hypoglycemic events should be avoided because of high cardiovascular risk in the patients. In general target HbA1c should be 7-7.5% (53-58 mmol/mol) (7, 124).

Lipids and blood pressure

Due to the high risk of cardiovascular complications it is generally recommended that statins should be given to all adult heart transplant recipients regardless of the cholesterol levels (125). Also the Kidney disease Improving Global Outcomes (KDIGO) 2013 guidelines recommend statin treatment to all kidney transplant recipients (126). Statin treatment for liver-and lung transplant recipients should be evaluated according to standard criteria. KDIGO guidelines have recommended that the target for blood pressure should be 130/80mm Hg in kidney transplanted patients although the evidence is weak (125). No particular target has been addressed in other SOT patients.

Glucose lowering treatment

More than 10 different drug classes have been developed for treatment of type 2 diabetes over the last 60 years (127). Only a few of them have been validated for use in PTDM, and mainly in kidney transplant recipients (5). Of the commonly used drug classes in type 2 diabetes, insulin (128), pioglitazone (129) and certain DPPIV inhibitors such as sitagliptin (130, 131) and vildagliptin (129) have been tried out and found safe to use without interaction with the immunosuppressant regimen. However, all studies have been short-term lasting for less than one year. Other studies are ongoing for the use of metformin (132) and the SGLT2 inhibitor empagliflozin (table 2) in renal transplant recipients. In the first few weeks after transplantation significant hyperglycemia should primarily be treated with insulin and not by oral hypoglycemic agents (7). In the following we will review treatment strategies for PTDM in patients long-term.

Initiatives not involving hypoglycemic agents. Life-style intervention with reduction of body fat mass and especially central obesity should in most cases be advocated, but evidence for efficacy in patients with or at risk for PTDM is scarce (44). A larger study is ongoing in renal transplant recipients (see table 2). We acknowledge that complete withdrawal of glucocorticosteroids may have beneficial effects on glucose metabolism as shown in a retrospective analysis from the US Organ Procurement and Transplantation Network (133) and also in a US single center study using historical controls (134). The down-side was, however, an increased risk of rejections (134). On the other hand, randomized controlled trials have not proven that steroid withdrawal generally prevents PTDM, while an increased the risk of acute rejections, at least in kidney transplant recipients, is seen (135, 136). Insulin sensitivity assessed with hyperinsulinemic euglycemic clamp technique was not improved

when prednisolone was withdrawn from a 5 mg daily dose in renal transplant recipients (74). Split dosing of prednisolone 20 mg daily may alleviate glycemia throughout the day in kidney transplant recipients (137). Tacrolimus is more diabetogenic than CsA when given in high doses (79). This is particularly the case in insulin resistant persons with hypertriglyceridemia (24). However, current knowledge indicates that the doses of tacrolimus can be kept lower than previously reported in kidney transplantation (77), and this may improve beta cell release capacity (73). An observational study in renal transplant patients reported improved glucose excursions tested with an OGTT 3 months after switch from tacrolimus to CsA (138). This particular study did not have a control group, but it is now supported by a recent randomized controlled trial showing that PTDM was more easily reversed in renal transplant patients 12 months after switch to CsA compared to continuation of tacrolimus in combination with prednisolone and mycophenolate (139). It is evident that most data on tailoring immunosuppression to prevent PTDM derive from renal transplantation, and one should be cautious about extrapolating these data to other organ transplant recipients. In a 3-year intervention study on heart transplant patients it was recently found that substitution of CNI with the mTor inhibitor everolimus was associated with lower incidence of PTDM. This, however, was not a pre-specified end-point and the number of observations was small (140). Nevertheless, in light of recent evidence there is a rationale for switching from tacrolimus to CsA in patients at high risk for PTDM (24, 139) and at lower risk for rejection. The benefit in switching from CNI to an mTor inhibitor awaits further studies.

Early insulin treatment. During the first 1-2 months after transplantation insulin therapy is always preferred. Oral agents may be preferred after that, and this sequence of therapy is the opposite of what is common in type 2 diabetes. Many transplant patients starting on

insulin may withdraw insulin treatment after the early post-transplant period. A rule of the thumb has been to consider withdrawal of insulin in favor of oral therapy when insulin need is <20 units/ day (124).

'Beta-cell rest' has been hypothesized to preserve long-term beta cell function. Intensified insulin treatment, normoglycemia and beta-cell rest have certainly been important during and shortly after islet transplantation in order to improve survival of the islets until vasculature and intra-islet circulation are established (141, 142). The situation is more unclear for native islets in situ in diabetic patients. In an interesting pilot study Hecking et al. showed that intensive insulin therapy the first few weeks after renal transplantation resulted in less cases of PTDM after one year compared to conventional treatment of glycemia (128). However, the sample size was limited, and we are awaiting the results of a larger multicenter study which was initiated to confirm these results (see Table 2, anti-diabetes drugs). It is worth noting that the principle of 'beta-cell rest' has previously been tested in prevention of type 2 diabetes, but the results were not unequivocal (143, 144).

Glucose lowering agents. While the major rationale for treating hyperglycemia in diabetes is to prevent microvascular disease (145), patients undergoing SOT have already developed end-stage organ disease and in many cases also cardiovascular disease. This applies particularly to renal transplant recipients, who have a long-term history of kidney disease, insulin resistance and uremia prior to transplantation. Thus, treatment of plasma glucose does not particularly aim at preventing microvascular disease, which usually takes 10-15 years to develop. On the other hand, data from the United States Renal Data System (USRDS) showed that several diabetes related complications present themselves early after

renal transplantation in PTDM patients (146). This raises the possibility that they progress more rapidly after transplantation, and/or that some of them are already present before transplantation in patients with undiagnosed diabetes. The study raises the argument that a) diabetes should be actively looked for among patients entering the waiting list, and b) PTDM should be actively treated with all tools available (lowering glucose, blood pressure and cholesterol) early after transplantation. Treatment of plasma glucose after SOT should aim at maintaining near normoglycemia without untoward side-effects, especially hypoglycemic events. Hypoglycemia is associated with cardiovascular events in patients with type 2 diabetes (147), and patients with both diabetes and renal disease have a three-fold increase in risk for cardiovascular disease and death compared to diabetic patients without renal disease (147, 148).

Life-style measures serve as basis for glucose lowering treatment and related metabolic risk factors also in PTDM, although the evidence for prevention of cardiovascular disease is lacking. Patients should be encouraged to increase physical activity and pertain to a weight-reducing diet or at least weight maintaining diet (44).

Metformin. International guidelines still recommend metformin as the first line glucose-lowering drug in type 2 diabetes since it turns out to be safe and showed some cardiovascular protection in overweight persons with type 2 diabetes in the UKPDS trial published 20 years ago (149). This finding has, however, never been confirmed in later studies which also include modern cardiovascular protection (use of ACE inhibitors, statins, salicylic acid) (150, 151). Although suggested as a potential treatment for PTDM (152), use of metformin as a primary drug has been limited because of lack of safety data in organ

transplanted patients. Metformin may accentuate gastrointestinal side-effects in patients using immunosuppressive drugs. There is also a safety concern in patients with reduced kidney function which is the case in almost all kidney transplanted patients and also in many other solid organ transplanted patients (153). It is therefore mandatory to address kidney function both initially and at regular intervals during treatment with metformin in solid organ transplant patients. Hopefully safety data may be obtained with an ongoing intervention trial in a renal transplant population (132). Interestingly, this trial aims at using metformin to prevent PTDM in renal transplant patients with glucose intolerance.

Glucose lowering agents other than metformin. Although the available amount of glucose lowering drugs for use in type 2 diabetes is plentiful, only a few have been tested for safety in organ transplant patients, and only in short-term studies lasting less than 6 months. Glinides (154, 155) and the DPP4 inhibitor sitagliptin (130, 131) have shown efficacy and safety in short- term studies in kidney transplanted patients. A randomized double-blind trial with the DPP4 inhibitor vildagliptin also demonstrated safety and efficacy in renal transplant patients with glucose intolerance (156). Treatment with DPP4 inhibitors is particularly tempting in PTDM since these drugs do not cause hypoglycemia. Furthermore, it was recently shown that GLP-1 action restores insulin secretion and suppresses glucagon release in PTDM patients (33). Long-term safety data have been published for sitagliptin in patients with type 2 diabetes (157), but not for vildagliptin. The thiozolidine pioglitazone was apparently safe to use in a case report on PTDM (158) and also in a placebo-controlled trial in renal transplant patients with glucose intolerance (129). A recent Cochrane review concludes that the evidence for long-term protective effect of glucose-lowering agents or intensive insulin therapy in PTDM is at present very limited (159).

A suggested algorithm for glucose lowering treatment in SOT patients is presented in figure 6. The algorithm is based on experience from renal transplant patients. In our hands insulin treatment is continued long-term if the insulin need is >20 units/ day. If insulin can be withdrawn, a DPPIV inhibitor with proven safety profile is initiated, e.g., sitaglipitin. Metformin can be used as a supplement if GFR is ≥ 60 ml/min. Use of SGLT2 inhibitors or GLP-1 RAs (receptor agonists) are pending until safety studies in SOT patients are at hand. Glinides (nateglinide, repaglinide) are not very often used anymore. An updated review on management of PTDM in kidney transplant patients was recently published (160).

Intervention on metabolic risk factors other than hyperglycemia. PTDM increases the risk of premature cardiovascular death. However, hyperglycemia itself is not considered the major cause of death, but is rather a bystander together with other cardiovascular risk factors such as hypertension, dyslipidemia, adverse effects of immunosuppressive drugs, low-grade inflammation and reduced kidney function per se. High doses of CNIs associate with reduced renal function over time. This may translate into renal failure in solid organ recipients (161). Unfortunately no intervention trials have been launched to reduce the excess mortality among PTDM patients. Thus, present initiatives for intervention will have to extrapolate experience from trials in non-transplanted subjects, and integrate safety issues in the multipharmacy strategy which includes the immunosuppressive agents.
Experience from trials in type 2 diabetes inflicts that multi-target treatment is very successful in preventing cardiovascular disease. Follow-up data from the Steno trial, which treated glycemia, blood pressure and cholesterol in type 2 diabetes patients, showed reduced incidence of cardiovascular disease after a mean of 8 years (162). Moreover, in

long-term follow-up of the same study it was calculated that life-expectancy was prolonged by 8 years (163). Recently it was shown that intervention on glycemia by certain glucose lowering drugs (SGLT2-inhibitors and GLP-1 RAs) in type 2 diabetes patients with high cardiovascular risk reduced cardiovascular events during 4 years of follow-up (164-167). The relevance of these findings for the treatment of PTDM will be discussed below.

Upcoming therapy in PTDM? Treatment with SGLT2 inhibitors (empagliflozin, canagliflozin) or GLP-1 RAs (liraglutide, semaglutide) in type 2 diabetes patients with high cardiovascular risk have been shown to improve cardiovascular survival (164-167). It is remarkable that this effect is seen on top of state-of-the-art cardiovascular protection (ACE-inhibitors, statins, salicylic acid). Results from a safety trial on the SGLT2 inhibitor dapagliflozin are expected to be published soon (168). SGLT2 inhibitors and GLP-1 RAs reduce blood pressure and body weight in addition to lowering plasma glucose, although by different ways of action. Furthermore, the drugs seem to be protective for the kidneys on top of ACE inhibition since the reported GLP-1 RAs reduce progression of proteinuria (164, 165) and the SGLT2 inhibitors both delay albuminuria and stabilize GFR (169, 170). None of these drugs has so far been recommended for use in PTDM. The concerns are as follows: First, efficacy studies with additional appropriate safety end-points, including drug-drug interaction with immunosuppressive drugs are lacking in PTDM, although such interactions are not expected from theoretical considerations. Second, GLP-1 RAs have until now generally been avoided in patients with moderate renal failure (GFR<30 ml/min/1.73 m^2) due to concerns of gastrointestinal side-effects and enhancement of prerenal filtration failure (171). Third, use of SGLT2 inhibitors is associated with genital fungal infections (166, 167) and more rarely infections in the lower urinary tract (172), which could be a problem in

immunocompromised patients. Fourth, the glucose lowering effect of SGLT2 inhibitors is reduced at GFR <60 ml/min/m^2) and is virtually absent at GFR <30 ml/min/m^2 (173) which may represent a problem in renal transplanted patients with reduced glomerular filtration surface area due to a single grafted kidney.

The experience with treating organ transplanted patients with GLP-1 RAs and SGLT2 inhibitors is so far limited to case reports. The following considerations would argue in favor of these drugs in treatment of PTDM, even in renal transplant patients. Although concerns about gastrointestinal side-effects and augmentation of prerenal filtration failure have been raised in patients with GFR <30 ml/min/1.73 m^2, the recent type 2 diabetes LEADER study with liraglutide included 224 patients with GFR <30 ml/min/1.73m^2 at baseline and did not observe any renal events during the study (165). Second, although the glucose lowering effect of SGLT2 inhibitors is significantly reduced with GFR < 60 ml/min/1.73m^2, this is not the case with GLP-1 RAs. Third, the reported blood pressure reduction with SGLT2 inhibitors seems to be sustained in patients with GFR as low as 30 ml/min/1.73m^2 and is discordant with the glucose lowering effect (166, 167). Forth, and most importantly, PTDM patients in general have a high cardiovascular risk, and any intervention that could reduce this risk is appreciated. Intervention trials with these drug classes are highly needed in PTDM patients. This is a position that should be taken seriously by health care providers and also by the pharmaceutical industry. At present, small, investigator-initiated single center safety studies are launched addressing short-term efficacy and safety issues (table 2).

Drug-drug interactions in PTDM

Several issues have to be considered regarding multi-pharmacy and drug-drug interactions in PTDM patients. Most importantly interaction with the immunosuppressive agents may put

patients either at risk for rejection due to reduced blood levels of immunosuppressive drugs or toxicity due to increased drug levels. Such interactions may be relevant for many pharmaceutical agents commonly used in PTDM patients for cardiovascular protection. The opposite type of interaction may also be relevant: Immunosuppressive drugs may interact with, e.g., oral anti-diabetic drugs and modulate their effects. The vast majority of solid organ transplant patients use a CNI based immunosuppressive regimen. Most centers use tacrolimus, but CsA is still widely used. Mycophenolate and steroids are commonly used in combination with a CNI, while mTOR inhibitors (sirolimus and everolimus) are used only in a minority of patients. The most frequent drug-drug interaction relates to interactions with the CNIs. These interactions mainly occur when tacrolimus or CsA are administered together with inhibitors or inducers of cytochrome P450 3A or P-glycoprotein as these have significant overlap in substrate specificities (174). CsA, tacrolimus and sirolimus/everolimus are all metabolized by CYP3A4, but also CYP3A5 plays a significant role for sirolimus/everolimus, and especially for tacrolimus (175).

Glucose-lowering agents

The potential for glucose-lowering agents interacting with CNIs and sirolimus/everolimus is rather low. So far no significant interaction has been established for oral antidiabetic drugs acting on the pharmacokinetics of tacrolimus, CsA or mTOR inhibitors. On the other hand, increased bioavailability of some of these drugs which are metabolized by CYP3A4 has been reported (176). This is the case for some gliptins (saxagliptin, linagliptin) and repaglinide. A greater concern is however that their half-life may be prolonged since kidney function is reduced in most organ transplant recipients, and kidney function may also vary over time (161).

Cardiovascular drugs

Statins are frequently used in SOT patients with or without PTDM. The risk of statin associated side effects are well acknowledged with simultaneous use of CNIs, and lower doses of statins are generally used in these patients. Because of significant interaction and increased bioavailability of many statins, e.g., lovastatin, simvastatin, and pitavastatin, they should be avoided, particularly when combined with CsA (177). However, the bioavailability of the CNIs remains unaltered. Rosuvastatin, atorvastatin, fluvastatin and pravastatin may be considered for use with CsA, tacrolimus and sirolumus (177).

Warfarin is mainly metabolized by CYP2C9 and no interaction would therefore be suspected with immunosuppressive drugs. It is generally accepted that warfarin is safe to use in combination with immunosuppressive drugs since the drug dosing is guided by the treatment effect as measured by INR. Today the focus concerning anticoagulant therapy has been the safety of using NOAC (Non Vitamin K antagonist oral anticoagulants) in SOT patients. In a recent study the risk of bleedings with NOAC seems to be lowered when used with CsA and many other drugs metabolized by CYP3A4 (178). On the other hand, a study in liver transplant patients showed increased levels of rivaroxaban levels when combined with CsA but not with tacrolimus (179). Restrictions for use with reduced kidney function also apply for some NOACs (180). Obviously more experience is needed before the use of NOACs can be generally recommended for use in SOT patients.

Antihypertensive drugs are generally effective and safe in SOT patients except for some calcium channel blockers. Calcium channel blockers of the dihydropyridine group are safe since they generally show only slight or non-significant interaction with CNIs, but co-

administration of diltiazem with CsA may lead to as much as 20 % increase in CsA blood concentrations. This is less seen with tacrolimus (181). Non-dihydropyridine calcium channels antagonists can cause manifold increase in bioavailability of these drugs restricting their clinical use (182).

Ongoing trials

Table 2 shows the intervention trials that are ongoing according to the web-site clinicalTrials.gov as of March 20, 2018. The trials in the table are sorted according to type of intervention in PTDM. Six studies concern efficacy and safety of anti-diabetes drugs, eight studies address the effects of immunosuppressive treatment including steroids. Two studies concern supplementation with magnesium or vitamin D and one concerns effect of life-style on glucose control. All data are retrieved as registered on clinicalTrials.gov. Some trials have not been updated for years and may have been stopped. The responsible persons for the different trials have not been approached for supplementary information.

Conclusions

PTDM is a common condition after solid organ transplantation. Its incidence increases with age, central obesity, high-dose immunosuppressive regimens, magnesium depletion, and viral infections such as CMV and HCV. HCV-associated PTDM is particularly common in liver transplant patients, and more so in patients with hepatic steatosis. PTDM is associated with early cardiovascular disease and death, and therefore prevention would seem more successful than treatment, although data are scarce. Patients entering the waiting list should be assessed according to conventional risk for type 2 diabetes, e.g., glucose indices and central obesity. PTDM cannot be diagnosed the first two months post-transplant because of

drug-induced hyperglycemia. The diagnostic criteria should include fasting plasma glucose and an OGTT since the HbA1c criterion has too low sensitivity in the early phase. Switch from tacrolimus to CsA has reversed PTDM in renal transplant patients (139). Hyperglycemia the first 2 months after transplantation should primarily be treated with insulin, while some DPP4 inhibitors have been tested safe in renal transplant patients. Ongoing studies are testing safety and efficacy with metformin and the SGLT2 inhibitor empagliflozin in kidney transplanted patients with PTDM. The major issues to be addressed in the future are: 1) Effect of life-style intervention pre- and posttransplant to prevent and treat PTDM. 2) The optimal immunosuppressive regimen in high-risk persons. 3) Large-scale intervention trials on newer hypoglycemic agents that have proven to lower cardiovascular events in high risk type 2 diabetes patients.

Key points

- PTDM is mostly studied in kidney transplant recipients, but risk factors for development of PTDM seem to be similar in heart, liver and lung recipients.
- PTDM develops in 10-40 % of patients during the first year after solid organ transplantation, and represents a major risk for cardiovascular disease and death.
- Major risk factors for development of PTDM are metabolic side-effects of immunosuppressive drugs, post-transplant viral infections and hypomagnesemia on top of traditional risk factors as seen with type 2 diabetes.
- Prevention of PTDM can be obtained by tailoring of the immunosuppressant regimen, and probably also by life-style intervention which however is less studied.

- DM patients should be treated with hypoglycemic agents that have been tested for efficacy and safety regarding multipharmacy, immunosuppressant drugs and organ function.
- Large-scale long-term studies on new glucose lowering drug classes that have shown cardiovascular protection in high risk diabetic patients, e.g., GLP-1 analogues and SGLT2-inhibitors, are warranted also in PTDM patients.

Author contributions

Both authors contributed to all aspects of the manuscript

Competing interest statement

T.J. has received lecture honoraria from AstraZeneca, Merck Sharpe and Dome, NovoNordisk and Boehringer Ingelheim. He also has received an unrestricted research grant from Boehringer Ingelheim Norway. A.H. has received lecture honoraria from AstraZeneca.

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Legends to figures

Figure 1. Acknowledged contributors to hyperglycemia in PTDM are shown with bold arrows. Broken arrows depict contributing organs in type 2 diabetes, but not yet examined in PTDM. Common pathways in type 2 diabetes and PTDM are impaired insulin release and impaired suppression of glucagon release. This is not fully compensated for by GLP-1 release from the intestinal tract. Insulin-stimulated glucose uptake is reduced in muscle and fat cells, and insulin-mediated suppression of hepatic glucose output is also reduced. In type 2 diabetes it is documented that both renal gluconeogenesis and tubular reabsorption of glucose are increased, and cross-talk between insulin, brain and systemic metabolism is also present. These mechanisms may also be operative in PTDM, but this has not yet been documented.

Figure 2. Incidence of PTDM after renal transplantation. Patients were tested every 6th month with an OGTT. (A) New cases of PTDM at different time-points. (B) Accumulated incidence of PTDM over time considering the cases with persistent and excluding those with reverted PTDM at every time point. More than 75% of all cases occurred within the first 3 months after transplantation (fig 2a). The incidence of PTDM was 25% during the first months after transplantation (fig 2b) followed by a reversal in some cases and then a late increase in PTDM incidence. Adapted from (46).

Figure 3.

Effects of immunosuppressive agents on beta cell and insulin sensitive tissues promoting PTDM. Beta cell: *Free fatty acids (FFA) promote lipotoxicity in the cell, which together with tacrolimus (tac) modulate intranuclear pathways connected to beta cell proliferation (increased nuclear Fox01) and insulin production (decreased nuclear MafA), both leading to reduced insulin release. Both tac and CsA (cyclosporine) inhibit the calcineurin/NFATc signal which is conveyed to the nucleus and reduce both insulin release and beta cell proliferation. FFA release and liptoxicity is further accentuated by mTor inhibition, which also down-regulates gene expression for insulin release and beta cell proliferation.* Insulin resistance: *Glucocorticosteroids (GCS) induce a dose-dependent reduction in insulin sensitivity for glucose uptake in fat- and muscle cells, and also ameliorates the suppression of hepatic glucose output. This is reinforced by increased FFA from fat tissue. mTor inhibition reduces insulin signaling by suppressing insulin-stimulated Akt phosphorylation in liver, fat and muscle cells.. Akt phosphorylation mediates insulin signaling down-stream of the insulin receptor.*

(→ *Pathways leading to impaired beta cell function.* → *Pathways leading to insulin resistance.) NFAT=nuclear factor of activated T-cells.*

Figure 4. Incidence rates of early PTDM (blue columns) and IGT (red columns) in per cent over the last decades in a national cohort of kidney transplant recipients from 1997 (55), 2005 (96) and 2010 (19). Adapted from (19, 55, 96).

Figure 5a-d.

The figure shows long-term outcomes in the different organ transplant recipients according to PTDM status.

Panel A shows overall mortality in kidney transplant recipients that is highest in patients with PTDM and impaired glucose tolerance (IGT) compared to normal glucose tolerance. Adapted from (22).

Panel B shows overall mortality in heart transplant recipients that is highest in patients with preexisting diabetes (pre DM) and those with PTDM compared with normal glucose tolerance. Adapted from (12).

Panel C shows major cardiovascular events in liver transplant recipients. PTDM patients have a higher incidence than patients with normal glucose tolerance or those with early PTDM reverting within 6 months (t-PTDM). Adapted from (15).

Panel D shows overall mortality in lung transplant recipients across categories of diabetes status. The incidence is highest in PTDM patients and patients with preexisting diabetes (Pre DM). Adapted from (122).

Figure 6.

A suggested algorithm for glucose lowering in PTDM, as experienced from renal transplant recipients. An oral glucose tolerance test (OGTT) is not carried out the first two months after transplantation. Hyperglycemia should be actively treated if fasting plasma glucose is consistently ≥7 mmol/l, or more than half of random glucose recordings are ≥10 mmol/l. Insulin is the primary agent for glucose lowering during the first 1-2 months, and immunosuppression is modulated to a less diabetogenic profile if considered safe. Withdrawal of insulin may be considered when insulin dose is <20 units/day, and if needed

replaced by non-insulin based agents. At a later stage (>8 weeks post-transplant) PTDM may be diagnosed by an OGTT or HbA1c, but a normal HbA1c does not exclude PTDM.

*Recommended non-insulin based treatment :

Glipizide, repaglinide, nateglinide, vildagliptin and sitagliptin have been reported safe in short-term studies, albeit with low statistical power. Metformin is considered safe with GFR>60 ml/min/1.73 m^2. Ongoing safety studies will give further information on the use of SGLT2-inhibitors and hopefully also GLP-1 receptor agonists.