



# Post-liver transplantation diabetes mellitus — a clinical challenge for diabetologists?

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Liver transplantation has become an effective therapy for patients with acute or chronic end-stage liver disease. With improvement in operative techniques and immunosuppressive regimens, long-term survival after liver transplantation has markedly increased. However, with increased longevity, the attention has shifted towards long-term complications, which are primarily related to the immunosuppressive treatment. One such complication is new-onset diabetes after transplantation (NODAT), often referred to as posttransplantation diabetes mellitus (PTDM).

New-onset diabetes after transplantation refers to individuals who develop new-onset diabetes following solid organ, bone marrow, and hematopoietic stem cell transplant. *It characteristically excludes patients with pretransplant diabetes that remained undiagnosed and posttransplant hyperglycemia that resolves by the time of discharge* [1]. On the other hand, PTDM theoretically describes the presence of diabetes in the posttransplant setting irrespective of the time of onset of diabetes [1, 2]. Nevertheless, in routine clinical practice, the two terms are often used interchangeably.

Hyperglycemia is not uncommon during the early posttransplant period; nearly 90% of liver transplant recipients exhibit hyperglycemia in the immediate posttransplant period [3]. In the majority of the cases, such stress- or steroid-induced hyperglycemia resolves by the time of discharge. Whereas posttransplantation hyperglycemia is an important risk factor for subsequent PTDM, *a formal diagnosis of PTDM should ideally be made once the patient is stable on maintenance immunosuppression and in the absence of acute infection* [4].

The diagnosis of PTDM, which in the context of liver transplantation is referred to as post-liver transplantation diabetes mellitus (PLTDM), has long been a matter of debate [5].

Earlier, the most commonly used clinical definition was the requirement of insulin for a minimum period (usually 30 days) posttransplantation. This definition had resulted in underestimating the prevalence of diabetes after transplantation because it excludes patients treated with oral antidiabetic drugs and those with untreated hyperglycemia, impaired fasting glucose (IFG), or impaired glucose tolerance (IGT). Furthermore, it does not distinguish between patients with new-onset disease from those with preexisting disease [6].

The *International Consensus Guidelines on new-onset diabetes after transplantation 2003* recommended that the diagnosis should be based on the American Diabetes Association (ADA) criteria for type 2 diabetes mellitus [6], which are as follows:

- Fasting plasma glucose (FPG)  $\geq 7.0$  mmol/l (126 mg/dl) with no calorie intake for at least 8 h, or
- Two-hour plasma glucose during an OGTT (2-h PG post-OGTT)  $\geq 11.1$  mmol/l (200 mg/dl), or
- Casual plasma glucose  $\geq 11.1$  mmol/l (200 mg/dl) with classic symptoms of diabetes, all being documented on 2 different occasions.

Thus, the diagnostic criteria for PLTDM are the same as those for diabetes in the general population [5]. Since postprandial hyperglycemia is much more prevalent than fasting hyperglycemia among liver transplant patients [7], the ideal screening test for PLTDM is the oral glucose tolerance test (OGTT) [8]. However, performing an OGTT under supervision might not always be feasible, thereby clinicians might have to rely solely on FPG.

Even in the posttransplant setting, a fasting plasma glucose level of  $< 5.5$  mmol/l (100 mg/dl) is considered to be normal, and 5.5–6.9 mmol/l (100–125 mg/dl) is considered to be IFG. A 2-h post-OGTT plasma glucose level of  $< 7.7$  mmol/l (140 mg/dl) is considered to be normal, and 7.7–11.1 mmol/l (140–199 mg/dl) is considered to be IGT. The importance of diagnosing the pre-diabetic states (IFG and IGT) in the post-liver

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transplant context lies in their relevance as predictors of future risk of PLTDM [5]. Apart from the aforementioned diagnostic criteria, post-liver transplant patients whose blood glucose levels are normal but are using insulin or oral antidiabetic drugs are also diagnosed as having PLTDM [9].

*Glycated hemoglobin (HbA<sub>1c</sub>) has a limited role* in the diagnosis of PTDM (or PLTDM). Due to blood loss associated with the transplant procedure, preexisting anemia (and subsequent shortened red blood cell survival), and especially lack of robust evidence regarding its use in the early posttransplant period, HbA<sub>1c</sub> is not recommended as a first-line diagnostic test for PLTDM, especially in the first 3 months posttransplant [10]. Beyond 3 months, the new hemoglobin would be synthesized and glycated for an appropriate period of time; in such setting, HbA<sub>1c</sub>  $\geq$  6.5% can be utilized to diagnose PTDM. On the contrary, many studies do not recommend the use of HbA<sub>1c</sub> alone as a screening tool for diagnosing PTDM in the first year after transplant [11].

Although the diagnostic criteria for defining PLTDM have been standardized, the timing of the tests remains controversial and unresolved. Most believe that the first month after liver transplantation still falls within the period of surgical stress; hence, plasma glucose levels *beyond 1 month after liver transplantation* should be used as the determining criterion [9, 12]. On the contrary, others opine that if rejection or surgical complications do not occur in the postoperative period, stress-related hyperglycemia would be resolved in most patients until the end of the first month [13].

In this issue of the *International Journal of Diabetes in Developing Countries*, Topaloğlu et al. report on the prevalence of NODAT after liver transplantation in patients with acute liver failure. The diagnosis of NODAT was based solely on fasting blood glucose (FBG) measured at frequent time intervals. Accordingly, the prevalence of NODAT was 26.98%, 14.54%, and 8.3% based on FBG measured at 1 month, 3 months, and 12 months post-liver transplant, respectively [14]. Although a significant fraction of patients who were alive at 1<sup>st</sup> month had subsequently succumbed at the 3<sup>rd</sup> month and 12<sup>th</sup> month, it remains unclear whether NODAT diagnosed in the 1<sup>st</sup> month could have been one of the predisposing factors contributing to the later demise of the patients. Similarly, it remains unanswered whether the marked decline in the prevalence of NODAT at the 3<sup>rd</sup> and 12<sup>th</sup> month could have resulted from the selective demise of patients diagnosed with NODAT in the 1<sup>st</sup> month, or a spontaneous reversal of stress-related hyperglycemia with time.

Thus, it does not seem to be prudent to label a liver transplant recipient as having NODAT on the basis of blood glucose values measured as early as 1 month posttransplant. The diagnosis of NODAT (or PLTDM) should ideally be based on 2-h PG post-OGTT (or FPG) or need for insulin/antidiabetic drugs beyond 1 month after liver transplant. Nevertheless, putting aside semantics, appropriate management of any

degree of hyperglycemia in the posttransplant period is imperative as those with early perioperative hyperglycemia and PTDM have higher rates of graft rejection, infection, and re-hospitalization [4, 15, 16].

Data derived from randomized controlled trials on the short- and long-term use of anti-hyperglycemic agents in the setting of PTDM is limited. Insulin remains the agent of choice for the management of hyperglycemia, PTDM, preexisting diabetes and diabetes in the hospital setting. After discharge, PTDM patients with poor glucose control should continue insulin with frequent home self-monitoring of blood glucose to help titrate insulin doses accordingly [4].

Hitherto, there is insubstantial data on the use of noninsulin agents in the context of PTDM. The choice of an appropriate agent is usually made after taking into consideration the side effect profile of the drug and possible interactions with the patient's ongoing immunosuppression regimen. Frequent drug dose adjustments may be needed because of a decline in the glomerular filtration rate, a common complication in transplant patients. A short-term pilot study reported the use of metformin in renal transplant recipients, but the same has not been replicated in other types of organ transplant [17]. Thiazolidinediones have been successfully used in patients with liver and renal transplants; however, frequent side effects that include fluid retention, heart failure, and osteopenia limit its use in the posttransplant setting [18, 19]. Dipeptidyl peptidase-4 inhibitors (DPP4i) have demonstrated safety in some recent clinical trials [20, 21]. Besides, DPP4i do not interact with most immunosuppressant drugs and hence can be safely used in most PTDM patients. Nevertheless, in view of limited clinical data, it would not be prudent to advise one antidiabetic drug (noninsulin) over the other. Well-designed randomized controlled trials examining the efficacy and safety of these and other antidiabetic agents in patients with PTDM are needed.

## Declarations

**Ethical approval** Not required

**Informed consent** Not applicable

**Conflict of interest** The authors declare no competing interests.

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