Viewpoint

New onset diabetes mellitus after liver transplantation

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The recently published article, "*New-onset diabetes after adult liver transplantation in the Korean Organ Transplantation Registry (KOTRY) study*" by Man Kim *et al.* has generated significant renewed interest in New Onset Diabetes after Transplant (NODAT) (1). NODAT was defined by International Consensus (2003) and by American Diabetes Association by the same criteria as Type 1/Type 2 diabetes. Anyone after liver or another solid organ transplantation (SOT) on antidiabetic medication for more than one month or who fulfills one of these criteria on stable immunosuppression is deemed to have NODAT: (I) fasting blood sugar (FBS) >7 mmol (126 mg/dL); (II) random blood sugar (RBS) on two occasions or a 2-hour blood sugar on a 75-gm oral glucose tolerance test (OGTT) of >11.1 mmol (200 mg/dL); (III) HbA1c >6.5% (2). Unfortunately, this definition lumps together, patients with varying degrees of pancreatic β cell dysfunction and Insulin resistance. This is problematic both in terms of optimizing individualized care and preventing/predicting development of complications downstream. Measuring Insulin levels along with glucose levels during a 2-hour OGTT will be able to better define the mechanism(s) involved in the causation of hyperglycemia and help with tailoring management (3).

HbA1c significantly underestimates average blood sugars in post liver transplant patients, especially in those with congestive splenomegaly and therefore it should not be used for diagnosis or management of NODAT. Many experts are considering change of terminology back to Post Transplant Diabetes Mellitus (PTDM) as a significant number of patients may have undiagnosed DM and in most NODAT patients, the risk factors for development of DM are present pre-transplantation (4).

The incidence of NODAT varies significantly among studies of NODAT in the 3 major solid organ transplants due to varying definitions and ranges from 10–40% over 1–5 years for liver transplantation. Highest incidence (80% of total) is in the first 6–12 months after transplantation. It drops to about 3–4% per year for the next 4 years (1). Liver transplant patients have relatively low induction and maintenance Immunosuppressant use. Also, unlike heart and kidney, it is the organ most involved in sugar and energy metabolism. As the new organ functions better, and the portal blood flow is corrected, the donor liver should have a major protective effect on the recipient. Hence, LT should have the lowest incidence of NODAT among SOT. So far, there is precious little published to explain why this is not actualized.

Mechanism/s of causation of NODAT/PTDM

(I) A fertile soil of insulin resistance with obesity, family history of diabetes and sarcopenia is present in most patients even before liver transplantation.

(II) Impact of immunosuppression on β cell mass and function (5) (calcineurin and mTOR inhibitors) and simultaneous increase in Insulin resistance in the muscle, adipose tissue and liver produced by glucocorticoids is unique to transplant and is the most important driver in the first 3 months post liver transplantation when the seed of NODAT is sowed.

(III) Dysfunction of the donor liver due to any cause: (i) preexisting hepatitis C infection; (ii) donor age, diabetes and liver steatosis; (iii) ischemia reperfusion injury (as in donation after circulatory death); (iv) vascular or biliary complications (v) opportunistic infections such as CMV; (vi) rejection both acute and chronic.

(IV) Post-transplant weight gain: the maximum rate occurs between 3 months and 1-year post-transplantation (and it is generally more adipose tissue than lean body mass) and so it is not surprising that the incidence of NODAT is also the highest during this period (6).

(V) Impact on morbidity and mortality in liver transplantation: Many single-center and most registry studies overall suggest worse graft and patient outcomes associated with NODAT/PTDM. The graft outcomes likely influence NODAT more than vice-versa. Infections, renal and cardiovascular outcomes are worse in patients with NODAT/PTDM. However, the problem is quite complicated—there is a lot of interplay between rejection/immunosuppression and NODAT/PTDM and therefore a direct cause and effect of diabetes with outcomes is difficult to prove without more granular data. Longer and more well designed and multicenter studies controlled for age ethnicity and immunosuppression are needed.

Prevention and management of NODAT

Age, BMI, African and Hispanic race, presence of Hep C, prediabetes, family history of T2DM and sarcopenia are pre-transplant risk factors for developing NODAT/PTDM.

In patients with two or more risk factors, periodic monitoring with weight, BMI, fasting glucose and Insulin levels at one month post transplantation and monthly till 3 months and then Q 3 monthly till 1 year and Q 6 monthly thereafter can identify patients at high risk for NODAT/PTDM. OGTT with Insulin level measurement periodically is ideal but may be inconvenient and expensive.

Those prediabetic and insulin resistant can be targeted for intensive global management. The same strategy should be employed in all patients discharged on Insulin or other anti-diabetic therapy after transplantation. Weekly consultation by transplant dietician with patient/caregiver can be most helpful in the first month.

The donor factors are not controllable, so also biliary/vascular complications and unexpected rejection. These can increase risk for NODAT/PTDM directly or indirectly.

Using Induction therapy that avoids or minimizes corticosteroids in high-risk patients. Early addition of Mycophenolate can help wean steroids without risking rejection. Also, with this strategy, most patients can be managed with tacrolimus dosing to achieve trough levels under 7–8 ng/mL.

Limiting glucose in IV fluids especially in those on steroids, minimizing sugar in tube feeds and nutritional supplements along with a diabetic diet can decrease the insulin requirements early post- transplantation and decrease pancreatic β cell exhaustion. Use of continuous glucose monitoring (CGM) devices once approved in the hemodynamically stable inpatients will go a long way in achieving euglycemia along with diet and short acting insulin in the inpatient setting.

If possible, would use extended-release Metformin at tolerated doses with DPP-4 inhibitors/GLP-1 agonists in those who are hyperglycemic at discharge along with a strict no sugar/low carbohydrate diet and CGM for monitoring so that weaning from Insulin over the next 3 months is made a major priority. Lowering the blood Insulin levels while keeping blood sugars controlled, will decrease (fat) weight gain and decrease NODAT/PTDM during the first year after transplantation when they are at the highest risk. An approach to management of NODAT/PTDM in the first year after LT is presented in the *Figure 1*.

Conclusions

Heightened awareness among patients, caregivers and hepatologists of NODAT/PTDM and its consequences can lead to optimal and individualized management. This will decrease its incidence, even reverse/resolve the problem in a significant majority and thus improve long term outcomes.

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Footnote

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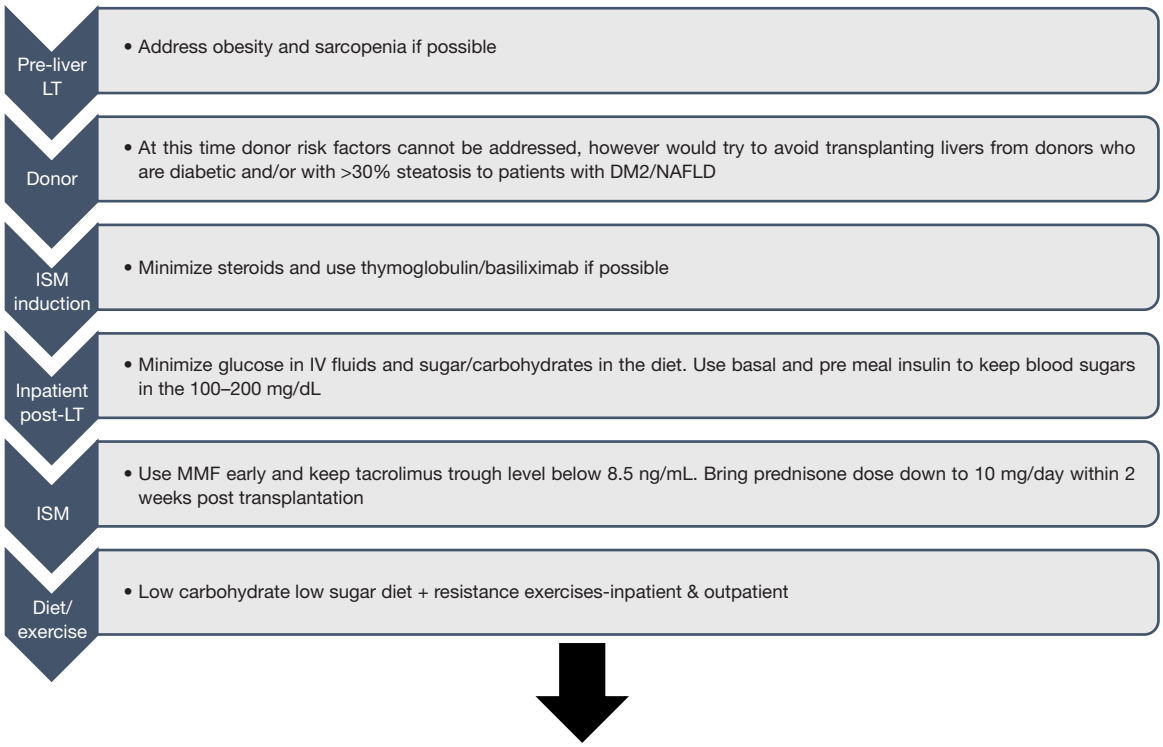

	No hyperglycemia	Transient hyperglycemia	Persistent hyperglycemia	Pre-transplant DM2
0 week	No medication	Low dose metformin ER	Metformin + DPP-4 + lowest dose Insulin	Metformin + GLP-1 + lowest dose Insulin
1–4 weeks	Weekly dietary counsel + FBS/ insulin level	Weekly dietary counsel + FBS/insulin	Weekly dietary counsel + wean insulin gradually	Weekly dietary counsel + wean insulin gradually
4–12 weeks	Monthly dietary counsel + FBS/ insulin*	Monthly dietary counsel + FBS/insulin	Monthly dietary counsel + FBS/insulin level + weight loss measures	Quarterly dietary counsel + weight loss measures + wean insulin gradually
>12 weeks	Monthly dietary counsel + FBS/ insulin*	Monthly dietary counsel + FBS/insulin	Quarterly dietary counsel + weight loss measures + wean insulin gradually	Quarterly diet counsel + weight loss measures + wean insulin

*, consider OGTT + insulin.

Figure 1 Post-transplant diabetes mellitus prevention and management.

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