CHAPTER 8.6 Post-transplant diabetes mellitus

Daniela Choukair

Heidelberg University, Medical Faculty, Department of Paediatrics I, University Children's Hospital, Heidelberg, Germany

ORCID:
https://orcid.org/0000-0002-1631-3883

Introduction

Post-transplant diabetes mellitus (PTDM) is associated with an increased risk of cardiovascular morbidity, increased mortality and decreased graft survival [1]. The incidence varies from 10% to 74% in adults [2] and from 3% to 20% in children [3].

Definition

Hyperglycaemia in the first days and weeks after transplant surgery should be differentiated from PTDM, which should be diagnosed at the earliest six weeks to six months after transplantation and in the setting of stable immunosuppressive therapy [1, 2]. According to the diagnostic criteria of the American Diabetes Association (ADA), PTDM is present when one of the following criteria is met [1, 2, 4]:

- Randomly elevated plasma glucose ≥ 200 mg/dL with symptoms of diabetes mellitus (DM) such as polyuria, polydipsia or unexplained weight loss.
- Fasting plasma glucose ≥ 126 mg/dL after a fasting period of at least eight hours.
- Two-hour plasma glucose ≥ 200 mg/dL during a standardised oral glucose tolerance test (OGTT).
- HbA1c ≥ 6.5%.

Published in: Tönshoff & Pape (eds.), Management of the paediatric kidney transplant recipient. Heidelberg: heiBOOKS 2026, pp. 263–271. DOI: https://doi.org/10.11588/heibooks.1732.c25471

Causes and risk factors

Risk factors that predispose to type 2 DM in the non-transplant population have also been identified as risk factors for post-transplant patients [2]:

- Overweight (> 90th BMI percentile) and obesity (> 97th BMI percentile)
- African American or Latino heritage
- Impaired glucose tolerance or pre-diabetes prior to transplantation
- Positive family history of DM
- Genetic predisposition, such as variants in the *HNF-1B* gene [5]

Specific risk factors for kidney transplant patients [1]:
- HLA mismatch especially on HLA-DR
- Male gender
- Deceased donor organ
- Hepatitis C infection
- Risk constellation for cytomegalovirus (donor CMV seropositive/recipient CMV seronegative)
- Polycystic kidney disease as primary kidney disease
- Perioperative hyperglycaemia
- Immunosuppressive therapy

Immunosuppressants:
Glucocorticoids [3]:
- Diabetogenic effect is dose-dependent and can cause weight gain
- Reduced binding of insulin to its receptor and increased gluconeogenesis in the liver.
- The effect of steroid-free immunosuppression on the reduction of PTDM is unclear. Steroid-free immunosuppression appears to have little effect on the development of PTDM compared to low-dose steroid medication [6]. In a group of paediatric kidney transplant patients, the use of steroid-based immunosuppression at discharge was not a risk factor for the subsequent development of PTDM [7]

Calcineurin inhibitors [1]:
- Tacrolimus (Tac): direct toxic effect on ß-cells, resulting in reduced secretion of insulin

- Ciclosporin A (CsA): Dysfunction of ß-cells with reduced insulin secretion (animal study)
- The diabetogenic effect of Tac is more pronounced than that of CsA [1]

mTOR inhibitors:
diabetogenic effect, as ß-cell proliferation is reduced [1], but no increased incidence of PTDM is described in other studies [8]

Antiproliferative agents:
Mycophenolate mofetil (MMF) or azathioprine (AZA) tend to have a protective effect with regard to the development of PTDM. It is unclear whether this is a direct effect or whether glucocorticoids and calcineurin inhibitors can be spared through the use of antiproliferative agents [3].

Diagnostics

Glucose metabolism should be carefully assessed before transplantation. After transplantation, the management of PTDM includes close monitoring of glucose metabolism and, in individual cases, modification of immunosuppressive therapy, treatment of DM and reduction of other cardiovascular risk factors in patients with impaired glucose metabolism. The KDIGO guidelines recommend weekly monitoring of glucose metabolism for the first four weeks after transplantation, then quarterly and annually after the first year following transplantation [9].

HbA1c and fasting glucose are commonly used to assess glucose metabolism. The high false-negative rate of fasting glucose and HbA1c must be taken into account [1]. In addition, after glucocorticoid administration in the morning, spontaneous glucose levels are elevated, especially in the afternoon and evening [10]. Therefore, the gold standard for the diagnosis of PTDM is the OGTT [11]. It can also be used to identify patients with impaired glucose tolerance and initiate appropriate screening. Continuous glucose monitoring (CGM) systems are increasingly being used to monitor treatment [12]. PTDM requires multidisciplinary care by an experienced diabetes team [2] and screening for diabetes complications should be included in transplant aftercare.

Therapy

Postoperative hyperglycaemia after transplantation occurs in about 60% of adults [13] and requires insulin therapy, mostly intravenously initially [2]. If PTDM is diagnosed during outpatient follow-up, modification of immunosuppression should always be weighed against the risk of potential rejection. Glucocorticoid therapy should be reduced as soon as possible, although steroid-free immunosuppression is not mandatory [1]. However, a switch from tacrolimus to ciclosporin may be considered in cases of difficult-to-control diabetes [1]. According to the current KDOQI recommendations, drug therapy for diabetes should be initiated immediately and should be accompanied by lifestyle changes such as increased physical activity, dietary changes, weight loss and treatment of other cardiovascular risk factors [14].

When selecting antidiabetic drugs, it is important to consider the potential for interaction with immunosuppressants, and some drugs are contraindicated in cases of impaired GFR [2]. Data on the safety and efficacy of these drugs in PTDM are sparse in adults [2] and not available in children. The group of drugs used in adults with PTDM, such as dipeptidyl peptidase 4 (DPP4) inhibitors, thiazolidinediones, sulfonylureas, meglitinides and alpha-glucosidase, are not approved for use in children in Germany [1].

New classes of drugs, such as sodium-glucose co-transporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, are now an integral part of the guidelines for the treatment of type 2 diabetes in adults with chronic kidney disease [14, 15]. Both classes of drugs have been shown to reduce cardiovascular risk and the progression of kidney disease [15]. In Germany, there are still official limitations on the eGFR up to which SGLT2 inhibitors can be used. Based on small studies in transplant patients, the use of SGLT2 inhibitors appears to be safe [16]. However, it should be noted that there may be a transient increase in creatinine and urogenital infections; euglycaemic ketoacidosis may occur, and discontinuation of SGLT2 inhibitors is required in the event of prolonged fasting periods or acute illness [17].

In Germany, SGLT2 inhibitors are approved for children aged 10 years and older; their use in children with an eGFR < 60 ml/min/1.73 m^2 has not been tested. Publications on the use of SGLT2 inhibitors in paediatric kidney transplant patients are not yet available. As PTDM often involves a combination of insulin resistance and insulin deficiency, insulin deficiency should always be ruled out before using this group of drugs to minimise the risk of life-threatening ketoacidosis.

In one case series, kidney transplant patients were treated with GLP-1 receptor agonists and liraglutide appeared to be safe and effective in these adults [18]. The benefits of these agents include facilitation of weight loss in obesity, absence of hypoglycaemia, improvement in insulin sensitivity, and substantial independence from eGFR (particularly with liraglutide). Due to the initial main side effects of inappetence, nausea and very rarely vomiting, the dose must be increased slowly with close monitoring of immunosuppressive drug levels. GLP-1 receptor agonists are approved for use in children from 12 years of age and may be considered as combination therapy in obese children with type 2 DM, although long-term data on cardiovascular risk reduction are lacking [19]. No data are available on their use in paediatric kidney transplant patients.

Paediatric societies continue to recommend metformin as the first-line treatment for type 2 DM in children [19]. If GFR is impaired, the benefit of metformin must be carefully weighed against the risk of lactic acidosis. Insulin therapy should be initiated if fasting blood glucose is > 200 mg/dL, metabolic decompensation is present, oral antidiabetic medications are ineffective, or HbA1c is persistently > 10% [19]. Comprehensive patient education should be provided and therapy should be monitored by an experienced multidisciplinary diabetes team. Continuous blood glucose monitoring is helpful as steroids are taken by transplant patients in the morning and a significant rise in blood glucose levels is observed in the late afternoon or early evening.

Although current recommendations for the treatment of type 1 diabetes mellitus no longer include medium-acting sustained-release insulin (usually NPH insulin (neutral protamine Hagedorn)), it can be given in the morning in PTDM in order to control the steroid-induced rise in blood glucose levels in the late afternoon or early evening [20]. Alternatively, detemir can be used, which has a similar efficacy profile. In the evening, a long-acting insulin analogue such as glargine, Glargine U300® or degludec is recommended to control the morning blood glucose rise and minimise the risk of nocturnal hypoglycaemia [20]. Rapid-acting insulin analogues such as insulin aspart or insulin lispro are recommended for prandial substitution. Insulin pumps are a useful therapeutic option, but are rarely used. Only human insulin or insulin analogues should be used in children [20].

Despite the ongoing development of new antidiabetic agents, and in the absence of recommendations from professional societies for the treatment of PTDM in children, it can be concluded from the reviewed studies that insulin therapy is recommended for the treatment of PTDM after intensive patient and parent education and care by an experienced paediatric diabetes team.

Depending on the severity of the hyperglycaemia, insulin therapy should be individualised. SGLT2 inhibitors and GLP-1 receptor agonists may be considered on a case-by-case basis after weighing the benefits and risks.

Complications

Children and adolescents with PTDM after organ transplantation have a threefold increased risk of death compared with healthy peers [21]. Cardiovascular mortality increases significantly when other risk factors such as arterial hypertension or hyperlipidaemia are also present. Patients with PTDM also have an increased risk of developing serious infections or sepsis, particularly urinary tract infections, pneumonia and cytomegalovirus infections [2]. Diabetic sequelae such as ophthalmological and neurological complications should not be neglected [19].

Summary

PTDM is defined as (i) fasting glucose ≥ 126 mg/dL, or (ii) symptoms of hyperglycaemia with random blood glucose of ≥ 200 mg/dL, or (iii) 2-hour glucose during an oral glucose tolerance test ≥ 200 mg/dL, or (iv) HbA1c ≥ 6.5%. The incidence of PTDM in children varies from 3% to 20%. Glucocorticoids, calcineurin inhibitors and mTOR inhibitors have a diabetogenic effect, with tacrolimus showing an increased risk of PTDM compared with ciclosporin. In patients with PTDM, modification of immunosuppression should always be weighed against the risk of potential rejection. In addition to the recommendations for lifestyle changes, diabetes should be treated promptly with medication.

The current consensus guideline for adults with PTDM recommends an individualised therapy with metformin, SGLT2 inhibitors, GLP-1 receptor agonists, DPP4 inhibitors and insulin, taking into account the risk-benefit ratio. In Germany, DPP4 inhibitors are not approved for use in children with diabetes mellitus. Metformin is still approved by the paediatric diabetes associations for the treatment of type 2 diabetes mellitus, but must not be used in cases of severely impaired renal function because of the risk of lactic acidosis. SGLT2 inhibitors are approved in Germany for children from 10 years of age and have a favourable risk profile for cardiovascular complications. Side effects such as

life-threatening euglycaemic ketoacidosis must be taken into account when prescribing them.

GLP-1 receptor agonists are approved in Germany for use in children 12 years and older to facilitate weight loss in obesity. Gastrointestinal side effects, which may interfere with the absorption of immunosuppressive drugs, must be considered. There are no expert recommendations for the treatment of PTDM in children. Early insulin therapy in children with PTDM is reasonable, especially as insulin therapy is approved for use in children and does not interact with immunosuppressants. This therapy requires intensive patient education and should be supervised by an experienced paediatric diabetes team. In individual cases, the use of SGLT2 inhibitors and GLP-1 receptor agonists may be considered on a risk-benefit basis. Screening for long-term complications of PTDM should be included in transplant aftercare.

References

1 Sharif A, Chakkera H, de Vries APJ, Eller K, Guthoff M, Haller MC, et al. International consensus on post-transplant diabetes mellitus. Nephrol Dial Transplant. 2024;39(3):531–49.
2 Shivaswamy V, Boerner B, Larsen J. Post-Transplant Diabetes Mellitus: Causes, Treatment, and Impact on Outcomes. Endocr Rev. 2016;37(1):37–61.
3 Grundman JB, Wolfsdorf JI, Marks BE. Post-Transplant Diabetes Mellitus in Pediatric Patients. Horm Res Paediatr. 2020;93(9–10):510–8.
4 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021;44(Suppl 1):S15–s33.
5 Bellanné-Chantelot C, Chauveau D, Gautier JF, Dubois-Laforgue D, Clauin S, Beaufils S, et al. Clinical spectrum associated with hepatocyte nuclear factor-1beta mutations. Ann Intern Med. 2004;140(7):510–7.
6 Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ. Diabetes mellitus after kidney transplantation in the United States. Am J Transplant. 2003;3(2):178–85.
7 Woodle ES, First MR, Pirsch J, Shihab F, Gaber AO, Van Veldhuisen P. A prospective, randomized, double-blind, placebo-controlled multicenter trial comparing early (7 day) corticosteroid cessation versus long-term, low-dose corticosteroid therapy. Ann Surg. 2008;248(4):564–77.

8 Montero N, Quero M, Melilli E, Pérez-Sáez MJ, Redondo-Pachón D, Bestard O, et al. Mammalian Target of Rapamycin Inhibitors Combined With Calcineurin Inhibitors as Initial Immunosuppression in Renal Transplantation: A Meta-analysis. Transplantation. 2019;103(10):2031–56.
9 KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant. 2009;9 Suppl 3:S1–155.
10 Hecking M, Werzowa J, Haidinger M, Hörl WH, Pascual J, Budde K, et al. Novel views on new-onset diabetes after transplantation: development, prevention and treatment. Nephrol Dial Transplant. 2013;28(3):550–66.
11 Kurnikowski A, Nordheim E, Schwaiger E, Krenn S, Harreiter J, Kautzky-Willer A, et al. Criteria for prediabetes and posttransplant diabetes mellitus after kidney transplantation: A 2-year diagnostic accuracy study of participants from a randomized controlled trial. Am J Transplant. 2022;22(12):2880–91.
12 Tauschmann M, Forlenza G, Hood K, Cardona-Hernandez R, Giani E, Hendrieckx C, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Diabetes technologies: Glucose monitoring. Pediatr Diabetes. 2022;23(8):1390–405.
13 Cohen E, Korah M, Callender G, Belfort de Aguiar R, Haakinson D. Metabolic Disorders with Kidney Transplant. Clin J Am Soc Nephrol. 2020;15(5):732–42.
14 Mottl AK, Nicholas SB. KDOQI Commentary on the KDIGO 2022 Update to the Clinical Practice Guideline for Diabetes Management in CKD. Am J Kidney Dis. 2024;83(3):277–87.
15 Sarafidis P, Ferro CJ, Morales E, Ortiz A, Malyszko J, Hojs R, et al. SGLT-2 inhibitors and GLP-1 receptor agonists for nephroprotection and cardioprotection in patients with diabetes mellitus and chronic kidney disease. A consensus statement by the EURECA-m and the DIABESITY working groups of the ERA-EDTA. Nephrol Dial Transplant. 2019;34(2):208–30.
16 Lim JH, Kwon S, Jeon Y, Kim YH, Kwon H, Kim YS, et al. The Efficacy and Safety of SGLT2 Inhibitor in Diabetic Kidney Transplant Recipients. Transplantation. 2022;106(9):e404–e12.
17 Zinman B, Lachin JM, Inzucchi SE. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2016;374(11):1094.
18 Liou JH, Liu YM, Chen CH. Management of Diabetes Mellitus With Glucagonlike Peptide-1 Agonist Liraglutide in Renal Transplant Recipients: A Retrospective Study. Transplant Proc. 2018;50(8):2502–5.

19 Shah AS, Zeitler PS, Wong J, Pena AS, Wicklow B, Arslanian S, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Type 2 diabetes in children and adolescents. Pediatr Diabetes. 2022;23(7):872–902.
20 Cengiz E, Danne T, Ahmad T, Ayyavoo A, Beran D, Ehtisham S, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Insulin treatment in children and adolescents with diabetes. Pediatr Diabetes. 2022;23(8):1277–96.
21 Chanchlani R, Kim SJ, Dixon SN, Jassal V, Banh T, Borges K, et al. Incidence of new-onset diabetes mellitus and association with mortality in childhood solid organ transplant recipients: a population-based study. Nephrol Dial Transplant. 2019;34(3):524–31.