Original Article

Incidence of New-Onset Diabetes and PostTransplant Metabolic Syndrome after Liver Transplantation - A Prospective Study from South India

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Abstract

Background and Aims: Liver transplantation has become an effective therapy for patients with end-stage liver disease. The risk of new-onset diabetes after transplantation (NODAT) and posttransplant metabolic syndrome (PTMS) is high among patients after liver transplantation. These are thought to be associated with increased risks of graft rejection, infection, cardiovascular disease, and death. Our study aimed to document the incidence of NODAT and PTMS and analyze pre and posttransplant predictive factors for their development in patients undergoing a liver transplant. **Methods:** This was a prospective comparative study on 51 patients who underwent live donor liver transplantation. They were evaluated at baseline, 3 and 6 months after transplantation with fasting glucose, lipids, serum insulin levels, C-peptide, and HbA1C. They were followed up at 5 years to document any cardiovascular events or rejection. **Results:** The incidence of preoperative diabetes mellitus (DM) in the study group was 25/51 (49%). The incidence of NODAT was 38.5% (10/26 patients) and PTMS 29% (10/35), respectively. Age (47.7 ± 5.4 vs 41.5 ± 12.7 years), HOMA2 -IR (2.3 ± 1.8 vs 2.1 ± 1.6), serum insulin (16.1 ± 12.0 vs 17.9 ± 14.5), and C-peptide (4.6 ± 0.5 vs 4.8 ± 0.7) were similar at baseline in the NODAT group compared to those who did not develop it. Mean tacrolimus levels were higher in PTMS group (6.8 ± 2.9 vs 5.0. ± 2.0 *P* value = 0.042). By the end of 5 years, 7 patients expired; 6 due to rejection and one due to cardiovascular disease. Moreover, 2 of these patients had preexisting DM and 2 had NODAT. **Conclusions:** None of the baseline metabolic factors in patients undergoing liver transplant were predictive of the development of NODAT or PTMS. Mean tacrolimus levels were significantly higher in the PTMS group. A 5-year follow-up showed no excess risk of cardiovascular events or rejection in those with preexisting DM or in those who developed NODAT.

Keywords: Live donor liver transplantation, metabolic syndrome, new-onset diabetes after transplantation, orthotopic liver transplantation, posttransplant metabolic syndrome

Introduction

Liver transplantation has become an effective therapy for patients with acute or chronic end-stage liver disease. Since operative techniques and immunosuppressive management have improved, long-term survival after liver transplantation has increased with 5- and 10-year patient survival reaching 70% and 60%, respectively.[1] With improved survival, increased attention is being given to complications that develop in the long-term, and that are highly related to the immunosuppressive treatment. The most frequent long-term complications are chronic renal failure, systemic arterial hypertension, diabetes mellitus (DM), dyslipidaemia, obesity, bone or neurological complications, and the development of de novo tumours.

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New-onset diabetes after transplantation (NODAT) refers to the occurrence of DM in a previously nondiabetic person after organ transplantation. The incidence rates of NODAT vary depending upon the organ transplanted and posttransplant interval. The estimated rates of NODAT at 12 months posttransplant are 9–30% for a liver transplant.[1]

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A number of retrospective studies have reported the prevalence of the individual components of MS, which include DM, hypertension, dyslipidaemia, and obesity, among patients who have undergone liver transplantation. Nevertheless, studies conducted worldwide have reported the prevalence of posttransplant metabolic syndrome (PTMS) ranging from 44% to 58%.[1,2]

Among liver transplant recipients, NODAT is found to be associated with increased cardiovascular morbidity and mortality, more severe infections, higher incidence of rejection, and poorer graft survival.[2] Although there is controversy regarding the impact of PTMS on the overall survival rates following orthotopic liver transplant (OLT), these patients are at an increased risk for cardiovascular morbidity and mortality.[3]

Living donor transplantation (LDLT) is the primary mode of liver transplantation in India as compared to deceased donor liver transplantation (DDLT) which is more common in the western countries. However, there is a paucity of data from India regarding the different aspects of liver transplantation. The available data from post renal transplant patients from India showed an incidence of 16–20% for NODAT following renal transplantation.[4]

The current study was aimed at studying the incidence of NODAT and PTMS in our center following living donor liver transplantation. The pre and postoperative risk factors for the development of NODAT were also analyzed.

Materials and Methods

The study was conducted as a prospective comparative study involving 51 patients who underwent liver transplantation from June 2012 to August 2013 and were selected after applying the inclusion and exclusion criteria. Based on the results observed in the existing literature, the sample size for NODAT was calculated to be 25.[1,2] These patients were followed up for a minimum period of 6 months. The study was conducted as per the approval and guidelines of the Institutional Ethics Committee of AIMS - School of Medicine, and written informed consent was obtained from the participants. The patients were then followed up 5 years later to estimate the risk of vascular complications.

Inclusion criteria included all patients undergoing liver transplantation, aged >18 years over the specified period. Those patients who expired within 3 months of transplantation were excluded from further analysis.

The pretransplant assessment included a detailed history, physical examination, and laboratory assessment. NODAT was defined by (i) presence of fasting plasma glucose (FPG) of >/=126 mg/dL, or (ii) symptoms of DM i.e. polyuria, polydipsia, or unexplained weight loss plus random blood glucose >/=200 mg/dL, or (iii) 2-h oral glucose tolerance test (OGTT) of >/=200 mg/dL; on 2 different occasions.[5] All patients with NODAT had documented absence of DM during pretransplant workup. Type of treatment offered for NODAT was also recorded. Patient and laboratory characteristics of NODAT were compared with the patients who did not develop posttransplant DM, to find out various risk factors associated with the occurrence of NODAT.

Metabolic syndrome (MS) was defined by the modified adult treatment panel III criteria (ATP-III), including obesity, dyslipidaemia, hypertension, and DM.[6] MS was defined as the presence of 3 or more of the following: central obesity (BMI >25 kg/m^2), high fasting glucose levels (>110 mg/dL), hypertriglyceridemia (>150 mg/dL), low high-density lipoprotein (HDL) levels (<40 mg/dL in men and <50 mg/dL in women), high blood pressure (>130/85 mmHg), or specific treatment for each of these conditions.

Body mass index (BMI) was defined as the weight in kg divided by the square of the height in m (kg/m2). Obesity was defined as a BMI ≥25 kg/m^2 and nonobese as BMI <25 kg/m^2. This was based on the consensus statement that the cutoffs for overweight and obesity need to be revised for Asian Indians.[7] In this cohort, BMI was considered as an index of obesity due to deviations resulting from ascites.

All patients were evaluated at baseline and after transplantation at 3 months and 6 months for fasting glucose, triglycerides, total, HDL and LDL cholesterol, and HBA1C. Wherever possible, pretransplant patients were also evaluated for fasting insulin levels. Insulin resistance was then estimated by the homeostatic model assessment-insulin resistance (HOMA 2-IR) index.[8]

Blood glucose was estimated by the hexokinase method on Olympus AU2700 analyzer. HDL, LDL, and triglycerides were estimated by enzymatic method on Olympus AU2700 analyzer. Hemoglobin A1C (HbA1c) was assessed by the use of HPLC method, National Glycohemoglobin Standardization Program-certified, and Diabetes Control and Complications Trial-standardized method. Fasting insulin levels were assessed by chemiluminescence immunoassay (Abbot Architect). Tacrolimus blood levels were assessed by chemiluminescence immunoassay (Abbot Architect).

All patients received immunosuppressant according to a standard protocol including glucocorticoids, tacrolimus, and azathioprine/mycophenolate mofetil. Posttransplant patients were followed up for a minimum of at least 6 months. Mean tacrolimus levels, cumulative doses of glucocorticoids as prednisolone equivalents, and insulin requirement were measured at 3 months and 6 months.

Statistical analysis

Statistical analysis was done using IBM SPSS Statistics 20 Windows (SPSS Inc., Chicago, USA). To compare the average of continuous variables between the time points, the paired *t*-test and Wilcoxon signed-rank test were used. To compare the means of continuous variables between two groups, which follow a normal distribution, Student's independent samples *t*-test was performed. To compare the averages of continuous variables between two groups, which

do not follow a normal distribution, the Mann-Whitney U test was performed. To compare the average of continuous variables between three groups, the Kruskal-Wallis test was applied.

Results

A total of 51 patients were followed up for a minimum of 6 months. Baseline characteristics of the study population are given in Table 1. The mean age was 45.6 (±9.6) years. 49% of the study population had preexisting DM (n = 25).

The incidence of NODAT was 38.5% (n = 10/26). The baseline characteristics of patients, who developed NODAT is shown in Table 1. Those who developed NODAT were older and had a higher HOMA-IR but were not statistically significant. All the patients who developed NODAT were diagnosed in the immediate postoperative period. Out of the 10 patients with NODAT, 1 patient had normal blood sugar control by the end of the third month and was off-insulin treatment. By the end of 6 months, 2 more patients had come off-insulin therapy.

Postoperative variables were compared between preoperative DM, NODAT, and no NODAT group as shown in Table 2. Those who developed NODAT had a higher cumulative steroid dose at discharge as well as at 6 months and were on a higher tacrolimus dose at discharge but were not statistically significant. Those who developed NODAT required much lower insulin dose per kg body weight than those who had preexisting DM.

The prevalence of metabolic syndrome was 31% (n = 16) before transplantation. Out of 35, who had no metabolic syndrome, the incidence of PTMS at 6 months following transplantation was 29% (n = 10). Fasting blood glucose at baseline was noted to be significantly higher in those who developed PTMS when compared to those without (P = 0.05) [Table 3].

The PTMS group had significantly higher BMI and TG levels at 6 months compared to no PTMS group [Table 4]. There was a trend of higher mean levels of steroid doses and insulin requirement in the PTMS group but it did not reach significance.

All the patients received immunosuppressant according to a standard protocol containing glucocorticoids, tacrolimus, and azathioprine/mycophenolate. About 73% of the patients were on the combination glucocorticoids, tacrolimus, and azathioprine at discharge and the rest were on mycophenolate

Table 1: Baseline characteristics of patients who underwent liver transplant (n=51) and those who developed NODAT

Patient characteristics	All patients (n=51)	NODAT (n=10)	No NODAT (n=16)	P
Age (years)	45.69±9.62	47.70±5.43	41.5±12.70	0.159
Weight (kg)	69.02±15.57	70.70±15.72	69.94±20.73	0.922
BMI (kg/m^2)	24.52±4.63	24.81±5.02	24.36±6.22	0.852
FBS (mg/dL)	113.26±43	91.2±9.52	93.81±16.90	0.661
PPBS (mg/dL)	170.51±62	125.30±18.66	129.63±19.89	0.586
HBA1C (%)	5.48±1.20	4.79±0.72	4.66±0.49	0.617
TC (mg/dL)	91.83±41.64	103.3±58.04	76.78±38.39	0.172
TG (mg/dL)	71±46.21	57.1±27.07	62.99±33.17	0.642
HDL (mg/dL)	25.63±15.84	27.5±17.63	22.46±15.52	0.451
LDL (mg/dL)	60.6±29.01	68.5±42.04	51.11±22.63	0.182
HOMA-2 IR*	2.24±1.50	2.35±1.80	2.08±1.56	0.689
MELD	21.59±5.59	21.89±4.59	24±5.54	0.324
Insulin uIU/mL (26 subjects)		16.06±12.03	17.98±14.46	0.194
C-peptide (ng/mL) (26 subjects)		4.6±0.49	4.79±0.72	0.87
Duration of hospital stay (in days)		25±8	24±7	0.740

Data are expressed as mean±SD. BMI: Body mass index, FBS: Fasting blood glucose, PPBS: Postprandial blood glucose, TC: Total cholesterol, TG: Triglycerides, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, HOMA-2 IR Homeostatic Model assessment for insulin resistance MELD: Model for end-stage liver disease

Table 2: Postoperative factors in patients who had preoperative DM compared to patients with and without NODAT

Variables	Preop DM (n=25)	NODAT (n=10)	No NODAT (n=16)	P
Hospital stay in no. of days	27.52±11.71	25±8.04	24.81±7.71	0.642
BMI at 6 months	24.63±3.55	24.12±3.50	22±3.97	0.087
Cumulative steroid dose at discharge (mg)	2034±1470	1813±1118	1442±1199	0.387
Cumulative steroid dose at 6 months	2249±2516	1088±2296	377±1082	0.109
Mean tacrolimus level at discharge	3.33±2.33	3.96±3.04	2.925±1.39	0.527
Mean tacrolimus level at 6 months	6.51±2.57	4.43±1.44	5.44±2.46	0.059
Insulin dose (U/kg) at d/c	1.13±0.68	0.62±0.24		0.008
Insulin dose (U/kg) 6 months	0.83±0.50	0.31±0.16		0.002

Table 3: Baseline characteristics of patients developing PTMS

Patient characteristics	PTMS at 6 months ($n=10$)	No PTMS ($n=25$)	*P*
Age (years)	47±7	44±10	0.393
BMI (kg/m^2)	25±4	24±4	0.508
FBS (mg/dL)	138±59	99±21	0.006
PPBS (mg/dL)	190±72	159±53	0.168
HBA1C (mg/dL)	5.9±1.2	5.2±1.1	0.106
TC (mg/dL)	104±44	85±39	0.218
TG (mg/dL)	71±28	71±53	
HDL (mg/dL)	28±14	24±16	0.494
LDL (mg/dL)	70±33	55±25	0.153
HOMA-2 IR*	3.2±1.9	1.8±1.1	0.009
MELD	21±5	21±5	

Data are expressed as mean±SD. BMI: Body mass index, FBS: Fasting blood glucose, PPBS: Postprandial blood glucose, TC: Total cholesterol, TG: Triglycerides, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, HOMA-2 IR Homeostatic Model assessment for insulin resistance MELD: Model for end-stage liver disease

Table 4: Postoperative factors in patients developing PTMS at 6 months

Variables	PTMS (10)	NO PTMS (25)	*P*
BMI at 6 months	25±3	22±2	0.001
Cumulative steroid dose at 6 months	1800±4020	1175±1897	0.532
Mean tacrolimus level at 6 months	6.8±2.85	5.0±2.0	0.042
HBA1C at 6 months	6.1±1.3	5.5±1	0.150
TC 6 months	198±54	215±56	0.418
TG 6 months	191±71	138±34	0.005
HDL 6 months	43±13	48±16	0.386
LDL 6 months	134±36	146±37	0.388

with glucocorticoids and tacrolimus. Glucocorticoids were stopped in the majority by 6 months (84%). No significant association could be found out from the different immunosuppressive regimens on the development of NODAT or PTMS. The dose or the duration of glucocorticoids had no significant association with the development of NODAT or PTMS. Similarly, there was no association seen between steroid duration and occurrence of complications or duration of hospital stay.

A follow-up of 48 patients was done 5 years later (3 lost to follow-up). Of the 7 patients who had expired, 6 died of rejection and 1 secondary to stroke. One patient developed chronic kidney disease (CKD) and one had recurrence of chronic liver disease (CLD). Among those who died of rejection, 4 had no DM while one patient each had preexisting DM and NODAT. The patient who died of a stroke had NODAT. Among 10 patients with NODAT, 2 expired, 5 had gone into remission, and 3 had ongoing DM for which they were on insulin.

Discussion

There was a high incidence of preoperative DM in our cohort (49%). Previous studies have documented 60–80% glucose intolerance and 10–15% DM among patients with cirrhosis of the liver.[9] The incidence of preoperative DM in the Japanese cohort studied by Harada *et al*.[10] was only 9%. The higher incidence of DM in our cohort may be a reflection of the increased prevalence of DM in the Indian population as well as the selection criteria adopted by our transplant team in comparison to other groups.[11]

The incidence of NODAT was 38.5% (10/26). The reported incidence in the western population ranges from 9–30%.[1] Similar incidence has been noted previously in a Japanese cohort of LDLT patients. The higher incidence in LDLT patients could be related to the requirement of a higher dose of glucocorticoids as part of the immunosuppressive regime.[10] Among those who developed NODAT, 70% were on insulin at the end of 6 months. In the Japanese cohort, 45.5% were on insulin at 6 months.[10] This is perhaps a reflection of the choice of therapy by the physicians and patients. By the end of 5 years, only 30% were still continuing insulin suggesting that a significant proportion of patients with NODAT recovered over time especially after discontinuing steroid regime.

The incidence of metabolic syndrome was 31% before transplantation and a further 29% developed it posttransplant. In previous studies, MS has been described in 44–58% of patients followed up for 6 months after transplantation.[3]

Older age, alcohol-related liver disease, cryptogenic cirrhosis, hepatitis C infection, and immunosuppressive medication have all been previously shown to be associated with MS.[1] In our study, there was no difference in preoperative or postoperative variables in the groups with or without PTMS. The mean age and the cumulative glucocorticoids showed a trend towards the PTMS group which was, however, not significant.

The most frequent complication requiring admission in our study was biliary complications followed by acute rejection. Previous studies have shown that NODAT and PTMS were associated with increased infections, higher rejection rates, and poorer graft survival.[12-15] The recent study by Harada *et al*.[10] has shown that the presence of DM after liver transplant has no impact on patient outcome. In our study group, there was no significant association between complications and NODAT or PTMS, although the smaller numbers may have been responsible for our results.

The limitations of the study include small sample size and short duration, which could have influenced the correlation of preoperative and postoperative variables and incidence of NODAT and PTMS. Both BMI and WHR can be influenced by ascites. Mild ascites may increase body weight without increasing hip circumference.

Among liver transplant recipients, NODAT is associated with increased cardiovascular morbidity and mortality, more

fatal infections, more neuropsychiatric complications, higher rejection rates, and poorer graft survival.[12-15] Our study did not show any significant association with complications or rejections and the development of NODAT. The smaller numbers and short duration of follow-up may be the reason for the lack of association.

Conclusions

Incidence of NODAT and PTMS in our study was 38% and 29%, respectively. The higher incidence of preoperative DM and MS probably reflects the higher background prevalence of DM and MS in our population. The high incidence of NODAT in our population emphasizes the need for close follow-up of metabolic parameters to prevent and treat further development of MS as these could predispose to increased cardiovascular morbidity in the future. No preoperative risk factors for the development of PTMS and NODAT could be identified in the present study, probably due to small numbers. Furthermore, large-scale prospective studies with longer duration of follow-up are required to further clarify the pathogenesis of NODAT and PTMS and also to assess their effects on the long-term outcome in the Indian population.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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