

Hyperglycemia in the Posttransplant Period: NODAT vs Posttransplant Diabetes Mellitus

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Objective: To characterize the types of hyperglycemia that occur up to 1 year following liver transplant and to clarify the nomenclature for posttransplant hyperglycemia.

Design: We analyzed 1-year glycemic follow-up data in 164 patients who underwent liver transplant and who had been enrolled in a randomized controlled trial comparing moderate to intensive insulin therapy to determine if patients had preexisting known diabetes, transient hyperglycemia, persistent hyperglycemia, or new-onset diabetes after transplantation (NODAT).

Results: Of 119 patients with posttransplant hyperglycemia following hospital discharge, 49 had preexisting diabetes, 5 had insufficient data for analysis, 48 had transient hyperglycemia (16 resolved within 30 days and 32 resolved between 30 days and 1 year), 13 remained persistently hyperglycemic out to 1 year and most likely had preexisting diabetes that had not been diagnosed or insulin resistance/insulinopenia prior to transplant, and 4 had NODAT (*i.e.*, patients with transient hyperglycemia after transplant that resolved but then later truly developed sustained hyperglycemia, meeting criteria for diabetes).

Conclusions: Distinct categories of patients with hyperglycemia following organ transplant include known preexisting diabetes, persistent hyperglycemia (most likely unknown preexisting diabetes or insulin resistance/insulinopenia), transient hyperglycemia, and NODAT. Those with preexisting diabetes for many years prior to transplant may well have very different long-term outcomes compared with those with true NODAT. Therefore, it would be prudent to classify patients more carefully. Long-term outcome studies are needed to determine if patients with true NODAT have the same poor prognosis as patients with preexisting diabetes (diagnosed and undiagnosed) undergoing transplant.

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Freeform/Key Words: diabetes mellitus, hyperglycemia, NODAT, PTDM, transplant

Hyperglycemia occurring in patients following organ transplant and other surgeries is common, occurring in over 75% of patients following surgery such as heart surgery and transplant [1, 2]. Many of these patients have preexisting diabetes mellitus, although in some it is only detected for the first time following surgery. The term new-onset diabetes after transplantation (NODAT) had been used routinely before 2014 and referred to the development

Abbreviations: A1c, hemoglobin A1c; NODAT, new-onset diabetes after transplantation; PTDM, posttransplant diabetes mellitus.

of diabetes posttransplant in patients who were previously nondiabetic [3]. In some but not all studies, the term NODAT is restricted to those in whom early posttransplant hyperglycemia had resolved. Furthermore, the time at which NODAT is diagnosed (1 month, 1 year, *etc.*) has not been specified carefully. NODAT, as loosely defined, has been associated with increased rates of acute transplant rejection, infection, late cardiovascular events, and decreased survival [2, 3]. In our opinion, NODAT should *not* include patients who might have undiagnosed preexisting diabetes before transplant and who remained hyperglycemic following transplant. The term posttransplant diabetes mellitus (PTDM) was reintroduced in 2014 and refers to patients who are first found to have diabetes after transplant when they are stable on their maintenance immunosuppression, with stable allograft function and in the absence of acute infections; however, the exact timing when this term applies is not stated [4]. Thus, PTDM would include patients with persistent hyperglycemia (likely due to preexisting diabetes that had not been diagnosed prior to transplant), those with NODAT, and those with transient posttransplant hyperglycemia that resolves within 1 year of transplant. Part of the reasoning for using the PTDM terminology is that screening for undiagnosed diabetes at the time of transplant is often not done effectively in many centers [4]. Hyperglycemia after transplant, whether classified as NODAT and/or PTDM, has been associated with a variety of adverse outcomes, including increased mortality, organ rejection, and infections as well as hospital costs [2, 3, 5–7].

There is a move by some investigators to do away with the NODAT terminology and just use the PTDM term [4]. However, an argument against such a change in nomenclature is the different pathophysiologies of posttransplant persistent hyperglycemia, transient hyperglycemia, and NODAT. Transient hyperglycemia after transplant is thought to be due to the surgical stress-induced hyperglycemia-related insulin resistance from counterregulatory stress hormone release (*e.g.*, cortisol, growth hormone) and high-dose steroids as well as suppression of insulin secretion by stress-induced catecholamine release [1, 2]. NODAT is thought to be due to effects on insulin secretion and action related to the immunosuppression regimen and generally takes months to years to manifest and is more likely to occur in people otherwise at risk for type 2 diabetes [1, 2, 5]. Those with hyperglycemia that persists permanently after transplant most likely had diabetes that preexisted the transplant but had not been diagnosed or insulin resistance/insulinopenia, although it is possible that a portion of these could be patients who had surgical stress/high-dose steroid hyperglycemia that transitioned directly into rapid-onset NODAT due to the adverse effects of the immunosuppression regimen. Thus, the duration of hyperglycemia is different for these groups, and thus the long-term outcomes for these groups may be very different.

The objective of the current investigation was to perform an in-depth characterization of the types of hyperglycemia that occur up to 1 year following liver transplant, to clarify the nomenclature of posttransplant hyperglycemia, and to analyze the most common causes of transient hyperglycemia in patients who underwent liver transplant. A unique finding of our investigation was the large number of patients who had hyperglycemia that only resolved between 30 days and 1 year following transplant.

1. Methods

We analyzed 1-year glycemic follow-up data in 164 patients who underwent liver transplant who had been enrolled in a randomized controlled trial comparing moderate insulin [target glucose ~180 mg/dL (10 mmol/L) group] to intensive insulin [target glucose ~140 mg/dL (7.8 mmol/L) group] therapy at Northwestern Memorial Hospital from April 2009 to December 2014 (ClinicalTrials.gov no. NCT01211730) [8]. The patient or authorized family member provided written informed consent as established by the Northwestern University institutional review board. Data examined included fasting glucose levels, random glucose levels, and hemoglobin A1c (A1c) levels that were obtained at routine posttransplant visits. Values obtained prior to 8:00 AM were arbitrarily designated as fasting glucose levels. It is possible that, in some cases, these blood samples obtained prior to 8:00 AM were not truly fasting. However, this population would be less likely to be affected by shift working; in

addition, patients are asked to be fasting for their morning laboratory testing at the transplant clinic. Hyperglycemia and diabetes were defined as fasting glucose levels ≥ 126 mg/dL (7 mmol/L) and/or random glucose levels ≥ 200 mg/dL (11.1 mmol/L) and/or A1c levels $\geq 6.5\%$ (48 mmol/mol) or the use of diabetes medications. Oral glucose tolerance tests for determination of diabetes status were not routinely performed in the follow-up of these patients.

The posttransplant immunosuppressive regimen was fairly uniform during the period studied and was not influenced by factors such as preexisting diabetes or prediabetes and included methylprednisolone 500 mg before and after surgery for induction and then a rapidly tapering schedule of prednisone over 8 weeks to 10 mg daily. Over the next several months, patients were then tapered to 5 mg daily of prednisone, and this was usually stopped at 24 weeks. The usual calcineurin inhibitor was tacrolimus, which was started immediately posttransplant; cyclosporine and mammalian target of rapamycin inhibitors were used very infrequently. Rejection episodes were treated with 500 mg of methylprednisolone daily for 3 days with a subsequent taper over 1 week.

Of the 164 patients, 49 had diabetes that had been diagnosed prior to transplant. Of the remaining 115 patients, 70 were found to have hyperglycemic episodes following discharge and up to 1 year following transplant and were analyzed further. Five patients were excluded from further analysis because of incomplete data: 2 were lost to follow-up, 2 died within 1 year of transplant, and 1 had a second liver transplant. The remaining 65 participants underwent manual chart review to determine concomitant illness, steroid dosing, and immunosuppression regimen.

2. Results

The 65 patients who were found to have hyperglycemic episodes following initial hospital discharge and up to 1 year following transplant were divided into three groups (Fig. 1) (i) transient (resolved within 1 year) posttransplant hyperglycemia ($n = 48$); (ii) persistently hyperglycemic after transplant out to 1 year ($n = 13$); and (iii) NODAT, patients whose transient hyperglycemia after transplant resolved but then later truly developed hyperglycemia, meeting criteria for diabetes ($n = 4$).

Of the 48 patients who had transient hyperglycemia, 16 had resolution of their hyperglycemia within 30 days of transplant, and the remaining 32 had persistent hyperglycemia after transplant with resolution of their hyperglycemia between 30 days and 1 year (Fig. 2). Of this latter group of 32 patients, the hyperglycemia was attributed to higher-than-maintenance steroid doses in 25, to high tacrolimus doses in 15, to infections in 14, and to rejection in 6. These numbers add up to more than 32 because some patients had more than one cause. It should be noted that 13 of those with transient hyperglycemia (6 in those with resolution within 30 days and 7 with resolution between 30 days and 1 year) were treated with diabetes medications for several weeks while hyperglycemic before becoming normoglycemic without medications.

3. Discussion

Of the 159 of our 164 patients who underwent liver transplant who had sufficient data for analysis, 114 (71.7%) had hyperglycemia following transplant after initial hospital discharge. Forty-nine of these 114 patients (43%) had known, preexisting diabetes. However, 65 of 114 (57%) were not known to have diabetes. Thirteen of these 114 (11.4%) had hyperglycemia that was persistent out to 1 year and most likely had preexisting diabetes that had not been diagnosed prior to transplant. However, it is possible that a portion of these could be patients who had surgical stress/high-dose steroid hyperglycemia that transitioned directly into rapid-onset NODAT due to the adverse effects of the immunosuppression regimen.

A unique finding of our study is the very high proportion of patients with transient posttransplant hyperglycemia, being present in 48 of these 65 (or 48 of 114 = 42.1%) with

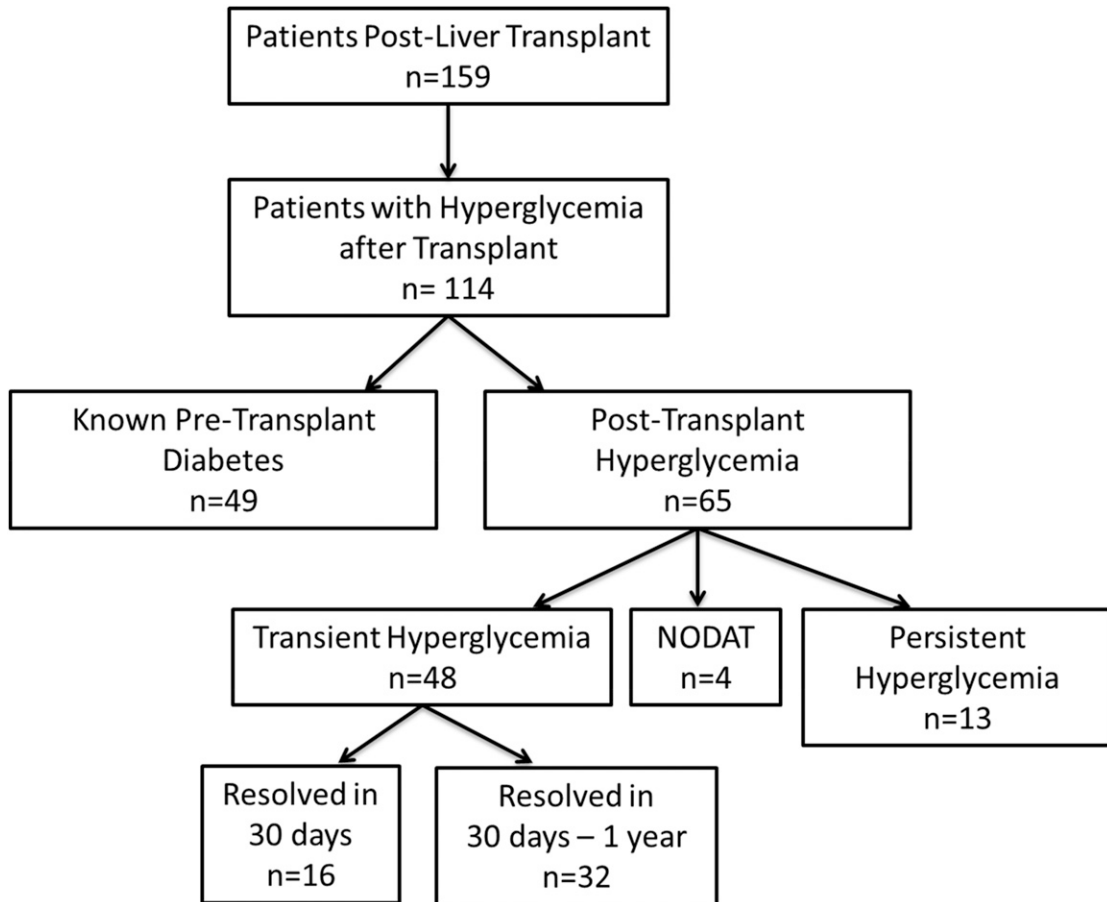


Figure 1. Of the 164 patients in the controlled study, 159 patients had posttransplant glycemetic data sufficient for analysis: 49 had preexisting diabetes and 65 had posttransplant hyperglycemia (48 had transient hyperglycemia that resolved before 1 year: 16 within 30 days and 32 between 30 days and 1 year; 13 had persistent hyperglycemia; and 4 developed NODAT).

posttransplant hyperglycemia in patients not previously known to have diabetes. In this group, 16 had resolution of their hyperglycemia within 30 days of transplant, and their hyperglycemia was likely due to a combination of factors, such as postoperative stress, high-dose steroids used for induction of immunosuppression, early rejection, and postoperative infections [1, 2, 9]. However, in 32, the hyperglycemia lasted longer than 30 days but had disappeared between 30 days and 1 year and was due to a multitude of causes, including higher-than-maintenance steroid doses, high doses of tacrolimus, infections, and rejection. The entity of true NODAT (*i.e.*, patients with a return to normoglycemia after transplant but then the later development of diabetes) was quite low, with only four patients (4 of 114 = 3.5%) meeting criteria for this diagnosis at 1 year. However, it is known that in subsequent years, the diagnosis of NODAT increases [10], primarily due to adverse effects of calcineurin inhibitors, mammalian target of rapamycin inhibitors, and steroids on insulin secretion/action and also just the general increase in incidence of type 2 diabetes with age [1, 2, 6, 11, 12]. Neither PTDM nor NODAT previous classifications took into consideration that hyperglycemia occurring more than 1 month after transplant could be transient, and many such patients were then included under the rubrics of PTDM and NODAT. Based on our experience, it appears that, in most of these patients, the hyperglycemia resolves, and only a much smaller proportion develop true NODAT.

Limitations of this study are that it was carried out in a single center and with only patients who underwent liver transplant. However, there is no reason to think that other

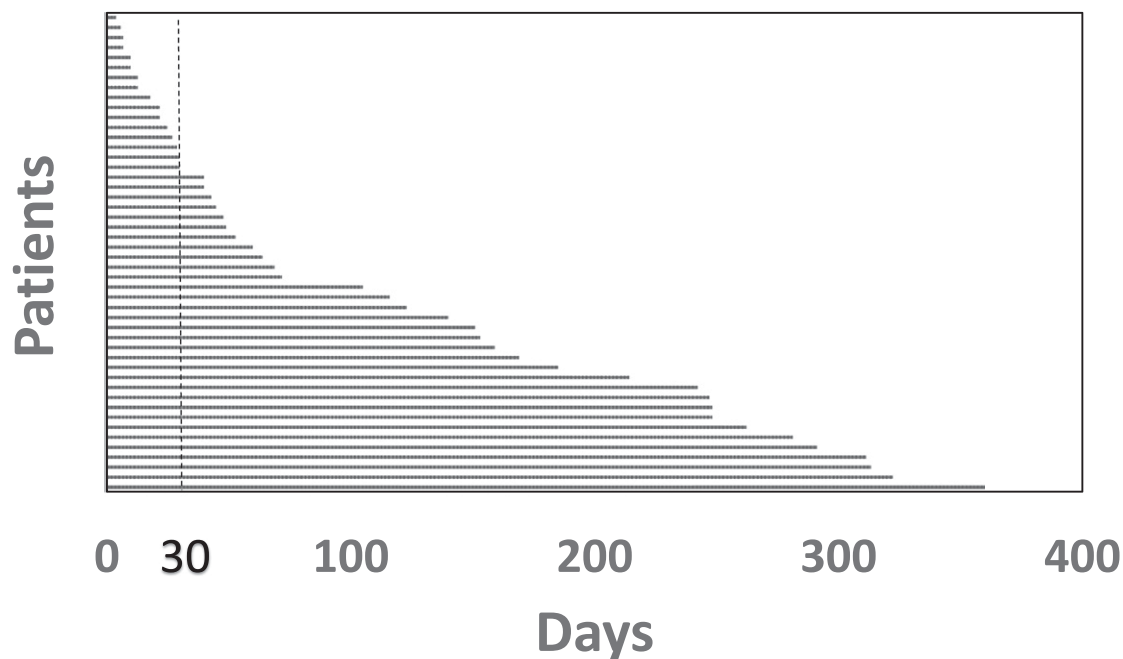


Figure 2. Transient hyperglycemic patients. Shown are the number of days following transplant that each patient remained hyperglycemic before becoming normoglycemic. The vertical, dashed line indicates the 30-day time point. Sixteen patients had resolution of their hyperglycemia in the first 30 days, and 32 patients had resolution between 30 days and 1 year.

centers or other organ transplant patients would show substantially different results with respect to the proportions of patients in the different categories we have outlined. The diagnosis of diabetes was made on the basis of elevated fasting blood glucose levels and/or elevated A1c levels but not by oral glucose tolerance tests, which are still the gold standard for diagnosing diabetes, as this was a retrospective analysis of routine care. In future studies in which prospective analyses of glycemic status are done, oral glucose tolerance tests should be carried out on a uniform basis in those individuals who revert to normoglycemia to detect early NODAT. Patients were followed for only 1 year after transplant, and longer-term follow-up will help to determine whether those with hyperglycemia that resolved between 30 days and 1 year are at increased risk for the later development of NODAT.

Based on this review of our experience, it is clear that there are distinct, separable categories of patients with diabetes following organ transplant. The largest group (43%) are those with preexisting, known diabetes. Another 11.4% have persistent hyperglycemia out to 1 year that is likely due to previously undiagnosed but preexisting diabetes or insulin resistance/insulinopenia. Only 3.5% at 1 year had true NODAT. Postoperative, transient hyperglycemia that resolved was present in 42.1%, with one-third of these resolving by 1 month and the remainder by 1 year following transplant. This group with transient hyperglycemia could very well have been included in prior studies of outcomes of patients with PTDM and NODAT, but it is difficult to tell from those studies.

Those with preexisting diabetes for many years prior to transplant may very well have very different long-term outcomes compared with those with true NODAT. Therefore, it would be prudent to classify patients more carefully, and long-term outcome studies are needed to determine if patients with true NODAT have the same poor prognosis as patients with preexisting diabetes (diagnosed and undiagnosed) undergoing transplant.

Acknowledgments

Financial Support: This work was supported by American Diabetes Association Junior Faculty Award 1-13-JF-54 (to A.W.).

Clinical Trial Information: ClinicalTrials.gov no. NCT01211730 (registered 29 September 2010).

Author Contributions: S.G., M.E.M., and A.W. participated in the writing of the paper, the performance of the research, and in data analysis. T.P., C.F., K.S., and D.J.O. participated in the performance of the research and in data analysis.

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Disclosure Summary: A.W. receives research support from Eli Lilly and NovoNordisk and serves as a consultant for Glytec. M.E.M. receives research support from Novartis, NovoNordisk, Bayer, and Johnson and Johnson and receives honoraria for consultations from NovoNordisk, Sanofi, Novartis, Merck, and Pfizer. The remaining authors have nothing to disclose.

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