

Effects of hyperglycemia on the development of new-onset diabetes after liver transplantation

Context—New-onset diabetes after transplantation (NODAT) has been associated with cardiovascular and thrombotic complications, acute rejection, and infection in transplant recipients. NODAT in kidney transplantation is well described; however, data are lacking in liver transplant recipients.

Objective—To evaluate the incidence of new-onset diabetes within 6 months postoperatively in adult liver transplant recipients.

Design, Participants, Setting, and Interventions—Patients who underwent a liver transplantation at our institution between January 2004 and December 2005 were retrospectively evaluated. NODAT was defined according to the diagnostic criteria of the American Diabetes Association/World Health Organization, persistent hyperglycemia (serum glucose ≥ 200 mg/dL occurring 2 weeks after initial steroid induction and persisting for more than 2 weeks), or the need for hypoglycemic agents upon discharge.

Main Outcomes—Incidence of NODAT within 6 months after transplantation in patients with poor glycemic control within the first 2 weeks after transplantation, acute rejection episodes, infections, hospital readmissions, and cardiovascular and thrombotic events.

Results—Forty-five patients were evaluated. Within the first 6 months after transplantation, NODAT developed in 11 (24%). Acute rejection, infection, hospital readmissions, cardiovascular events, and thrombotic events did not differ between the groups.

Conclusion—Elevated fasting levels of blood glucose during the first 2 weeks after liver transplantation may be associated with an increased incidence of NODAT and may have predictive value. More studies are needed to determine the effects of recognition and treatment of hyperglycemia in recent transplant recipients.

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New-onset diabetes after transplantation (NODAT), also known as posttransplant diabetes mellitus, is associated with increased mortality, morbidity, and occurrence of cardiovascular sequela.¹ This complication is defined as persistent hyperglycemia developing in any patient who had no history of diabetes mellitus before transplantation and hyperglycemia requiring any antidiabetic therapy after transplantation. Persistent hyperglycemia is a serum glucose level of 200 mg/dL or higher (to convert to millimoles per liter, multiply by 0.0555) occurring more than 2 weeks after the initial steroid induction cycle and persisting for more than 2 weeks.² Additionally, NODAT is characterized by the diagnostic criteria defined by the American Diabetes Association and the World Health Organization of a fasting plasma level of glucose of at least 126 mg/dL³ or random plasma level of glucose of 200 mg/dL or higher.

Transplant recipients require the use of immunosuppressive agents (eg, calcineurin inhibitors) and systemic

corticosteroids for improvement of graft function and survival³; however, these agents can adversely affect blood glucose levels. Hyperglycemia is reported to occur in 10% to 30% of adult liver transplant recipients and can be associated with the use of immunosuppressive therapy.² The exact mechanism of diabetes induced by calcineurin inhibitors is not known, but it is suggested that these agents affect the synthesis and secretion of insulin by β cells.⁴ Additionally, tacrolimus has a greater diabetogenic effect than does cyclosporine.⁵ Diabetogenic effects can also be seen with systemic corticosteroid therapy via decreased glucose utilization and hepatic glucose production.³ This phenomenon is dose-dependent and may have a lesser effect with shorter duration of therapy.⁵

Many researchers have investigated the diabetogenicity of immunosuppressive agents such as calcineurin inhibitors and corticosteroids. Sulanc et al⁶ evaluated the risk of NODAT after kidney transplantation

Table 1 Demographics of patients participating in the study^a

Characteristic	New-onset diabetes after transplantation (n = 11)	Normoglycemic (n = 34)
Age, mean (SD), y	51.9 (8.0)	50.9 (9.8)
Sex		
Female	3 (27)	12 (35)
Male	8 (73)	22 (65)
Ethnicity		
African American	0 (0)	1 (3)
White	11 (100)	32 (94)
Hispanic	0 (0)	1 (3)
Family history of diabetes		
Yes	1 (9)	10 (29)
No	10 (91)	24 (71)
Model for End-Stage Liver Disease score, mean (SD)	21.4 (8.3)	20.9 (8.4)
Acute Physiology and Chronic Health Evaluation score, mean (SD)	73.6 (15.0)	64.6 (22.7)
Body mass index, mean (SD)	27.8 (4.6)	29.6 (7.4)
Cause of liver transplant		
Alcoholic cirrhosis	4 (36)	13 (38)
Hepatitis B	0 (0)	1 (2.2)
Hepatitis C	6 (55)	16 (47.1)
Primary biliary cirrhosis	1 (9)	2 (5.9)
Other	2 (18)	10 (29.4)
Preoperative serum level of glucose, mean (SD), mg/dL	109.8 (20.8)	106.4 (21.2)
Length of hospitalization (range), days	11 (6-59)	9 (5-30)

^a Values are expressed as No. (%) of patients unless otherwise indicated.

and found that patients treated with tacrolimus had a risk of NODAT developing 5 times as high as the risk faced by patients treated with cyclosporine. Dansirikul et al⁷ investigated the relationship between tacrolimus pharmacokinetics and adverse outcomes such as nephrotoxicity, hypertension, hyperkalemia, and hyperglycemia in stable liver transplant patients. Their data showed that 7 of 55 patients (13%) experienced hyperglycemia; however, they were unable to demonstrate a significant association between tacrolimus concentrations, area under the curve, and adverse effects.⁷

Many complications may be associated with persistent hyperglycemia such as graft rejection, infection, cardiovascular and thrombotic complications, and death; therefore, postoperative glucose monitoring and control are extremely important. The aim of this study was to assess whether postoperative hyperglycemia could be used as a predictor for NODAT developing in liver transplant recipients. We hypothesized that patients with poor glycemic control within the first 2 weeks after transplantation will have an increased risk of NODAT within 6 months.

Patients and Methods

In this retrospective study, new-onset diabetes was defined according to the diagnostic criteria of the American Diabetes Association and the World Health

Organization (a fasting plasma level of glucose of at least 126 mg/dL or random plasma level of glucose of 200 mg/dL or higher), persistent hyperglycemia for greater than 2 weeks, or the need for hypoglycemic agents after transplantation.

The study was approved by the institutional review board at our institution. It included an analysis of adult patients who underwent liver transplantation between January 2004 and December 2005. Additional eligibility criteria included patients 18 years old or more receiving calcineurin inhibitors or systemic corticosteroids and surviving to discharge. Exclusion criteria were multiorgan transplantation, retransplantation, history of diabetes, death before discharge, and incomplete records.

Data were extracted from patients' clinical records and the transplant center database and clinic records. Variables collected included demographic characteristics, body mass index, diabetes status before transplantation, cause of liver disease, Model for End-Stage Liver Disease⁸ score, Acute Physiology and Chronic Health Evaluation III⁹ score on admission to the intensive care unit, preoperative serum level of glucose, postoperative serum and fingerstick glucose levels, use of immunosuppressive agents and corresponding serum concentrations and corticosteroid doses on postoperative days 1, 2, 7, 14, 30, 90, and 180 (Tables 1 and 2),

Table 2 Regimen for tapering methylprednisolone dose

Preoperative dose	Postoperative dose given intravenously every 6 hours, mg				
	Day 1	Day 2	Day 3	Day 4	Day 5
500 mg given intravenously once	25	20	15	10	5

use of antidiabetic agents, infections, acute rejection episodes, cardiovascular and thrombotic events, length of hospitalization, and readmission to the hospital within 6 months. The mean serum and fingerstick blood glucose levels were determined by averaging the blood glucose levels for postoperative days 1, 2, 7, 14, 30, 90, and 180. Based on mean serum and fingerstick blood glucose concentrations, the study population was divided into 2 groups, NODAT and normoglycemic. The NODAT group consisted of patients who had diabetes develop within 6 months after transplant, whereas the normoglycemic group included patients who did not have diabetes develop during that period.

The quantitative variables were expressed as the means (standard deviation) and medians (range), whereas the categorical variables were expressed as percentages. The Student *t* test was used to compare means and the Wilcoxon rank sum test was used to compare medians between groups. Categorical data were compared by using the Fisher exact test to determine significant differences between groups.

Results

Of the 87 patients initially screened, 42 patients were excluded from the study. Excluded patients included 30 patients with a history of diabetes (defined as a previous diagnosis of diabetes mellitus and/or the use of antidiabetic agents), 5 patients who underwent retransplantations, 2 patients who received multiorgan transplants, 2 patients who died before discharge, and 3 patients with incomplete medical records. Therefore the study population included a total of 45 patients. Eleven of the 45 patients included had NODAT develop. The demographic characteristics of each group of patients are shown in Table 1. Only 1 patient (9%) in the NODAT group had a family history of diabetes compared with 10 patients (29%) in the normoglycemic group. Overall, the patients in the 2 groups were similar in age, Model for End-Stage Liver Disease score, body mass index, preoperative serum level of glucose, and length of hospitalization. The 2 groups did not differ significantly in demographic characteristics.

The mean serum glucose values were similar in the 2 groups for postoperative days 1 and 2; however, the NODAT cohort had higher mean serum glucose levels overall (see Figure). At 2 weeks, patients who

went on to develop NODAT had higher fasting blood glucose values than did patients in whom NODAT did not develop (116.4-151.8 mg/dL versus 101.7-148.4 mg/L, respectively). Both groups had mean serum levels of blood glucose of 148 mg/dL on postoperative day 1, but patients in whom diabetes did not develop returned to normoglycemia on postoperative day 2. The NODAT group had increased fingerstick blood glucose and insulin usage compared with the normoglycemic group, while the dose of insulin required for the normoglycemic group decreased steadily for 2 weeks.

Of the 45 study subjects, 14 patients deviated from the corticosteroid protocol (Table 2), 27% of the NODAT group (ie, 3 patients) versus 32% of the normoglycemic group (11 patients). The various corticosteroid regimens included 11 patients (1 NODAT patient and 10 normoglycemic patients) who received prednisone 10 mg per day, 2 patients (1 NODAT and 1 normoglycemic patient) who received prednisone 20 mg per day 3 months postoperatively and then decreased to 15 mg at 6 months, and 1 patient in the NODAT group who received methylprednisolone 500 mg intravenously 3 months postoperatively. Tacrolimus serum concentrations were monitored on a routine basis in this population; however, for the purpose of the study, we measured tacrolimus levels on postoperative days 1, 2, 7, 14, 30, 90, and 180 (Table 3). The serum concentrations on the same days were similar between the 2 groups.

Table 4 displays the secondary end points. Although the 2 groups did not differ significantly, NODAT patients experienced more infectious episodes and cardiovascular complications such as atrial fibrillation, hypertension, non-ST-segment myocardial infarction, supraventricular tachycardia, ventricular tachycardia, and ventricular fibrillation than did normoglycemic patients. Infections occurred in 36.4% of NODAT patients versus 23.6% of normoglycemic patients ($P = .21$), and cardiovascular complications occurred in 27.3% of NODAT patients versus 5.9% of normoglycemic patients ($P = .09$). However, 11.8% of patients in the normoglycemic group (ie, 4 patients) experienced a thrombotic event such as hepatic artery thrombosis, deep vein thrombosis, or disseminated intravascular coagulation compared with 2.9% of patients in the NODAT group (ie, 1 patient; $P = .42$).

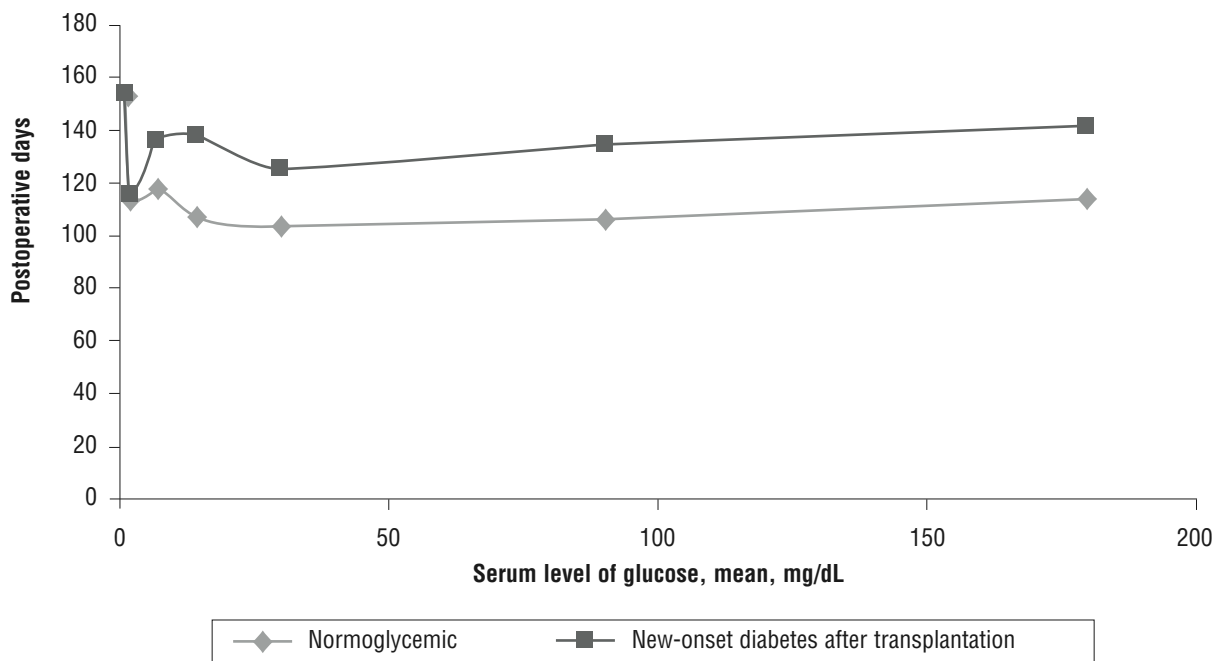


Figure Mean serum concentrations of glucose after transplantation. Multiply glucose values by 0.0555 to convert to mmol/L.

The occurrence of acute rejection was similar in the 2 groups ($P = .30$), but the normoglycemic group had a higher rate of hospital readmissions (58.8% vs 36.4%, $P = .12$). No secondary end points differed significantly between the 2 groups.

Discussion

The incidence of NODAT may be underestimated because of the disparate definitions of the condition. However, Montori et al¹⁰ systemically reviewed the incidence of NODAT for heart, liver, and kidney

transplantation and reported a 12-month cumulative incidence to be within the range of 2% to 53%. Saliba et al⁵ showed an incidence of new-onset diabetes of 22.7% in liver transplant recipients, with diabetes developing within the first 3 months after transplantation in 81.3%. We evaluated the incidence of NODAT within the first 6 months after transplantation. In our study population, 24% of patients had NODAT develop within this time frame, and these patients had higher mean serum levels of glucose and fingerstick blood sugar than did patients in the normoglycemic group. However, both groups had elevated blood glucose levels on postoperative day 1, which may be explained by the 500-mg bolus of methylprednisolone used for

Table 3 Serum concentrations of tacrolimus

Postoperative day	Tacrolimus, serum concentration, mean (SD), ng/mL	
	New-onset diabetes after transplantation (n = 11)	Normoglycemic (n = 34)
1	6.8 ^a	— ^b
2	5.4 ^a	3.7 (1.2)
7	8.4 (3.6)	8.1 (3.7)
14	11.1 (7.4)	9.2 (4.0)
30	9.2 (3.4)	11.1 (7.6)
90	9.3 (3.6)	8.7 (3.0)
180	10.9 (3.4)	9.9 (4.3)

^a Tacrolimus serum concentration was measured in only 1 patient on postoperative days 1 and 2.
^b Tacrolimus concentration not measured.

Table 4 Secondary end points: patients with new onset of diabetes after transplantation versus normoglycemic patients^a

Secondary end points	No. (%) of patients	
	New-onset diabetes after transplantation (n = 11)	Normoglycemic (n = 34)
Acute rejection	3 (27.3)	9 (26.5)
Infection	4 (36.4)	8 (23.6)
Cardiovascular complications	3 (27.3)	2 (5.9)
Thrombotic events	1 (2.9)	4 (11.8)
Readmissions	4 (36.4)	20 (58.8)

^a Differences between the 2 groups in the secondary end points were not statistically significant.

Table 5 Regimen for tapering immunosuppressive agents and desired serum concentrations

Drug	Postoperative	3 months	6 months	12 months	24 months
Prednisone	10 mg/d	5 mg/d	5 mg/d	5 mg every 48 h	Stop
Mycophenolate mofetil	500 mg twice a day	250 mg twice a day	Stop		
Tacrolimus serum concentrations, ng/mL	8-10	8-10	5-8		

induction intraoperatively. Additionally, patients received a continuous intravenous infusion of insulin postoperatively to control blood glucose while in the critical care setting, which may have affected our ability to correctly gauge the incidence of hyperglycemia in these patients.

The effects of immunosuppressive medications including bolus administration of a steroid and subsequent rapid tapering as well as use of tacrolimus must be considered in the development of NODAT in liver transplant recipients. The immunosuppressive protocol for liver transplantation used at our institution includes administration of a calcineurin inhibitor (ie, tacrolimus), mycophenolate mofetil, and corticosteroids (Tables 2 and 5). However, tacrolimus may be discontinued and cyclosporine and/or sirolimus initiated if patients experience adverse effects. In our study, 1 patient in the NODAT group later received sirolimus, and 2 patients from the normoglycemic group were treated with cyclosporine. Additionally, liver transplant recipients were typically prescribed similar corticosteroid regimens. However, 11 patients' regimens differed, and the deviation may be due to acute rejection or unknown causes.

In addition to immunosuppressive agents, factors such as race, age, obesity, family history of diabetes, and etiology of liver disease are risk factors for the development of posttransplantation diabetes.^{11,12} However, we did not discover a correlation between NODAT and these risk factors. The majority of our NODAT patients were white, with no family history of diabetes. However, approximately 34.5% of the liver transplant recipients who underwent a transplant during the 2-year study period were diabetic and therefore were excluded from the study.

Glycemic control after transplantation is important to decrease the development of NODAT, acute rejection, infectious episodes, and cardiovascular and thrombotic complications. Thomas et al¹³ evaluated perioperative hyperglycemia, defined as a serum level of glucose greater than 8 mmol/L (144 mg/dL), in relation to renal allograft rejection in patients without diabetes. The incidence of hyperglycemia had no relationship to the perioperative glucose level; however, 73% of patients had hyperglycemia develop, and 31%

of these patients had serum glucose levels greater than 11.2 mmol/L (201.6 mg/dL) immediately following surgery.¹³ Thomas et al also showed that 71% of patients who experienced acute rejection had serum glucose levels greater than 8 mmol/L (>144 mg/dL) compared with the 42% without hyperglycemia.¹³ Therefore, transplant recipients with better glycemic control after transplantation had a lower risk of complications due to hyperglycemia developing. In our study, the preoperative serum level of glucose was similar in the NODAT patients (109.8 mg/dL) and the normoglycemic patients (106.4 mg/dL); however, the mean serum level of glucose after transplantation was higher in the NODAT group and was greater than 126 mg/dL on postoperative days 2, 7, 14, 30, 90, and 180.

Limitations

Our study does have some limitations. First, we evaluated patients for only 6 months after transplantation. The incidence of new-onset diabetes increases linearly with time after transplantation.¹⁴ Additionally, we collected data for postoperative days 1, 2, 7, 14, 30, 90, and 180 instead of collecting data for postoperative days 1 through 14. Analyzing the serum level of glucose for 14 days may have provided a more accurate assessment of early hyperglycemia. Even with aggressive glucose control in the immediate postoperative period, glucose levels differed between the groups; therefore, the use of insulin infusions in intensive care units may also limit our ability to correctly monitor hyperglycemia while the patient is in the intensive care unit. Additional limitations include the retrospective study design and inconsistent documentation, the single-center analysis, the sample size of population, and the duration of the study.

Conclusions

Our findings, in conjunction with those of previous investigators, support the importance of screening patients and assessing risk factors for the development of diabetes mellitus before transplantation to help reduce the occurrence of NODAT. Glycemic monitoring before and after transplantation is also important. Because of the lack of published studies about NODAT in liver transplantation, future large-scale multicenter studies are needed to elucidate further the

incidence and adverse effects of this complication in transplant recipients.

Financial Disclosures

None reported.

References

1. Marin M, Renoult E, Bondor CI, Kessler M. Factors influencing the onset of diabetes mellitus after kidney transplantation: a single French center experience. *Transplant Proc.* 2005;37(4):1851-1856.
2. Romero R, Melde K, Pillen T, Smallwood GA, Heffron T. Persistent hyperglycemia in pediatric liver transplant recipients. *Transplant Proc.* 2001;33(7-8):3617-3618.
3. Mora PF. Post-transplantation diabetes mellitus. *Am J Med Sci.* 2005;329(2):86-94.
4. Markell M. New-onset diabetes mellitus in transplant patients: pathogenesis, complications, and management. *Am J Kidney Dis.* 2004;43(6):953-965.
5. Saliba F, Lakehal M, Pageaux GP, et al. Risk factors for new-onset diabetes mellitus following liver transplantation and impact of hepatitis C infection: an observational multicenter study. *Liver Transpl.* 2007;13(1):136-144.
6. Sulanc E, Lane JT, Puumala SE, Groggel GC, Wrenshall LE, Stevens RB. New-onset diabetes after kidney transplantation: an application of 2003 International Guidelines. *Transplantation.* 2005;80(7):945-952.
7. Dansirikul C, Staats CE, Duffull SB, Taylor PJ, Lynch SV, Tett SE. Relationships of tacrolimus pharmacokinetic measures and adverse outcomes in stable adult liver transplant recipients. *J Clin Pharm Thera.* 2006;31(1):17-25.
8. Wiesner R, Edwards E, Freeman R, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology.* 2003;124(1):91-96.
9. Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest.* 1991;100(6):1619-1636.
10. Montori VM, Basu A, Erwin PJ, et al. Posttransplantation diabetes: a systematic review of the literature. *Diabetes Care.* 2002; 25(3):583-592.
11. Khalili M, Lim JW, Bass N, et al. New-onset diabetes mellitus after liver transplantation: the critical role of hepatitis C virus infection. *Liver Transpl.* 2004;10(3):349-355.
12. Bigam DL, Pennington JJ, Carpentier A, et al. Hepatitis C-related cirrhosis: a predictor of diabetes after liver transplantation. *Hepatology.* 2000;32(1):87-90.
13. Thomas MC, Moran J, Mathew TH, Russ GR, Rao MM. Early peri-operative hyperglycaemia and renal allograft rejection in patients without diabetes. *BMC Nephrol.* 2000;1:1.
14. Cosio FG, Pesavento TE, Oseil K, Henry ML, Ferguson RM. Post-transplant diabetes mellitus: increasing incidence in renal allograft recipients transplanted in recent years. *Kidney Int.* 2001;59(2):732-737.