# Risk Factors for Development of New-Onset Diabetes Mellitus and Progressive Impairment of Glucose Metabolism After Living-Donor Liver Transplantation

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ABSTRACT

Background. New-onset diabetes mellitus (NODM) has a negative impact on graft and patient survivals. Hepatitis C virus (HCV) infection, high body mass index, increased donor and recipient ages, and calcineurin inhibitor (CNI) type have been identified as risk factors for the development of NODM. We aimed to elucidate the risk factors for the development of NODM and those for progressive glucose intolerance in adult living-donor liver transplant (LDLT) recipients.

Methods. We collected data from 188 primary liver transplant recipients (age > 16 years) who underwent LDLT from June 1991 to December 2011 at Hiroshima University Hospital. Risk factors for NODM and progressive impairment of glucose metabolism in pre-transplantation diabetes mellitus (DM) recipients were examined.

Results. Pre-transplantation DM was diagnosed in 32 recipients (19.3%). The overall incidence of NODM was 6.0% (8/134 recipients). Multivariate analysis revealed that old recipient age (≥55 years) is a unique predictive risk factor for developing NODM. The incident of pre-transplantation DM was significantly higher in recipients with HCV infection than in those without HCV. A high pre-transplantation triglyceride level was an independent risk factor for progressive impairment of glucose tolerance among 32 LDLT recipients with pre-transplantation DM. All of the NODM patients were being treated with tacrolimus at the time of diagnosis. Switching the CNI from tacrolimus to cyclosporine allowed one-half of the patients (4/8) to withdraw from insulin-dependent therapy. NODM and post-transplantation glucose intolerance had no negative impact on patient and graft outcomes.

Conclusions. Older age of the recipient (≥55 years) was a significant risk factor for NODM. Hypertriglyceridemia in the recipients with DM is an independent risk factor for post-transplantation progressive impairment of glucose metabolism. NODM had no negative impact on outcomes in the LDLT recipients.

NEW-ONSET DIABETES MELLITUS (NODM) is recognized as a common complication in organ transplantation, one of the risk factors that affect graft and patient survival in solid organ transplantation. NODM contributes to the risk for infection, cardiovascular disease, and neurologic complications [1]. The prevalence of NODM after liver transplantation is 18%–50% [2–5]. Risk factors for the development of NODM include increased age, ethnicity, family history of type 2 diabetes, obesity, hepatitis C virus (HCV) and cytomegalovirus infections, glucocorticoid treatment, and the use of other immunosuppressive medications

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[2,6]. Recent reports indicate that some gene polymorphisms may be related to NODM after solid organ transplantation [7]. These characteristics likely reflect inherited and acquired defects in insulin sensitivity and β-cell function that contribute to hyperglycemia.

NODM is thought to result from the combination development of insulin resistance and decreased insulin secretion. The use of transplantation immunosuppressive medications in addition to weight gain or steroid pulse therapy could aggravate pre-transplantation glucose intolerance [8]. Tacrolimus, one of the most frequently used calcineurin inhibitors (CNIs), seems to have the most pronounced diabetogenic effect. Kurzawski et al [7] showed that individuals taking tacrolimus had a significantly higher incidence of NODM than those not taking it. Compared with patients on cyclosporine treatment, those medicated with tacrolimus had a significantly higher incidence of NODM or impairment of glucose tolerance after 6 months of therapy (26.0% vs 33.4%, respectively) [9].

Some reports have shown that HCV infection causes a high rate of NODM in renal and liver transplant recipients [10,11]. The prevalence of pretransplant diabetes mellitus (DM) and glucose intolerance was apparently higher in recipients with HCV infection [12]. Soule et al [13] reported the HCV infection contributes to the development of DM in orthotopic liver transplant recipients.

However, most published data about NODM have come from single-center studies with relatively small sample sizes and from deceased-donor liver transplantation in Western populations. Harada et al [14] reported that higher body mass index (BMI), male sex, and older age were independent predictive factors for developing NODM after living-donor liver transplantation (LDLT) among Asian adult recipients, whereas the impact of HCV infection did not reach significance. In the present study, we aimed to investigate risk factors for development of NODM and to identify risk factors for progressive impaired glucose metabolism in recipients with pre-transplantation DM after LDLT at a single transplant center.

## METHODS

A total of 188 adult patients underwent LDLT from June 1991 to December 2011 at Hiroshima University Hospital. Of the 188 patients, 16 recipients who died within 6 months after LDLT, 2 who required re-LDLT, and 4 who underwent deceased-donor liver transplantation were excluded from the study. Pre-transplantation DM was diagnosed in 32 recipients (19.3%). The procedures for donor evaluation, donor surgery, recipient surgery, and perioperative management followed in our hospital have been described elsewhere [15,16].

NODM was defined by the American Diabetes Association/World Health Organization criteria that were recommended in the 2003 International Consensus Guidelines to diagnose DM after transplantation [1]. Diagnostic criteria include the following: fasting blood glucose levels ≥126 mg/dL (7.0 mmol/L) on 2 separate occasions and/or a 2-hour postprandial blood glucose level ≥200 mg/dL (11.1 mmol/L) on 2 separate occasions. Alternatively, DM was defined as the requirement of glucose-lowering medications (insulin or oral hypoglycemic agents). Transient DM was defined as DM present in <2 follow-up post-transplantation intervals. Persistent DM was defined as DM present in ≥3 follow-up post-transplantation intervals with ≥1 interval beyond the 3rd post-transplantation month [10]. In our study, patients with postoperative progressive impairment of glucose metabolism were identified as those who needed to be medicated with new or higher doses of insulin and who later had diabetes-related renal failure or diabetic complications.

The basic immunosuppressive regimen after LDLT consisted of tacrolimus/cyclosporine and methylprednisolone, with doses gradually tapered off. In patients with HCV infection, the methylprednisolone dose was rapidly tapered off and administration was stopped within 1 month after LDLT, which would be beneficial for preventing enhanced viral replication [17].

The assessed recipient-related risk factors included age, sex, pre-transplantation BMI (kg/m$^2$), Model for End-Stage Liver Disease (MELD) score, and presence of HCV infection. HCV infection was defined in recipients with a positive anti-HCV test or an HCV-related diagnosis. Sustained virologic response (SVR) was defined as undetectable HCV RNA in the serum after the completion of HCV therapy. Baseline recipient factors according to the presence of postoperative impaired glucose metabolism or persistent and improved glucose metabolism were compared with the use of the chi-square test. Multivariate analysis was performed with the use of a logistic regression test. All $P$ values were 2 tailed, and $P \leq .05$ was considered to be statistically significant. All analyses were performed with the use of the SPSS statistical software (IBM Japan, Tokyo, Japan).

## RESULTS

The study population with which to identify NODM risk factors consisted of 51 female and 83 male recipients without pre-transplantation DM. As observed in Table 1, NODM was diagnosed in 8 (6.0%) of the 134 recipients. We analyzed recipient and donor risk factors for developing NODM in a univariate analysis. A total of 48 (35.8%) of the 134 patients were infected with HCV, whereas 86 (64.2%) of the 134 patients were not infected with HCV before LDLT. HCV infection and increased recipient age were risk factors for developing NODM on univariate analysis; recipient sex, recipient BMI, MELD score, donor age, donor sex, donor BMI, cold ischemia time, and operation time demonstrated no statistically significant differences. Older recipient age was considered to be the unique and important predictive risk factor for developing NODM on multivariate analysis (odds ratio, 9.191; 95% confidence interval, 1.083−76.478; $P = .042$). Table 2 shows that among the 166 patients, the HCV-positive recipients showed significantly higher proportional rate of pretransplant DM (19/67, 28.4%) than the HCV-negative recipients (13/99, 13.1%; $P < .05$, Fisher exact test). The outcomes of the patients with DM or non-DM were not significantly different regarding graft and patient survival (data not shown).

Next, a subgroup analysis was performed in the patients with pre-transplantation DM recipients with a special focus on the patients with post-transplantation progressive