

Immunosuppression and post-transplant hyperglycemia

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KEYWORDS:

Review, Transplantation, Immunosuppression

GRAPHICAL ABSTRACT:

Immunosuppression is the major modifiable risk factor for development of PTDM but risk versus benefit analysis is required to balance risk of developing PTDM versus rejection.

ABSTRACT

Background: Post-transplant diabetes mellitus is a significant risk factor for cardiovascular disease in solid organ transplantation. The main underlying pathophysiological mechanism of PTDM is pancreatic beta cell dysfunction in the context of insulin resistance, but the relative importance of each of these important components of glycemic metabolism is under intense debate.

Methods: We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials to January 15, 2015. We selected systematic reviews and meta-analyses and randomized clinical trials. When no such reports were found for a given topic or drug, observational studies were included in the assessment.

Results: There are agents with known diabetogenic effects: corticosteroids, calcineurin inhibitors including tacrolimus and cyclosporine, as well as the mammalian target of rapamycin inhibitors (sirolimus and everolimus). The association between the use of induction agents and PTDM is very scarce. No diabetogenic effects have been found with the use of azathioprine, mycophenolate mofetil and its derivatives.

Conclusions: Immunosuppression is the major modifiable risk factor for development of PTDM but risk versus benefit analysis is required to balance risk of developing PTDM versus rejection. Caution is advisable in immunosuppressant adjustments in the event that PTDM develops based on current evidence. Physicians should choose and use immunosuppression regimens shown to have the best outcome for patient and graft survival, irrespective of PTDM risk.

Epidemiology and pathogenesis of posttransplant diabetes mellitus

The clinical importance of post-transplant diabetes mellitus (PTDM) relies on its unquestionable impact as a significant risk factor for cardiovascular disease in solid organ transplantation[1,2]. Cardiovascular disease is one of the leading causes of death with functioning graft and is associated with reduced kidney graft survival, infections and increased health-care costs. Based upon classical diagnostic approaches, a recent systematic review highlighted the incidence of PTDM to be a mean of 19.5% at one-year post-transplantation in studies from the last decade [3]. However heterogeneity was observed across different centers and organs [4]. There was some debate regarding the incremental incidence of PTDM beyond the first year post-transplantation and whether that differs between transplant versus the general population. Moreover it is unclear whether incidence of PTDM is increasing; Valderhaug et al. have reported reduced odds of developing PTDM (odds ratio 0.42, 95% CI 0.23-0.77) comparing a contemporary 2004-2005 versus a historical 1995-1996 cohort (incidence 13% versus 20%) respectively[5]. However recent output from the United States Renal Data System (USRDS) has reported PTDM rates approaching 40% in the adult population by the third year after transplantation [6]. Modality of diagnosis differs between these two cohorts and it is imperative to obtain definitive population-based cohort analyses to determine the true incidence and prevalence of PTDM. It is important to correctly identify patients with PTDM, which refers to newly diagnosed diabetes mellitus with persistent hyperglycemia in the posttransplantation period (symptoms of diabetes plus random plasma glucose ≥ 200 mg/dl(11.1mmol/L) or fasting plasma glucose (FPG) ≥ 126 mg/dl(7mmol/L); or FPG ≥ 200 mg/dl during an oral glucose tolerance test; or HbA1c $\geq 6.5\%$)[7]. It is different for those patients with impaired fasting glucose (IFG) (FPG 100-126mg/dl (5.6-6.9mmol/L) and/or impaired glucose tolerance (IGT) (FPG < 7 mmol/L and 2 hour plasma glucose after an oral glucose 7.8-11mmol/L) [8]. However, since few studies have used the American Diabetes Association or World Health Organization definitions for PTDM or IFG, and fewer have employed oral glucose tolerance testing, the incidence of glucose metabolism abnormalities in the renal transplant population is underestimated.

The term New-Onset Diabetes After Transplantation (NODAT) was coined to acknowledge the pathophysiological insult from the milieu of transplantation on glycemic metabolism. However recent consensus opinion was that the term is misleading, as diabetes may not be new but simply unrecognized[8]. It also inadequately describes allograft recipients who develop diabetes post-transplantation after an earlier transient hyperglycemic period that resolves. Consensus agreement was to adopt the term Post-Transplantation Diabetes Mellitus (PTDM) as it encompasses all diabetes-related episodes relevant after transplantation; new-onset, unrecognized, gestational etc. The term pre-diabetes should be utilized to identify recipients with early non-PTDM glycemic abnormalities post-transplantation.

The main underlying pathophysiological mechanism of PTDM is pancreatic β -cell dysfunction in the context of insulin resistance, but the relative importance of each of these important components of glycemic metabolism is under intense debate. Available studies support insulin resistance [9] versus beta cell dysfunction[10] as the primary pathophysiological defect. The latter study, comparing glycemic metabolic profiles in 1,064 kidney allograft recipients versus 1,357 non-transplant patients, provides compelling evidence for β -cell dysfunction as the primary defect in PTDM. This is an important issue to resolve, as increased understanding of underlying pathophysiological mechanism should facilitate targeted interventional trials. The inter-relationship between insulin secretion and sensitivity, termed the disposition index, may be of greater clinical importance. A recent consensus panel supports the notion that PTDM has to be considered a distinct pathophysiological and clinical entity from type 1 or 2 diabetes mellitus.

Risk factors for postransplantation diabetes mellitus

Relevant reviews have described PTDM risk factors[11]. Some proposed no modifiable factors are: age, ethnicity, family history of diabetes mellitus, cause of end-stage renal failure, gender, HLA-mismatch, genetic susceptibility, innate immunity, donor characteristics and education. On the other hand, the suggested modifiable factors are: obesity, impaired triglycerides

metabolism, previous stress diabetes, metabolic syndrome, high pretransplantation triglyceride level, cytomegalovirus infection, hepatitis C virus infection, rejection episodes, antihypertensive agents (β -blockers, thiazide diuretics), biochemical abnormalities (low magnesium, high uric acid), impaired glomerular filtration rate and immunosuppression (tacrolimus, ciclosporin, sirolimus, corticosteroids). The two most relevant findings in the recent years in this area have been our understanding of genetic polymorphisms leading to pancreatic β -cell dysfunction [12,13] and metabolic syndrome [2], as important PTDM risk factors. The literature continues to be updated describing PTDM risk factors such as lower alcohol consumption [14], hypomagnesemia [15], decreased regulatory T-cells [16], or high renal resistance index [17]. Further research is required to be able to distinguish associations from genuine risk factors in the context of PTDM.

Immunosuppression is acknowledged as the major modifiable risk factor for development of PTDM but risk versus benefit analysis is required to balance risk of developing PTDM versus rejection [11].

The potential diabetogenic effect of some immunosuppressant drugs are caused by renowned pathways described in numerous studies (Figure 1). These findings may be of relevance for tailoring specific immunosuppressive regimens to patients with particular needs [18]. However, a recent Consensus expert panel concluded that no specific recommendation may be done regarding specific immunosuppressive protocols to avoid PTDM, as the main focus should be placed in major outcomes such as patient and graft survival [8].

Insert Figure 1 here

Methods

To assess impact of immunosuppressive medications in the development of hyperglycemia and PTDM, we searched MEDLINE (via OVID), EMBASE (via OVID), Cochrane Central Register of Controlled Trials to 28 September 2014. No language restrictions were done. We selected

systematic reviews and meta-analyses and randomized clinical trials (RCTs). When no such reports were found for a given topic or drug, observational studies were included in the assessment. There are agents with known diabetogenic effects: corticosteroids, calcineurin inhibitors (CNI) including tacrolimus and cyclosporine (CsA). Other agents, such as the mammalian target of rapamycin (mTOR) inhibitors (sirolimus and everolimus) show controversial effects. The association between the use of induction agents and PTDM is very scarce. No diabetogenic effects have been found with the use of azathioprine, mycophenolate mofetil and its derivatives.

Discussion

Corticosteroids

The diabetogenic potential of corticosteroids is dose dependent. The originating factors of alteration of glucose metabolism are principally worsen insuline-resistance and also have deleterious effects on insulin secretion and β -cells [19]:

- Potentiation of insulin resistance. The insulin signalling cascades in skeletal muscles is related to glucocorticoid which produces a reduced glucose uptake and reduced glycogen synthesis [20–22]
- Less insulin secretion. The expression of GLUT 2 and glucokinase is reduced and imply a decrease of insulin secretion [20]. Also dexamethasone stimulates transcription of serum and glucocorticoid-inducible kinase 1, upregulating the activity of voltage-gated K^+ channels and leading to reduced Ca^{2+} entry through voltage-gated Ca^{2+} channels with resultant decreased insulin release [23–25].
- β -cells apoptosis. Glucocorticoids induce oxidative stress and the release of mitochondrial cytochrome c and suppress pro-survival factors such as nuclear factor- κB , leading to apoptotic cell death [26].

A number of randomised controlled trials compiled in several meta-analyses have been published in the last decade (Table 1). In the first meta-analysis analyzing this topic in kidney allograft recipients, steroid-sparing and withdrawal strategies showed limited benefits in reducing new-onset diabetes after transplantation requiring any treatment [27]. A second meta-analysis included more studies (n=16) with less strict criteria, showing a 36% reduction in risk of PTDM amongst all steroid avoidance or withdrawal studies. Meticulous analyses of existing evidence, however, conclude that the benefit is not very important. Steroid avoidance (or limited use for a maximal duration of 2 weeks) was apparently associated with less frequent diabetes requiring any treatment; however, this decrease was only evident with CsA (RR 0.54, 95% CI 0.30 to 0.98), whereas this difference was not significant analysing tacrolimus studies (RR 0.75, 95% CI 0.32 to 1.77) [27,28]. In tacrolimus treated allograft recipients, it seems that the more diabetogenic effect of tacrolimus outweighed the potential benefit of avoiding steroids in the development of new diabetes. Although the reduction in incidence was very significant in one European Tacrolimus study with steroid avoidance [29], the significance disappeared when joined with the US double-blind steroid avoidance study with tacrolimus, which did not show such effect [30]. It is possible that high tacrolimus levels were responsible for the absence of such beneficial effect in this last study [31]. In the US trial, the proportions of patients with PTDM requiring therapy were similar between groups, those requiring insulin were lower with steroid withdrawal (4/107, 3.7%) vs maintenance (10/86, 11.6%, P = 0.049). Moreover, the change in HbA1c from baseline was significantly smaller at all time points (except at 48 months) in the PTDM early steroid-withdrawal group, showing better diabetic control despite less insulin use [30].

Steroid withdrawal after 3 to 6 months of kidney transplantation showed even more limited benefits. It was associated with a lower relative risk in PTDM, but the difference did not reach statistical significance [3 RCTs, 656 participants, RR 0.58 (0.31; 1.09), p=0.089][32]. This outcome was addressed only in 3 RCTs, and the trend to a lower incidence in posttransplant diabetes may have reached significance with greater sample size. In addition, it is likely that the diabetogenicity of CsA and tacrolimus partially outweighed the benefits of steroid withdrawal

strategies in diabetes incidence.

The degree of glycemic burden from chronic low-dose corticosteroid therapy is unclear and therefore steroid avoidance/withdrawal strategies require careful risk/benefit assessment in the context of long-term outcomes[31].The impact of steroid avoidance/withdrawal in the current era is all the more uncertain given the tendency to lower CNI target levels and rapid weaning of corticosteroids. Other strategies that can be employed include split corticosteroid dosing to reduce glycemic variability and hyperglycemia[33].

A recent metaanalysis has assessed the very limited evidence available on steroid sparing strategies in patients with **pancreas** or kidney-pancreas transplantation[34]. At six months, no significant differences were found between the steroid avoidance and late referral groups HbA1c: mean difference 0.08% (95% CI -0.99 to 1.15). Thirteen cohort studies showed that steroid-sparing and withdrawal strategies have benefits in lowering HbA1c.

Finally, in the two analyses on the effect of steroid sparing strategies after **liver** transplantation in PTDM incidence, steroid free or steroid withdrawal at any time post-liver transplantation was associated with a decreased incidence of PTDM[35,36].

Calcineurin inhibitors

CNI cause a decrease in insulin secretion by a direct toxin effect on pancreatic β -cells [19] and other mechanisms:

- Decreased insulin secretion. CsA binds to cyclophilin D in the mitochondrial permeability transition pore, blocking its opening and interfering to stimulation of insulin secretion [37].
- Direct toxic effect on the pancreatic β -cells. CNIs regulate the dephosphorylation of nuclear factor of activated T-cell protein and CREB (cAMP-responsive element-binding transcription factor) activity-2. The dephosphorylation of these proteins regulates several target genes which are critical in β -cell survival, replication, and function. Tacrolimus binds intracellularly to FK506-binding protein 1B before docking in the calcineurin binding site, thus inhibiting calcineurin and decreasing β -cell replication and survival[20,38].

Furthermore, CsA induces inhibition of calcineurin activated leucine zipper-bearing-kinase, leading to β -cell apoptosis[39].

Our evidence-based search found five meta-analyses (three in kidney transplantation, one in liver and one in lung) and two additional RCTs in kidney transplantation (Table 2).

The first systematic review was published in 2005. Studies reporting disturbance of glucose metabolism used variable definitions. The most consistent definition used was the development of NODAT, defined as a requirement for insulin therapy for more than 30 days duration. The risk of new diabetes in previously non-diabetic recipients was significantly increased in tacrolimus treated recipients at six months (RR 2.56, 95% CI 1.37 to 4.78), one year (RR 1.86, 95% CI 1.11 to 3.09) and three years (RR 3.86, 95%CI 2.01 to 7.41)[40].

The DIRECT study confirmed the greater diabetogenic effect (composite endpoint of PTDM/impaired fasting glucose) comparing tacrolimus versus cyclosporine post kidney transplantation in a randomized controlled trial, with no difference in adverse events [41]. PTDM or IFG occurred in 73/281 CsA patients (26%) and 96/286 tacrolimus patients (33.6%), a marginal difference with a $p = 0.046$. Insulin secretion was reduced in both treatment arms with a more pronounced reduction in the tacrolimus arm. Insulin sensitivity was also reduced in both arms without difference between groups. However this was a short 6-month trial. In another long-term RCT comparing tacrolimus and CsA, The incidence of PTDM was significantly higher in tacrolimus arms, and the 1-year difference persisted throughout follow-up. Between the tacrolimus arms (twice-daily vs extended release), no meaningful difference in the incidence of diabetes markers existed [42]. The 4-year Kaplan-Meier rate estimate of HgbA1c levels above 6.5% was 41.1% in extended-release tacrolimus arm, 33.6% in Prograf, and 21.3% in CsA ($p=0.01$ and $p=0.0006$ respectively). In another recent meta-analysis, again no statistically significant difference was detected in PTDM incidence between standard twice-daily and extended-release once-daily tacrolimus formulations (RR 0.95, 95% CI 0.68 to 1.32; $P=0.75$).

A more contemporary approach is to use CNI sparingly. A recent meta-analysis of 56 RCTs demonstrated CNI-sparing was associated with less PTDM (odds ratio 0.74 [95% CI 0.55-0.99], $p=0.04$) and better overall graft survival if CNI-sparing strategies involved CNI-minimization (odds ratio 0.73 [95% CI 0.58-0.92], $p=0.009$) or CNI-avoidance strategies with new agents like belatacept or tofacitinib (odds ratio 0.61 [95% CI 0.39-0.96], $p=0.03$)[43]. The liver and lung trials also showed a higher incidence of PTDM with tacrolimus than with CsA [43,44].

mTOR inhibitors

There are a number of possible mechanisms by which sirolimus may cause PTDM, including impaired insulin-mediated suppression of hepatic glucose production, insulin resistance from ectopic triglyceride deposition, or direct β -cell toxicity [45–47].

- Insulin secretion. In vitro, sirolimus may facilitate the opening of ATP sensitive potassium channels thereby impairing the insulin secretion in addition to suppressing the glucose-stimulated insulin secretion via direct inhibition of Krebs cycle and decrease of mitochondrial ATP production[49]. In vivo, there is conflicting data, it shows that mTORC1 activation via protein kinase B (PKB/Akt) led to a progressive improvement in glucose tolerance and hyperinsulinemia as a result of increased cell mass and proliferation [50].
- Less growth and proliferation of β -cells. The direct inhibition of the mTOR complex 1 (mTOR C1) turns on a reduced regulatory effect on critical regulators of β -cell cycle and proliferation.
- Regulation of cellular response to nutrients. In a physiological situation, inhibition of mTOR may induce insulin resistance by inhibiting mTOR/S6K1 pathway. However, in obesity, there is persistent activation of S6K1 which inhibits insulin-receptor substrate and therefore, insulin resistance can be reversed by inhibiting mTOR/S6K1 pathway.

Results of published controlled studies and meta-analyses are very consistent: although mTOR

inhibitors may be diabetogenic, the incidence of PTDM is not increased by its use (Table 3). The first meta-analysis, published in 2005, included trials mainly with sirolimus and high exposure [51]. If mTOR inhibitors are associated with an increase risk of PTDM, this analysis should have been definitive. However, no differences in the incidence of PTDM comparing mTORi vs other immunosuppressive strategies were noted: mTORi CNI-free vs CNI RR 1.25 (95%CI 0.53 to 2.95); mTORi versus antimetabolites RR 0.97 (95%CI 0.68 to 1.39); low versus higher dose mTORi RR 0.67 (95%CI 0.36 to 1.25). mTORi and CNI: RR 0.89 (95%CI 0.45 to 1.74). The analysis showed that transient hyperglycaemia was more frequent with high vs low mTORi exposure: RR 0.72 (95%CI 0.58 to 0.90), $p=0.004$.

The recent controlled trial comparing CsA-everolimus with CsA-mycophenolic acid showed similar PTDM in both groups [52]. To date, only one controlled trial, prematurely withdraw due to excessive rejection incidence in the CNI-free arm, showed higher incidences of PTDM using the combination of tacrolimus-sirolimus than using sirolimus without CNI [53]. Johnston and colleagues analyzed data from the USRDS and found the use of sirolimus, regardless of whether it was combined with a CNI or an anti-metabolite (mycophenolate mofetil or azathioprine), was independently associated with an increased risk of NODAT [46]. Selection bias may be in the basis of these differences, as adjusted models are unable to compensate the propensity of using sirolimus combination in patients at higher risk of rejection and PTDM. Clearly, more information derived from unbiased controlled trials is needed to confirm that the combination tacrolimus plus mTOR inhibitor is not more diabetogenic than tacrolimus and mycophenolate.

Other recent trials have confirmed the absence of a meaningful effect of CNI-free mTOR inhibitor use in PTDM. In the kidney Symphony trial, the tacrolimus arm was associated with the highest incidence of PTDM defined as the need of stable insulin (10.6% vs 7.8% in sirolimus arm, $p=0.02$) [18].

In the only RCT assessing PTDM risk with the use of mTOR inhibitors after liver transplantation, tacrolimus-based regimen was associated with higher incidence of PTDM than sirolimus-MMF [54].

Induction antibody agents

Data in relation to the impact of induction therapy is very limited and no firm conclusions can be drawn. In a recent meta-analysis (5 studies, 492 patients), alemtuzumab was found to be associated with a borderline lower risk of developing PTDM than IL2 receptor antagonists [55]. This could be due to CNI- and steroid-sparing strategies employed with alemtuzumab use or a diabetogenic effect of IL2 receptor antagonists. A single-centre retrospective study of 264 renal transplant recipients, suggested that induction with basiliximab was associated with a significantly greater risk of developing PTDM compared to no induction (51.5% versus 36.9%, $p=0.017$) at 10-weeks post-transplantation [56].

Recommendations and future directions

Immunosuppression is the major modifiable risk factor for development of PTDM but risk versus benefit analysis is required to balance risk of developing PTDM versus rejection. Although the use of tacrolimus appears to be associated with more frequent PTDM, it is possible that its use improves hard outcomes such as acute rejection, and patient/graft survival. Clearly, the development of rejection and PTDM concomitantly result in the worst outcomes. Therefore, and in agreement with a recent Consensus document, no specific recommendation can be made to advocate a definitive immunosuppressant strategy for allograft recipients based upon PTDM risk alone[8]. Caution is advisable in immunosuppressant adjustments in the event that PTDM develops based on current evidence. Such changes must only be made after accounting for individualized patient-specific risk factors. Physicians should choose and use immunosuppression regimens shown to have the best outcome for patient and graft survival, irrespective of PTDM risk.

Conflicts of interest

The authors confirm that this article content has no conflict of interest.

Acknowledgements

This study was supported by grants PI13/000598 (Spanish Ministry of Health, ISCIII FIS-FEDER) and Redinren RD12/0021/0024.

Table 1. Studies focused on immunosuppression strategies based on steroids

Study	Design	Duration	n	Intervention	Organ	Conclusions
Pascual 2009 [27]	meta-analysis		30 RCTs (5949 participants)	- steroid avoidance (only 0-14 days of steroids) or steroid withdrawal (after 3-6 months) vs - steroid maintenance	kidney	Steroid-sparing and withdrawal strategies showed marginal benefits in reducing PTDM, but only with steroid avoidance and CsA. - Steroid-sparing versus steroid use and maintenance: RR 0.64, 95% CI 0.49 to 0.86 - Steroid withdrawal versus steroid use and maintenance: RR 0.58, 95% CI 0.33 to 1.02 - Steroid avoidance versus steroid use and maintenance: RR 0.58, 95% CI 0.35 to 0.95 - Steroid avoidance versus steroid withdrawal: RR 0.48, 95% CI 0.26 to 0.89 The reduced rate in NODAT requiring any treatment was only evident with CsA (CsA RR 0.55 (95% CI 0.37 to 0.83); TAC RR 0.72 (95% CI 0.42 to 1.25).
Knight 2010[57]	meta-analysis	last search: 18th January 2008	34 studies (5637 patients)	- maintenance steroids from the time of transplantation vs - steroids withdrawal at any time post-transplant or completely avoided	kidney	The rate of PTDM was significantly reduced with steroid avoidance or withdrawal (RR 0.64, 95% CI 0.50–0.83, P=0.0006)
Pascual 2010 [32]	meta-analysis		9 trials (1820 participants)	- steroid withdrawal (after 3-6 months) vs - steroid maintenance	kidney	No significant differences with steroid withdrawal vs maintenance
Pascual 2012[28]	meta-analysis		29 RCTs (5675 patients)	- steroid avoidance (only 0-14 days of steroids) vs - steroid maintenance	kidney	Steroid avoidance was associated with less frequent NODAT requiring any treatment, but this decrease was only evident with CsA (RR 0.54, 95% CI 0.30–0.98), whereas this difference was not significant analysing Tac studies (RR 0.75, 95% CI 0.32–1.77)
CARMEN 2005 [29]	RCT multicenter	May 2000 to Jun 2002 Follow-up: 6 months	548	- steroid avoidance (complete, no steroids) with TAC+MMF and induction treatment with daclizumab vs - steroid maintenance without induction	kidney	- preexisting glucose metabolism disorders at study entry: steroid avoidance (Tac/MMF) 245 patients, maintenance 259 patients. - PTDM (defined as long-term insulin requirement for >30 consecutive days in previously nondiabetic patients) occurred in: 1 steroid avoidance patient (0.4%) and in 14 steroid-maintenance (5.4%) (P=0.001)

						- incidence of decreased glucose tolerance was 0.4% in steroid avoidance group and 0.7% in steroid-maintenance
Woodle 2008[30]	RCT	November 1999 to Dec 2002 Follow-up: 5-year	386	- early (7 day) corticosteroid cessation vs - long-term, low-dose corticosteroids	kidney	Proportions of patients with PTDM: - requiring therapy were similar between groups (23/107 (21.5%); 18/86 (20.9) - requiring insulin was lower with steroid withdrawal (4/107 (3.7%) vs 10/86 (11.6%), P = 0.049). The change in HgA1c from baseline was statistically significantly smaller at all time points (except 48 months) in PTDM steroid-withdrawal group (better diabetic control despite less insulin use).
DOMINOS 2012 [58]	RCT multicenter	April 2007 and March 2009 follow-up: 6 months	222	- steroid avoidance (only perioperative dose on day -1 and day 0) vs - maintenance steroids	kidney	No difference in the incidence of PTDM: steroid-avoidance 8.7% (9/103), controls 13.0% (13/100), P = 0.33.
Montero 2014 [34]	meta-analysis	last search: 18 June 2014	3 trials with 144 participants	- steroid avoidance vs - withdrawal	pancreas or pancreas-kidney	At six months, no significant differences were found between the steroid avoidance and late referral groups HbA1c: mean difference 0.08% (95% CI -0.99 to 1.15). Thirteen cohort studies showed that steroid-sparing and withdrawal strategies have benefits in lowering HbA1c
Segev 2008 [36]	meta-analysis	last search: 29 January 2007	19 RCT (2029 participants)	- steroid-free (< 2 perioperative doses) vs - steroid-based therapy	liver	In steroid-free group the risk of diabetes was lower (RR 0.29, 95% CI 0.18-0.47, P < 0.001)
Knight 2011 [35]	meta-analysis	last search: 20 June 2011	9 RCTs	- maintenance steroids from the time of transplantation vs - steroids withdrawal at any time post-transplant or completely avoided	heart, liver, pancreas	Data regarding PTDM only in liver transplant patients (5 studies, 646 patients) A significant reduction in the risk of new-onset diabetes with steroid avoidance/withdrawal (RR 0.57, 95% CI: 0.42-0.77, P = 0.0002)

CI: confidence interval; OPTN: Organ Procurement and Transplantation Network; PTDM: Post-Transplant Diabetes Mellitus; RCT: randomised controlled trial; RR: risk ratio; vs: versus

Table 2. Studies focused on immunosuppression strategies based on calcineurin inhibitors (tacrolimus or cyclosporine).

Study	Design	Duration	n	Intervention	Organ	Conclusions
Webster 2005[40]	meta-analysis	from 1998 to 2003	30 RCT (4102 participants)	- TAC vs - CsA solution or CsA microemulsion	kidney	The risk of new diabetes in previously non-diabetic recipients was significantly increased in tacrolimus treated recipients at six months (RR 2.56, 95% CI 1.37 to 4.78), one year (RR 1.86, 95% CI 1.11 to 3.09) and three years (RR 3.86, 95%CI 2.01 to 7.41)
Sharif 2011[43]	meta-analysis	from 1966 to 2010	56 RCT (11337 participants)	- CNI avoidance vs - CNI minimization vs - delayed introduction of CNI	kidney	Reduced CNI exposure was associated with reduction in PTDM. It was reported in 8 studies: OR 0.74 (95%CI 0.55 to 0.99).
Ho 2013[59]	meta-analysis	search to June 2011	6 RCT (n=2499) and 15 observational studies (n=2886)	- daily tacrolimus formulation vs - twice-daily tacrolimus formulation	kidney	Three studies (n=2291) report results concerning PTDM and they found no statistically significant difference in PTDM incidence between formulations (RR 0.95, 95% CI 0.68 to 1.32); $P=0.75$.
DIRECT 2007 [41]	RCT	6 months	690	- CsA-ME (Neoral®) vs - Tacrolimus (Prograf®)	kidney	PTDM or IFG occurred in 73/281 CsA-ME patients (26%) and 96/286 tacrolimus patients (33.6%), $p = 0.046$. Insulin secretion was reduced in both treatment arms with a more pronounced reduction in the tacrolimus arm. Insulin sensitivity was also reduced in both arms without difference between groups.
Silva 2014[42]	RCT	Follow-up data: 4 years	638	- tacrolimus extended-release vs, - tacrolimus immediate-release vs, - cyclosporine	kidney	The incidence of PTDM was significantly higher in tacrolimus arms Log rank test: - Prograf vs. CsA $P = 0.01$; - Astagraf XL vs. CsA $P = 0.0006$; - Prograf vs. Astagraf XL $P = 0.38$ The 4-year Kaplan-Meier rate estimate of HgbA1c levels above 6.5% was 41.1% (95% CI: 32.8%, 49.4%) in Astagraf XL, 33.6% (95% CI: 25.3%, 41.9%) in Prograf, and 21.3% (95% CI: 13.3%, 29.2%) in CsA.
Haddad 2006 [44]	meta-analysis	to 30 August 2005	16 RCT (8813 participants)	- tacrolimus vs - cyclosporin	liver	The incidence of PTDM after the 1st year of the transplantation was higher in the tacrolimus immunosuppression based group: RR 1.27; IC 95%: 1.12 to 1.44. This difference did not change in the stratified analysis for formula of

						cyclosporin, for the use of azathioprine versus mycophenolate mofetil.
Penninga 2013 [45]	meta-analysis	search to 10 April 2013	3 RCT (413 participants)	- any dose and duration of tacrolimus vs - cyclosporin	lung	The incidence of PTDM was analysed in 2 studies (164 participants). When analysed using a fixed-effect model, diabetes occurred more frequently in the tacrolimus group (18/81; 22%) compared with the cyclosporin group (4/83; 5%) RR 4.24, 95% CI 1.58 to 11.40.

CI: confidence interval; CsA: cyclosporin; ERL: everolimus; IFG: impaired fast-glucose; MMF: mycophenolate mofetil; OPTN: Organ Procurement and Transplantation Network; PTDM: post-transplant diabetes mellitus; RCT: randomised controlled trial; RR: risk ratio; sir: sirolimus; TAC: tacrolimus; USRDS: United States Renal Data System; vs: versus.

Table 3. Studies focused on immunosuppression strategies based on mTOR inhibitors.

Study	design	duration	n	intervention	Organ	conclusions
Webster 2006 [51]	meta-analysis	search to June 2005	33 trials (7114 participants)	In the immediate post-transplant period: - mTORi vs - alternative drug regimens	kidney	No differences in incidence of PTDM comparing mTORi vs other immunosuppressive strategies: - mTORi versus CNI: outcomes up to 2 years (stratified by CNI): New, sustained diabetes requiring insulin: RR 1.25 (95% CI 0.53 to 2.95) - mTORi versus antimetabolites: outcomes up to 2 years (stratified by antimetabolite): New, sustained diabetes requiring insulin: RR 0.97 (95% CI 0.68 to 1.39) and transient diabetes/hyperglycaemia: RR 1.10 (95% CI 0.86 to 1.42) - Low versus higher dose mTORi: outcomes up to 2 years (stratified by CNI): New, sustained diabetes requiring insulin: RR 0.67 (95% CI 0.36 to 1.25) and transient diabetes/hyperglycaemia: RR 0.72 (95% CI 0.58 to 0.90), p=0.004 - mTORi and CNI: outcomes up to 1 year (stratified by CNI): New, sustained diabetes requiring insulin: RR 0.89 (95% CI 0.45 to 1.74) and transient diabetes/hyperglycaemia RR 1.26 (95% CI 0.65 to 2.44)
SYMPHONY 2004 [18]	RCT multicenter	Follow-up: 12 months	1645 patients	- low-dose CsA with daclizumab induction vs - low-dose TAC with daclizumab induction vs - SRL (CNI-free) with daclizumab induction vs - standard-dose CsA without induction	kidney	PTDM was not diagnosed based on the American Diabetes Association criteria and include a broad range of diagnoses. Low-dose Tac had the most reports of new-onset diabetes at one year (P=0.02): Stand-CsA: 6.4% of patients; Low-CsA: 4.7%; Low-TAC 10.6%; Low-SRL 7.8%. There was not a statistically significant difference in the use of anti-diabetes medication (P=0.37): Stand-CsA: 1.3% of patients; Low-CsA: 1.5%; Low-TAC 2.7%; Low-SRL 1.0%.
ASSET 2012 [60]	RCT multicenter	Follow-up: 12 months	228	- EVE(levels 3–8 ng/ml)+TAC (after 3 months target levels 1.5–3 ng/ml) vs - EVE(levels 3–8 ng/ml)+TAC (after 3 months target levels 4–7 ng/ml) plus basiliximab +steroids	kidney	No differences in incidence of PTDM comparing the two immunosuppressive strategies: EVE+low-TAC 14/109 (12.8%) 18/119 (15.1%)

ORION 2011 [53]	RCT multicenter	from March 2004 to May 2005 Follow-up: 322 to 558 days	443 patients	- SRL+TAC (TAC elimination on week13) vs - SRL+MMFvs - TAC+MMF	kidney	Two years after study initiation (1 year after all patients were accrued), Group 2 patients were discontinued from assigned therapy because of a higher-than anticipated biopsy-confirmed acute rejection. TAC-based therapy experienced more PTDM at 1 year: SRL+TAC and TAC+MMF incidence of 17.0%, 39 out of 230 patients versus SRL+MMF 6.0%, 7/117; p = 0.004. Results: - SRL+TAC group: 22.5% (27/120) (always before TAC elimination) - SRL+MMF: 6.0% (7/117) - TAC+MMF group (10.9%, 12/110)
Flechner 2013 [61]	RCT	June 2005 to Dec 2005 Follow-up 190 days (range, 5-441 days)	475 patients	- SRL vs - CsA (with MMF, CS, and an anti-interleukin-2 receptor antibody)	kidney	The study terminated early (before 48 months as it was planned) because of high acute rejection rates in the sirolimus arm. PTDM (defined as 30 consecutive days of new insulin use) was not assessed, but the rate of treatment-emergent diabetes mellitus was similar between the sirolimus and CsA groups (5.2% and 5.0%, respectively), as was the rate of hyperglycemia (12.6% and 13.7%)
Tedesco Silva 2010 [52]	RCT multicenter	Follow-up: 12 months	833 patients	- EVE 1.5mg/d (target levels 3-8)+CsA (reduced exposure) - EVE 3mg/d (target levels 6-12)+CsA (reduced exposure) - MPA+ CsA(standard exposure) (with basiliximab+/-steroids)	kidney	PTDM (as assessed by the investigator) was reported as an AE in a similar percentage of patients in each group (5.1%, 7.9% and 7.0% in the 1.5 mg, 3.0 mg and MPA groups, respectively).
Salvadori 2009 [62]	RCT multicenter	Follow-up: 12 months	285 patients	- standard exposure EVE (C0 3-8 ng/mL)+CsA (reduced exposure, C2 350-500 ng/mL) - higher EVE exposure (C0 8-12 ng/mL)+very low-concentration CsA (C2 150-300ng/mL)	kidney	New onset diabetes after transplantation was diagnosed in 2.1% of patients in group A and 4.9% in group B (NS).
Johnston 2008 [46]	observational retrospective		20,124	- CSA+MMF/AZA vs - TAC+MMF/AZA vs - SRL+MMF/AZA vs - SRL+CSA vs	kidney	From highest to lowest incidence (3 year cumulative incidence): - SRL+CNI (either CsA or TAC): SRL+CsA 21.9% and SRL+TAC 21.5% - TAC+MMF/AZA: 19% - SRL+MMF/AZA: 17.8%.

	USRDS registry			- SRL+TAC		- CsA+MMF/AZA 15.6%
Teperman 2013 [54]	RCT multicenter	from July 2005 to June 2007	293 patients	4 to 12 weeks after transplantation: - MMF/SRL (n=148) or - MMF/CNI (n=145)	liver	Number of patients with new or worsening diabetes at any time after randomization was significantly higher in the MMF/CNI group (39/146 or 26.7%) versus theMMF/SRL group (21/148 or 14.2%); P=0.01).

CI: confidence interval; CNI: calcineurin inhibitors; CsA: Cyclosporin; EVE: everolimus; MMF: micophenolate mofetil; MPA: mycophenolic acid; NS: not significant; PTDM: post-transplant diabetes mellitus; RCT: randomised controlled trial; RR: risk ratio; SRL: sirolimus; TAC: tacrolimus; mTORi: Target of rapamycin inhibitors; vs: versus

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Figure 1 legend

Pathophysiological mechanisms of posttransplant diabetes mellitus

