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Predictive Factors Associated with the Reversibility of Post-transplantation Diabetes Mellitus Following Liver Transplantation

Post-transplantation diabetes mellitus (PTDM) is reversible in a considerable number of patients. We examined the prevalence and predictive factors of transient PTDM following liver transplantation. Forty-two of 74 PTDM patients showed the clinical features of transient PTDM. Compared with the persistent PTDM patients, they were characterized by younger age at the time of transplantation (49±7 vs. 53±8 yr, P<0.05), longer time before the development of PTDM (44±59 vs. 13 ±20 days, P<0.05), lower rate of hepatitis c virus seropositivity (0.0 vs. 9.4%, P< 0.05), and use of mycophenolate mofetil (59.5 vs. 28.1%, P<0.05). Among these risk factors, age at the time of transplantation is the single independent predictive factor associated with the reversibility of PTDM.

Key Words : *Diabetes Mellitus; Liver Transplantation*

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INTRODUCTION

New-onset diabetes mellitus is a common metabolic complication following liver transplantation, and it is associated with poor outcomes in regard to a graft function and a patient survival (1). It has been reported that the post-transplantation diabetes mellitus (PTDM) can be reversed within weeks or months in a considerable number of patients (1, 2). Immunosuppressive agents such as calcineurin inhibitors and corticosteroids are largely responsible for the development of PTDM (3). Although the reversibility of PTDM is associated with the doses of immunosuppressive agents, it is not sufficiently enough to explain the reversibility of PTDM (4). In addition, a significant ethnicity-based difference has been observed in the development of PTDM (5). In this study, we examined the prevalence of PTDM and the predictive factors associated with its reversibility following liver transplantation in Koreans.

MATERIALS AND METHODS

Subjects and data collection

We reviewed the medical records of 328 patients who underwent liver transplantation from January 2004 to May 2007 at Seoul National University Hospital (SNUH); they were followed up for more than 6 months. Among these 328 patients, 97 had diabetes before transplantation and were excluded from the analysis.

The capillary plasma glucose levels were measured four times a day for the first week after transplantation and the venous plasma glucose levels were measured at least once a week during hospitalization. After discharge, the venous plasma glucose levels were measured at least once a month for the first 6 months after transplantation. PTDM was defined as either requirement of insulin/antidiabetic drugs or a fasting plasma glucose level of ≥7.0 mM/L on 2 consecutive occasions. Based on these criteria, 34 out of 231 (14.7%) patients were diagnosed with PTDM.

In addition, we enrolled 40 additional PTDM patients who underwent liver transplantation in China during the same period; they were followed up at SNUH for more than 6 months. The absence of diabetes mellitus prior to liver transplantation was confirmed by preoperative fasting plasma glucose levels (n=13) or patients' past medical history (n=27). The clinical characteristics of the 2 groups were similar (data not shown) and, therefore, they were analyzed as one group. Thus, a total 74 PTDM patients (52 men and 22 women) were analyzed in this study. Demographic data, clinical char-

acteristics, and data on drug therapy were obtained from medical records. The mean age of the subjects was 51±8 yr. Twenty-eight patients received liver allografts from living donors and 46 patients received liver allografts from cadaver donors. The primary causes of liver failure were hepatitis B virus (HBV)-related liver cirrhosis or hepatocellular carcinoma (n=67, 90.5%), hepatitis C virus (HCV)-related liver cirrhosis or hepatocellular carcinoma (n=3, 4.1%), alcoholic liver cirrhosis (n=2, 2.7%), fulminant hepatitis (n=1, 1.4%), and liver cirrhosis of unknown etiology (n=1, 1.4%). All the patients were administered tacrolimus plus steroid-based immunosuppressive therapy. Mycophenolate mofetil (MMF) was administered to 34 of 74 patients (45.9%). The preoperative clinical characteristics between patients who received or did not receive MMF treatment were similar (data not shown).

The PTDM patients were classified into 2 groups, namely, transient PTDM and persistent PTDM. Transient PTDM was defined as recovery from PTDM with the maintenance of fasting plasma glucose level at <5.6 mM/L and HbA1c at <6.0% without insulin or any antidiabetic medication for more than 6 months. Otherwise, they were classified into the persistent PTDM group. In transient PTDM group, 47.6% were diagnosed by requirement of insulin/antidiabetic drugs and 52.4% by high fasting plasma glucose levels; in persistent PTDM group, 56.3% were diagnosed by requirement of insulin/antidiabetic drugs and 43.7% by high fasting plasma glucose levels.

Statistical analysis

All continuous variables were expressed as mean±SD. Student's t test or Mann-Whitney U test was used to compare the continuous variables between the 2 groups. Pearson's chi-square test or Fischer's exact test was used for comparing categorical variables. Binary logistic regression analysis was used for determining the multiple predictive factors associated with transient PTDM. A P value <0.05 was considered statistically significant. All the analyses were performed using SPSS for Windows (SPSS, Chicago, IL, U.S.A.).

RESULTS

Among the 74 PTDM patients, 42 (56.8%) showed transient PTDM, while 32 (43.2%) showed persistent PTDM. In the transient PTDM group, the mean duration from diagnosis to recovery of PTDM was 6.6±6.6 months. Table 1 showed the clinical characteristics between the transient and persistent PTDM patients. Compared to the patients with persistent PTDM, those with transient PTDM were characterized by younger age at the time of transplantation (49±7 vs. 53±8 yr, P<0.05), longer time before the development of PTDM (44±59 vs. 13±20 days, P<0.05), a lower rate of HCV seropositivity (0.0 vs. 9.4%, P<0.05), and more frequent use of MMF (59.5 vs. 28.1%, P<0.05). In contrast, no significant differences were detected with regard to the body mass index (BMI) and fasting plasma glucose levels at the time of liver transplantation, and family history of diabetes. The cumulative dose of prednisolone during the previous 30 days of each time point did not show any difference between the 2 groups, and the plasma tacrolimus trough levels also did not show any difference. For initial treatment to control hyperglycemia, all the patients with persistent PTDM were treated by insulin and the patients with transient PTDM were treated by insulin (n=37, 88.1%), oral antidiabetic drugs (n=3, 7.1%), or life style modification alone (n=2, 4.3%).

Table 1. Comparison of clinical characteristics

	Transient group	Persistent group	*P*
Number	42	32	
Sex (M/F)	28/14	24/8	0.398
Age at transplantation (yr)	49±7	53±8	<0.05
Body mass index (kg/m^2)*	23.3±2.8	23.0±3.7	0.710
Family history of diabetes (%)	13.2	10.0	0.688
Time for PTDM development (days)	44±59	13±20	<0.05
HCV infection (%)	0	9.4	<0.05
Pretransplantation fasting plasma glucose (mM/L)	5.4±0.9	5.1±0.7	0.269
Cumulative prednisolone dose (mg/previous 30 days)			
1 month after transplantation	497.7±23.8	474.3±18.6	0.483
3 months after transplantation	310.9±80.0	299.2±62.5	0.662
6 months after transplantation	68.3±80.9	79.2±63.7	0.686
Tacrolimus trough level (ng/mL)			
1 month after transplantation	9.6±3.6	9.0±4.3	0.549
3 months after transplantation	8.7±2.7	8.3±2.9	0.628
6 months after transplantation	8.7±3.1	8.0±3.4	0.435
Use of mycophenolate mofetil (%)	59.5	28.1	<0.05

Data are expressed as mean±SD or percentage.
*Body mass index at the time of liver transplantation.
HCV, hepatitis C virus; PTDM, post-transplantation diabetes mellitus.

Based on a multivariate analysis (Table 2), age at the time of transplantation was determined as the single independent predictive factor associated with reversibility of new-onset diabetes mellitus following liver transplantation (odds ratio, 1.252 [95% confidence interval, 1.004-1.562]).

DISCUSSION

We hereby demonstrated that new-onset diabetes following liver transplantation was transient in 56.8% of the patients and the mean time period from the onset of PTDM to recovery was 6.6±6.6 months. Age at the time of transplantation was the single independent predictive factor associated with the reversibility of PTDM in a multivariate analysis.

It was reported that age at the time of renal allograft trans-

Table 2. Multivariate analysis of clinical parameters predicting the reversibility of PTDM

Risk factors	B*	SE†	Wald‡	*P*	Odds ratio (95% CI)
Age at transplantation (yr)	0.225	0.113	3.968	<0.05	1.252 (1.004-1.562)
Pretransplantation impaired fasting glucose level§	0.037	0.060	0.371	0.543	1.037 (0.922-1.168)
Time for PTDM development (≤30 days)	-0.071	0.062	1.301	0.254	0.932 (0.825-1.052)
Acute rejection	1.775	2.501	0.504	0.478	5.898 (0.044-793.617)
BMI at transplantation	0.106	0.334	0.101	0.750	1.112 (0.578-2.142)
Gender (female=0, male=1)	0.546	1.560	0.122	0.726	1.726 (0.081-36.746)
Cumulative prednisolone dose (mg/previous 30 days)					
1 month after transplantation	-1.607	1.902	0.714	0.398	0.201 (0.005-8.337)
3 months after transplantation	-0.269	0.454	0.351	0.554	0.764 (0.314-1.860)
6 months after transplantation	0.270	0.338	0.636	0.425	1.309 (0.675-2.540)
Tacrolimus trough level (ng/mL)					
1 month after transplantation	-0.080	0.242	0.111	0.348	0.923 (0.010-5.105)
3 months after transplantation	-0.209	0.301	0.486	0.460	0.811 (0.293-1.742)
6 months after transplantation	-0.049	0.298	0.027	0.869	0.952 (0.531-1.706)
Use of mycophenolate mofetil	-0.610	1.588	0.147	0.701	0.543 (0.024-12.223)
Constant	11.772	33.382	0.124	0.724	

*Regression coefficient; †Standard error; ‡z-score; §5.6 mM/L ≤fasting plasma glucose <7.0 mM/L.
BMI, body mass index; PTDM, post-transplantation diabetes mellitus; CI, confidence interval.

plantation (particularly ≥40 yr) was the predictive factor for the occurrence of future PTDM in Koreans (6). In addition, an age of ≥40 yr denoted a higher risk of persistent PTDM in Korean renal allograft recipients (7). Consistent with these findings in renal allograft transplantation patients, the current study showed that age at the time of transplantation was the single independent predictive factor associated with the reversibility of PTDM in liver allograft recipients. Interestingly, all patients with persistent PTDM were ≥40 yr of age at the time of transplantation (data not shown).

In the current study, 9.4% of persistent PTDM patients but none of the transient PTDM patients had HCV infection. HCV infection was not only associated with the development of PTDM but also associated with persistent PTDM (2, 8). It was recently shown that HCV infection was independently associated with increased insulin resistance in liver transplantation patients (9). In addition, HCV could directly infect human pancreatic beta cells, which might eventually lead to beta-cell dysfunction (10). For the generalization of the association between HCV infection and PTDM, a further study with sufficient number of patients would be necessary.

The time period from liver transplantation to PTDM development was shown to be significantly different between transient and persistent PTDM patients. It was expected that the earlier PTDM developed, the higher was the risk of persistent PTDM. This finding suggests that liver allograft recipients susceptible to the development of PTDM are also at a greater risk of developing persistent PTDM.

Reduction in the dose of tacrolimus and steroids was reported to be related to the reversibility of PTDM (4). In this study, we found that more frequent use of MMF was associated with transient PTDM, and that the mean trough level of tacrolimus was lower in the patients receiving MMF (8.3±2.5 vs. 9.7 ±2.8 ng/mL, $P<0.05$). Thus, dose-saving effect of MMF on tacrolimus might be partly responsible for the reversibility of PTDM.

There are several limitations in this study. First, the absence of oral glucose tolerance test might raise the possibility of ascertainment bias. Second, the retrospective study design cannot firmly conclude the data regarding the predictive factors. Third, the possible heterogeneity caused by including the patients who underwent liver transplantation in China could be the weak point of this study, even though there was no significant difference in their clinical characteristics compared to those of the patients who received the liver allograft at SNUH.

In conclusion, 56.8% of the patients with new-onset diabetes following liver transplantation showed transient PTDM and the age at the time of transplantation was the single independent predictive factor associated with the reversibility.

REFERENCES

1. Moon JI, Barbeito R, Faradji RN, Gaynor JJ, Tzakis AG. *Negative impact of new-onset diabetes mellitus on patient and graft survival after liver transplantation: long-term follow up. Transplantation 2006; 82: 1625-8.*
2. Khalili M, Lim JW, Bass N, Ascher NL, Roberts JP, Terrault NA. *New onset diabetes mellitus after liver transplantation: the critical role of hepatitis C infection. Liver Transpl 2004; 10: 349-55.*
3. Marchetti P. *New-onset diabetes after liver transplantation: from pathogenesis to management. Liver Transpl 2005; 11: 612-20.*
4. Shapiro R, Scantlebury VP, Jordan ML, Vivas C, Gritsch HA, McCauley J, Fung JJ, Hakala TR, Simmons RL, Starzl TE. *Reversibility of tacrolimus-induced posttransplant diabetes: an illustrative case and review of the literature. Transplant Proc 1997; 29: 2737-8.*

5. Davidson J, Wilkinson A, Dantal J, Dotta F, Haller H, Hernandez D, Kasiske BL, Kiberd B, Krentz A, Legendre C, Marchetti P, Markell M, van der Woude FJ, Wheeler DC. *New-onset diabetes after transplantation: 2003 International consensus guidelines. Proceedings of an international expert panel meeting. Barcelona, Spain, 19 February 2003. Transplantation 2003; 75 (10 Suppl): S3-24.*
6. Cho YM, Park KS, Jung HS, Jeon HJ, Ahn C, Ha J, Kim SJ, Rhee BD, Kim SY, Lee HK. *High incidence of tacrolimus-associated post-transplantation diabetes in the Korean renal allograft recipients according to American Diabetes Association criteria. Diabetes Care 2003; 26: 1123-8.*
7. Hur KY, Kim MS, Kim YS, Kang ES, Nam JH, Kim SH, Nam CM, Ahn CW, Cha BS, Kim SI, Lee HC. *Risk factors associated with the onset and progression of posttransplantation diabetes in renal allograft recipients. Diabetes Care 2007; 30: 609-15.*
8. AlDosary AA, Ramji AS, Elliott TG, Sirrs SM, Thompson DM, Erb SR, Steinbrecher UP, Yoshida EM. *Post-liver transplantation diabetes mellitus: an association with hepatitis C. Liver Transpl 2002; 8: 356-61.*
9. Delgado-Borrego A, Casson D, Schoenfeld D, Somsouk M, Terella A, Jordan SH, Bhan A, Baid S, Cosimi AB, Pascual M, Chung RT. *Hepatitis C virus is independently associated with increased insulin resistance after liver transplantation. Transplantation 2004; 77: 703-10.*
10. Masini M, Campani D, Boggi U, Menicagli M, Funel N, Pollera M, Lupi R, Del Guerra S, Bugliani M, Torri S, Del Prato S, Mosca F, Filipponi F, Marchetti P. *Hepatitis C virus infection and human pancreatic beta-cell dysfunction. Diabetes Care 2005; 28: 940-1.*