Post-transplantation diabetes mellitus: an overview

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This review presents an analysis of clinical and experimental studies related to post-transplantation diabetes mellitus (PTDM) — a specific complication after solid organ transplantation. A search of the databases eLibrary, PubMed and Scopus using the keywords «posttransplantation diabetes mellitus», «new onset diabetes after transplantation», «transplantation» and «immunosuppression» yielded in 523 results, including four from Russian literature (one original research manuscript). The analysis included original research, reviews, meta-analyses and monographs published not before 2005 in Russian and English. A total of 60 relevant original researches and reviews were included in this review. Diagnostic criteria, disease risk factors and potential pathogenic mechanisms were all considered. The mechanisms of the diabetogenic effect of modern immunosuppressive drugs were analysed. The principles of pre- and post-transplantation screening for PTDM and optimal management strategies for patients with PTDM are presented. The current controversial issues concerning the various aspects of PTDM are discussed.

Keywords: post-transplantation diabetes mellitus; transplantation; new onset diabetes; immunosuppressive agents; cytochrome P-450; hypoglycaemic agents

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Post-transplantation diabetes mellitus (PTDM) is a frequent complication occurring after the transplantation of major organs. Patients with PTDM are at a high risk of acute rejection, infections and cardiovascular events and have decreased long-term survival [1]. In the United States of America, medical costs are increased by $21,500 for renal transplantation recipients who develop PTDM [2].
tional guidelines on diabetes mellitus after transplantation \cite{4,5}. Based on these guidelines, PTDM was termed “diabetes mellitus first revealed after transplantation” (DMFRT), and its diagnosis was based on criteria for diabetes mellitus as described by the World Health Organization and the American Diabetes Association (ADA). These diagnostic criteria include fasting plasma glucose $\geq 7.0$ mmol/l ($\geq 126$ mg/dl), random plasma glucose at any time regardless of recent meals $\geq 11.1$ mmol/l ($\geq 200$ mg/dl) or plasma glucose $\geq 11.1$ mmol/l ($\geq 200$ mg/dl) within 2 h of an oral glucose tolerance test (OGTT). In 2010, the ADA added glycated haemoglobin (HbA1c) $\geq 6.5\%$ as a diagnostic criterion \cite{6}. In 2014, the international expert group released revised guidelines \cite{7} in which they acknowledged that the term DMFRP could be misleading because it implies the exclusion of diabetes mellitus before transplantation. However, appropriate comprehensive tests for the diagnosis of diabetes mellitus are not always performed before transplantation, and in some cases of so-termed DMFRP, diabetes mellitus may have been present before transplantation. Consequently, they recommended a return to the term PTDM, which accounts for this situation. The guidelines also recommended that the term “pre-diabetes mellitus” be used for patients with post-transplantation hyperglycaemia that does not reach threshold values for the diagnosis of PTDM (disorders of fasting glycaemia and/or disorders of glucose tolerance; Table 1).

## Incidence

The incidence of PTDM is 25\% in patients undergoing renal transplantation, 25\% for those undergoing liver transplantation, 30\%–35\% for those undergoing lung transplantation and 40\% for those undergoing heart transplantation \cite{8–11}.

The rate of morbidity related to PTDM depends on the duration of observation, presence of risk factors, type of transplantation and type of immunosuppressive therapy. A true increase in morbidity secondary to PTDM is observed mainly within the first year after transplantation. After this, the yearly morbidity in patients with PTDM is similar to that in patients on the waiting list for transplantation (approximately 6\% per year) \cite{2}. Therefore, in the longer term, it is difficult to distinguish between morbidity from PTDM and morbidity from true type 2 diabetes mellitus.

## Risk factors for PTDM

The risk factors for PTDM are usually divided into unchangeable, changeable and conditionally changeable (Table 2).

### Unchangeable risk factors

- **Age**
  - Older age is an important risk factor for PTDM. Recipients older than 45 years at the time of transplantation were found to be 2.2 times more likely to develop PTDM than younger recipients ($P < 0.0001$) \cite{3}.
  
  This finding was supported by analysis of the United States Renal Data System (USRDS) database, which includes data for more than 11000 people who received renal grafting from 1996 to 2000 \cite{13}. There was a strong relationship between age and PTDM. Compared with the control group aged 18–44 years, recipients aged 45–59 years had a relative risk (RR) of PTDM of 1.9 ($P < 0.0001$), while in recipients older than 60 years, the RR increased to 2.09 ($P < 0.0001$) \cite{13}.

- **Ethnic origin**
  - In a single-centre retrospective study of 122 renal transplantation recipients, the risk of PTDM was two times higher in Afro-Americans than in white Caucasians \cite{14}. The analysis of the USRDS data showed that PTDM is
more common among Afro-Americans (RR = 1.68, P < 0.0001) and Hispanics (RR = 1.35, P < 0.0001) than in Caucasians [13].

The difference in the risk of PTDM among patients from different ethnic groups may be partly explained by different pharmacokinetics in terms of the diabetogenic effect of immunosuppressive agents. For example, to achieve similar blood concentrations of tacrolimus, Afro-Americans require a 37% higher dose than white Caucasians [15].

Lifestyle differences among groups may also contribute to differences in the risk of PTDM.

Heredity

There is strong evidence that transplantation recipients with a family history of diabetes mellitus have an increased risk of PTDM, regardless of the transplantation organ [16]. In a Spanish multicentre cross-sectional study of 1410 renal transplantation recipients, 489 liver transplantation recipients, 207 heart transplantation recipients and 72 lung transplantation recipients, a family history of diabetes mellitus increased the risk of PTDM by 50% [odds ratio (OR) = 1.51] [17].

Early studies of an association between PTDM and single nucleotide polymorphisms of different genes were limited by the small volume of extracts and the absence of control groups. Therefore, it was not possible to make any meaningful conclusions.

Since 2007, a genetic link between PTDM and type 2 diabetes mellitus has been identified in many studies (Table 3) [18]. From the time of the first genome-wide association...
study (GWAS), more than 40 loci associated with development of type 2 diabetes mellitus have been identified in the general population. In most cases, the strength of the relationship between genetic variants and type 2 diabetes mellitus is small (OR = 1.10–1.20). One of the strongest relationships (OR = 1.55) is for genetic polymorphism rs7903146 (T allele) of the basic variant of the transcription factor 7-like 2 (TCF7L2) gene [19]. This allele is associated with reduced insulin secretion, incretin effects and an increased rate of hepatic glucose production. Ghisdal et al. demonstrated a relationship between polymorphism of the TCF7L2 gene and PTDM in a sufficiently large group of patients (n = 1076) [20].

The HLA phenotype (including HLA-A28, HLA-A30 and HLA-V42) is associated with a higher rate of PTDM. Incompatibility of HLA antigens, previous graft rejection and male donor are also risk factors for PTDM [12].

One recent report found that polycystic kidneys in the recipient increases the risk of PTDM [21]. However, this was not supported by the findings of another study [22].

**Conditionally changeable risk factors**

**Hepatitis C virus-associated PTDM**

It has been known for some time that there is a link between hepatitis C and type 2 diabetes mellitus in the general population. Potential mechanisms of the diabetogenic effect of hepatitis C virus (HCV) infection include a reduction in hepatic glucose absorption, increased gluconeogenesis, a direct cytopathic effect of the virus on pancreatic beta-cells and the development of insulin resistance [23]. A connection between HCV and PTDM has also been identified in recipients of major organ transplantation. However, the pathogenesis of HCV-associated PTDM has not yet been sufficiently studied. Clinical trials of recipients of orthotopic liver transplantation found that the main factor in the development of PTDM was insulin resistance associated with active HCV infection. There was a relationship between recurrent hepatitis, increased viral loading and PTDM [7, 23]. Furthermore, transplantation recipients with a positive response to antiviral therapy showed improvement of glycaemic control [7].

In a small study of 16 patients on the waiting list for renal transplantation and with a stable positive response to treatment of HCV-infection with interferon during the pre-transplantation period (mean 22.5 months, range 2–88 months), none developed PTDM [24]. Therefore, effective treatment of hepatitis C before transplantation may reduce the risk of PTDM.

**Cytomegalovirus-associated PTDM**

A link between cytomegalovirus (CMV) infection and PTDM was first identified in 1985 in renal transplantation recipients [25]. In that study, which included 160 recipients of kidney transplantation who were monitored for CMV infection, asymptomatic CMV infection increased the risk of PTDM within 3 months of surgery by 4 times (RR = 4.00, P = 0.025) [25]. Patients with active CMV had depressed insulin secretion compared with uninfected patients, suggesting that impaired insulin secretion from beta-cells may be involved in the pathogenesis of CMV-associated PTDM. In addition, CMV-induced release of pro-inflammatory cytokines may lead to apoptosis and a functional disorder of pancreatic beta-cells [26].

**Hypomagnesaemia**

Numerous studies have shown an inverse relationship between the level of blood magnesium and glycaemic control [27].

Hypomagnesaemia is an independent predictor of type 2 diabetes mellitus in the general population and of PTDM in recipients of renal and hepatic transplantation. In a single-centre retrospective study of 254 renal transplantation recipients, van Laecke et al. showed that hypomagnesaemia during the first month after transplantation was associated with an increased likelihood of PTDM, regardless of the immunosuppressive therapy protocol [28].

In a recent study, Augusto et al. found that hypomagnesaemia in the pre-transplantation period is also a risk factor for PTDM [29].

**Changeable risk factors**

**Metabolic syndrome**

Numerous studies have demonstrated that excess weight and obesity are associated with an increased risk of PTDM [30]. Analysis ofUSRDS data indicated that a high body mass index (BMI) is one of the most significant risk factors for PTDM (BMI > 30 kg/m2, RR = 1.85, P < 0.0001; BMI 25–29.9 kg/m2, RR = 1.39, P < 0.0001) [31].

In a retrospective study of 640 transplantation recipients, the chances of developing PTDM in the first year after transplantation was correlated with the number of metabolic syndrome components: 0, 0%; 1, 24.2%; 2, 29.3%; 3, 31.0%; 4, 34.8% and 5, 73.7% (P = 0.001). Multifactor analysis of separate metabolic syndrome components found that, of all pre-transplantation metabolic syndrome components, only the level of low-density lipoproteins was independently related to the risk of PTDM [32].

In a recent study, Israni et al. also indicated that metabolic syndrome is an independent risk factor for PTDM [33].

**Corticosteroid-associated PTDM**

The impact of glucocorticosteroids on the development of PTDM was first described by Starzl in 1964 in renal transplantation recipients [3].

Glucocorticoids dose-dependently increase hepatic glucose production (by stimulation of gluconeogenesis), increase insulin resistance, suppress insulin secretion and induce apoptosis of beta-cells at high doses [34].

In single-centre studies conducted in Norway, reduction of prednisolone dose by up to 5 mg per day significantly improved glucose tolerance within the first year after transplantation [35], while increasing the dose by
In a small study of 57 renal transplantation recipients, reduction of prednisolone dose from an average of 16 mg per day (range 10–30 mg per day) to an average of 9 mg per day (range 5–12.5 mg per day) increased the insulin sensitivity index by 24% [36]. In a retrospective analysis of the Organ Procurement Transplant Network/Scientific Registry of Transplant Recipient (OPTN/SRTR) database, which included more than 25,000 recipients of renal transplantations carried out from 2004 to 2006, Luan et al. found that the use of immunosuppressive therapy without steroids was associated with a significant reduction in PTDM compared with immunosuppressive protocols that included steroids. The rate of morbidity caused by PTDM within 3 years of transplantation was 12.3% when no steroids were used, compared with 17.7% when steroids were used (P < 0.001) [37]. In a retrospective study of 88 cardiac transplantation recipients, patients who developed PTDM had taken a higher average dose of prednisolone compared with recipients with no diabetes (0.21 ± 0.03 mg/kg/day versus 0.19 ± 0.03 mg/kg/day, P < 0.01) [38].

**PTDM associated with calcineurin inhibitors**

Calcineurin inhibitors (cyclosporine A, tacrolimus) constitute the basis of modern immunosuppressive therapy. However, their diabetogenic effect is also well known, and tacrolimus has a stronger diabetogenic effect than cyclosporine A [39, 40].
The schematics presented in Figure 1 show possible mechanisms of the diabetogenic effect of tacrolimus (I) and cyclosporine A (II).

**Influence on survival and replication of beta-cells**

Calcineurin and its signalling pathway are biologically significant in many tissues. In beta-cells, calcineurin phosphatase activity has at least two well-known targets: nuclear factor of activated T-cells (NFAT); and the co-activator of cAMP-dependent transcription factor (cAMP response element-binding protein; CREB)—transducer of regulated CREB activity 2 (TORC2) complex. Forming complexes with FK506-binding protein 1B and cyclophilin, respectively, tacrolimus and cyclosporine A are linked to calcineurin, inhibiting it and its signalling pathway [41]. Consequently, inhibition of calcineurin may contribute to PTDM by a direct toxic effect of tacrolimus and cyclosporine A.

Plaumann et al. demonstrated that, while inhibiting calcineurin, cyclosporine A activates dual leucine-zipper-bearing kinase (DLK), which leads to apoptosis of beta-cells [42]. Tacrolimus reduces phosphorylation of Akt kinase in the PI3K/AKT signalling pathway, which influences growth and proliferation of beta-cells. In addition, the mRNA and production of insulin receptor substrate-2 (Irs2) is decreased, which is probably caused by calcineurin inhibition, because NFAT, dephosphorylated by calcineurin, activates Irs2 transcription [43].

**Influence on insulin secretion and its effect**

There is evidence from in vitro and in vivo studies that pharmacologic calcineurin inhibition suppresses insulin secretion in a dose-dependent manner [41].

The effect of tacrolimus on insulin secretion may be related to high concentrations of the preparation in the blood. A decrease of the concentration improves beta-cell functioning. A decrease of tacrolimus concentration from 9.5 ng/ml to 6.4 ng/ml was associated with an increase in
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The level of S-peptide from 49.0 nmol/l to 66.6 nmol/l (P = 0.04) [41]. The secretory activity of beta-cells remained normal in renal or combined transplantation recipients treated with a low dose of glucocorticoids (5 mg per day) and a moderate dose of tacrolimus dosage (blood concentration 6–10 μg/ml) [44].

Mitochondria play a key role in insulin secretion. Cyclosporine binds with cyclophilin D in mitochondrial transitory pores (MTPs) and blocks the opening of these channels, increasing cytoplasmic calcium concentration, which impairs glucose-stimulated insulin secretion [41]. Rostambeigi et al. demonstrated that tacrolimus may inhibit the expression of genes that take part in cytoskeleton building, membrane transportation, ATP production and regulation of mitochondrial functions, all of which influence insulin secretion [41].

The mTORC1 signalling pathway regulates translation of 4EBP1 and S6K1, which have a role in beta-cell growth and proliferation. mTORC2 participates in Akt phosphorylation and activation and therefore plays an important role in beta-cell survival. Sirolimus impairs cellular regeneration and proliferation mainly by inhibiting mTORC1 (a) and probably mTORC2 (b). Sirolimus also reduces ATP mitochondrial production by suppressing the Krebs cycle (c) and inhibits closure of ATP-dependent potassium channels (d), which impairs glucose-dependent insulin secretion.

Some studies have indicated that calcineurin inhibitors increase insulin resistance. Calcineurin inhibition prevents activation of genes participating in muscular remodelling, including the myocyte enhancer factor-2 (MEF-2) gene, which leads to insulin-resistance in muscular fibres, and the perisome proliferator activated receptor gamma activator-1 (PGC-1) gene, which reduces insulin sensitivity in skeletal muscles [46]. However, more studies are needed to clarify the mechanisms underlying the development of insulin resistance.

**PTDM associated with mtor inhibitors**

The mammalian target of rapamycin (mTOR) is a serine-threonine specificity protein kinase consisting of 2 complexes [mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2)]. It participates in regulation of cellular growth and survival. Sirolimus (rapamycin) is a macro-lide that inhibits T-cell activation by binding with FK506 binding protein 1V (FK506-BP1B). The complex inhibits mTOR.
There is increasing evidence that sirolimus has a diabetogenic effect. According to USRDS data on 20,124 renal transplantation recipients, there is a clear association between the use of sirolimus and the development of PTDM [47].

Compared with patients treated with cyclosporine combined with mycophenolate mofetil (MMF) or azathioprine, patients treated with sirolimus combined with cyclosporine, tacrolimus, MMF, or azathioprine were more likely to develop PTDM.

In animal models, the effect of sirolimus on beta-cell functioning is paradoxical. At therapeutic doses, sirolimus significantly increased both basal (50%) and glucose-induced (40%) insulin secretion in pygmy pigs [41].

Sirolimus also increased insulin content in islets of Langerhans in a human study [41]. However, at doses higher than the therapeutic dose, sirolimus has been shown to suppress insulin secretion. Similar to calcineurin inhibitors, sirolimus may also suppress insulin secretion by inhibiting closure of ATP-dependent potassium channels [48].

In another study using rats, sirolimus suppressed glucose-stimulated insulin secretion, inhibiting the Krebs cycle, which reduced mitochondrial ATP production [49].

There is also strong evidence that sirolimus may impair the regeneration and proliferation of beta-cells. Because sirolimus inhibits mTORC1 and its signalling pathway, which regulates eukaryotic translation initiation factor 4E-binding protein (4EBP) translation and ribosomal S6 kinase (S6K) [50], beta-cell proliferation is impaired. Furthermore, the mTORC2 signalling pathway, which includes Akt phosphorylation and activation, also has a significant role in beta-cell function [51].

The schematic presented in Figure 2 shows the possible mechanism of the diabetogenic effect of sirolimus.

**Effects of other immunosuppressive agents**

To date, there is no evidence of a diabetogenic effect of azathioprine or inosine monophosphate dehydrogenase, the antimitabolite of MMF. On the contrary, simultaneous use of MMF reduced the diabetogenic effect of tacrolimus [13]. The combined use of azathioprine and MMF enables the use of lower doses of other immunosuppressants that have a diabetogenic effect.

**Glycated haemoglobin may be used to diagnose PTDM (HbA1c ≥ 6.5%) [6,7]. An HbA1c level of 5.7%–6.4% in the early post-transplantation period warrants additional diagnostic tests. It should be noted that anaemia, which often occurs after transplantation, could reduce HbA1c values and mask the diagnosis.**

**Observing patients with PTDM**

**Immunosuppressive therapy**

Immunosuppressive therapy is the most significant risk factor for PTDM. Changes in immunosuppressive therapy may improve the course of PTDM or even contribute to its regression. However, prudence is necessary when modifying immunosuppressive therapy. Currently, there is no consensus on this issue.

In accordance with the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [12], modification of immunosuppressive therapy may include the following:

- Reduction of tacrolimus, cyclosporine A, or corticosteroid dosage
- Termination of tacrolimus therapy, cyclosporine A therapy, or corticosteroid therapy.
- Replacement of tacrolimus with cyclosporine A, MMF, or azathioprine
- Replacement of cyclosporine A with MMF or azathioprine.
Combined therapy with calcineurin blockers and mTOR inhibitors [57] and replacement of tacrolimus by sirolimus are not recommended because of increased insulin resistance [58]. Reduction of the dose of tacrolimus [58] and sirolimus [57] to the lowest therapeutic dose is also not recommended because of rejection risk, especially in patients at high immunologic risk.

Data on the influence of induction therapy on the development of PTDM are currently limited. In a retrospective single-centre study of 264 renal transplantation recipients induction therapy with basiliximab was associated with a higher risk of PTDM (51.5%) compared with patients receiving no induction therapy (36.9%; P = 0.017) [59].

Glucose-lowering therapy

The 2003 international consensus guidelines suggest applying a graduated approach to treat PTDM. First, the guidelines suggest non-drug therapy based on lifestyle changes. The second stage is monotherapy with oral hypoglycaemic drugs (OHGDs). The third stage is treatment with a combination of OHGDs. The fourth stage is combined OHGD and insulin therapy, and the final stage is insulin monotherapy [4].

However, a step-wise approach may be impractical. These guidelines were revised with international consensus in 2014 [7]. In the first 6 months after transplantation, hyperglycaemia is more likely to reflect PTDM than true type 2 diabetes mellitus. Therefore, the treatment should be focussed on normalisation of carbohydrate metabolism, and should not rely completely on lifestyle changes. Furthermore, as mentioned above, hyperglycaemia in the first month after transplantation is in itself a risk factor for PTDM. Therefore, fasting hyperglycaemia must be corrected to reduce the risk of PTDM. In a randomized study of transplantation recipients, patients with glucose above 7.8 mmol/l (140 mg/dl) were treated with basal insulin [54]. The risk of PTDM was 73% lower in patients treated with insulin compared with the control group treated in accordance with the 2003 international guideline recommendations [54].

The choice of hypoglycaemic agent should be made based on specific side effects, the functional status of the transplanted organ and possible interactions with immunosuppressive agents (Table 4) [12]. Metformin proved to be safe in a study of 32 transplantation recipients who were treated for 16 months [60]. A possible limiting factor for the use of metformin is the potential aggravation of gastrointestinal side effects that often occur with MMF or mycophenolic acid. Several studies have indicated that thiazolidinedione is safe and effective after transplantation. However, side effects such as fluid retention and increase in body weight, aggravation of cardiac insufficiency and urinary bladder cancer limit the long-term use of this agent.

Preparations that stimulate insulin secretion (secretagogues) such as sulfonylurea and glinides may be used to treat PTDM when impairment of insulin secretion is the prevalent mechanism caused by calcineurin inhibitors or mTOR inhibitors.

Gliquidone does not affect the concentration of immunosuppressants in the blood and is a good option to treat patients with PTDM [18].

Currently, there are no reliable studies on the safety and efficiency of glucagon-like peptide-1 (GLP-1) to treat PTDM. In a recent randomized controlled study, Haideringer et al. found significant improvement both in post-prandial glycaemia and HbA1c in patients with PTDM treated with the dipeptidyl peptidase-4 (DPP-4) inhibitor vildagliptin [61]. Unlike sitagliptin and saxagliptin, vildagliptin is not metabolized by cytochrome P450 and does not affect the concentration of immunosuppressants in the blood [12], which makes it another good option to treat PTDM.

Further investigation of the pathogenesis of PTDM is warranted, and more clinical trials of a range of OHGDs are necessary to develop effective treatment protocols for PTDM.

<table>
<thead>
<tr>
<th>Class</th>
<th>Preparation</th>
<th>Drug interaction</th>
<th>CsA concentration</th>
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</thead>
<tbody>
<tr>
<td>1G sulfonylurea preparations</td>
<td>All preparations</td>
<td>glipizide, gliclazide, glibenclamide, glimepiride</td>
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</tr>
<tr>
<td>2G sulfonylurea preparations</td>
<td>repaglinide</td>
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<tr>
<td>glinides</td>
<td>Nateglinide</td>
<td>↑ concentration both of repaglinide and CsA</td>
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<tr>
<td>α-glucosidase inhibitors</td>
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<td></td>
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<td>Metabolized by R450* cytochrome</td>
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CsA, Cyclosporine A; GLP-1, Glucagon-like peptide-1; DPP-4, dipeptidyl peptidase-4; \* are likely to increase cyclosporine concentration, as well as tacrolimus and mTOR inhibitor.
Conclusion

PTDM is a frequent complication occurring after transplantation of major organs. PTDM is associated with increased cardiovascular risk, the development of infections and graft rejection. In addition to the risk factors associated with type 2 diabetes mellitus, PTDM carries risk factors directly related to the transplantation, such as rejection, incompatibility with HLA antigens, post-transplant hyperglycaemia and most importantly, interactions with the immunosuppressive therapy prescribed after transplantation. The assessment of risk factors for PTDM should become an integral part of patient management before and after transplantation. Patients with PTDM, or at high risk of PTDM, should be managed based on international guidelines, but at the same time, management should be tailored to each individual. The selection of the immunosuppressive protocol and its modification to prevent PTDM or to smooth its clinical course should be conducted considering individual immunologic risk factors. There are many unresolved questions related to the diagnosis of PTDM, its pathogenesis and the management of patients who develop the disease. Further studies are needed, and the inclusion of PTDM in the diabetes mellitus classification should be considered. Currently, there is no such diagnosis. The only wording applicable to this situation is ‘diabetes mellitus induced by preparations or chemicals’. In our opinion, this wording does not completely reflect the scope of risk factors for PTDM, or its pathogenesis, although it does indicate the key mechanism underlying its development.

Conflict of interest

The authors declare no conflicts of interest in relation to this paper.
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