Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Association between donor and recipient *TCF7L2* gene polymorphisms and the risk of new-onset diabetes mellitus after liver transplantation in a Han Chinese population

Qi Ling, Haiyang Xie, Di Lu, Xuyong Wei, Feng Gao, Lin Zhou, Xiao Xu*, Shusen Zheng*

Key Lab of Combined Multi-Organ Transplantation, Ministry of Public Health, Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China

Backgrounds & Aims: New-onset diabetes mellitus (NODM) is a frequent and serious complication arising after liver transplantation (LT). Transcription factor 7-like 2 (*TCF7L2*) polymorphisms have been reported to strongly associate with type 2 diabetes. In addition, the donor liver plays a vital role in regulating blood glucose levels. In this study, we aim at evaluating the association between donor and recipient *TCF7L2* gene polymorphisms with NODM after LT.

Methods: A total of 125 patients undergoing primary LT, without a history of diabetes were included. Four single nucleotide polymorphisms (rs290487, rs7903146, rs11196205, and rs12255372), closely associated with type 2 diabetes in the Eastern Asia population, were genotyped and analyzed.

Results: Both donor and recipient rs290487 polymorphisms (CC *vs*. TT genotype) were found to be significantly associated with NODM. In multivariate analysis, donor rs290487 genetic variation (OR = 2.172 per each C allele, $p = 0.015$), blood tacrolimus levels at 1 month post-LT >10 ng/ml (OR = 3.264, $p = 0.017$), and recipient age >55 years (OR = 2.638, $p = 0.043$) were identified as independent risk factors of NODM. Furthermore, donor rs290487 CC genotype could predict a high probability (>40%) of the onset of NODM. Predictive model containing donor rs290487 polymorphism showed a significantly higher prognostic ability on NODM than the model with only clinical parameters ($p = 0.031$).

Conclusions: Donor *TCF7L2* rs290487 polymorphism is associated with an increased risk of NODM after LT and has a potential clinical value for the prediction of NODM.

Keywords: Liver transplantation; New-onset diabetes mellitus; *TCF7L2* polymorphism.

Received 19 April 2012; received in revised form 20 September 2012; accepted 25 September 2012; available online 4 October 2012

* Corresponding authors. Tel./fax: +86 571 87236616 (X. Xu), tel./fax: +86 571 87236567 (S. Zheng).

E-mail addresses: zjxu@zju.edu.cn (X. Xu), zyzss@zju.edu.cn (S. Zheng).

Abbreviations: NODM, new-onset diabetes mellitus; LT, liver transplantation; TCF7L2, transcription factor 7-like 2; SNP, single nucleotide polymorphism; PCR-RFLP, PCR restriction fragment length polymorphism; AUROC, area under the receiver operating characteristic curve; HBV, hepatitis B virus; MELD, model for end-stage liver disease; HWE, Hardy–Weinberg equilibrium; OR, odds ratio; CI, confidence interval.

Introduction

New-onset diabetes mellitus (NODM) is common in liver transplant recipients and has a negative effect on both graft and patient survival [1–3]. Although the surgical technique and immunosuppressive management have improved, the prevalence of NODM remains very high, and has been recently reported as 17–36.5% [1,2,4–6]. The development of NODM after liver transplantation (LT) has shown to be closely associated with cardiovascular complications, infections, chronic rejection and renal failure, which subsequently lead to a reduced quality of life and high mortality [1–3,5]. Identifying patients at high risk of developing NODM is beneficial for preventing disease and improving the long-term prognosis after LT.

So far, no definitive risk factors have been clearly established, but clinical parameters such as advanced age, family history, obesity, hepatitis C virus infection, and immunosuppressive agents have been implicated [1,3,4,7,8]. As NODM shares many similarities with type 2 diabetes mellitus in both pathophysiology and clinical presentation, genetic variants that are involved in type 2 diabetes mellitus may also be associated with the development of NODM besides the clinical implications [9]. Recent genome-wide association studies have identified a number of novel type 2 diabetes-susceptibility genes, such as transcription factor 7-like 2 (*TCF7L2*), which is regarded as the most important one [10–12]. By isolating genomic DNA from peripheral blood lymphocytes of kidney transplant recipients, researchers have demonstrated that *TCF7L2* rs7903146 polymorphism is significantly associated with an increased risk of NODM after kidney transplantation [13–15].

However, unlike kidney transplantation, the liver plays a major role in blood glucose control and hepatic metabolism of insulin. Therefore, donors' phenotype and genotype may greatly affect glucose handling and relate to the occurrence of NODM in liver transplant recipients. Increasing evidence has shown that there is a tight link between *TCF7L2* and hepatic glucose metabolism. Several studies have indicated that the T allele of rs7903146 *TCF7L2* is associated with elevated rates of hepatic glucose production and reduced hepatic insulin sensitivity [16,17]. In addition, Wnt/β-catenin/TCF signaling pathway plays a key role in driving metabolic zonation in the liver [18], and liver *TCF7L2* expression has been reported to strongly associate with diabetes [19].

Table 1. Demographic data for NODM and non-NODM groups.

	NODM group (n = 25)	non-NODM group (n = 100)	*p* value
Donor age (yr)	36.8 ± 5.4	38.1 ± 7.1	0.398
Donor male/female (n)	24/1	91/9	0.680
Hepatic steatosis >30% (n)	6	9	0.039
Cold ischemia time (h)	11.0 ± 4.5	10.6 ± 4.0	0.612
Blood type mismatch (n)	5	17	0.953
Recipient age (yr)	50.9 ± 6.7	47.0 ± 11.1	0.030
Recipient male/female (n)	23/2	84/16	0.484
Follow-up duration (mo)	29.4 ± 18.7	31.9 ± 17.0	0.651
MELD score	18.8 ± 8.0	19.4 ± 9.5	0.716
HBV-related end stage liver disease (n)	20	84	0.858
Comorbidities (n)			
Hepatic encephalopathy	4	9	0.501
Hepatorenal syndrome	1	8	0.795
Ascites	10	43	0.786
Hyperlipidemia	4	8	0.404
Hypertension	2	5	0.923
Fasting plasma glucose (mg/dl)*			
At transplantation	5.12 ± 1.45	4.99 ± 1.24	0.339
At 3 months after LT	7.78 ± 2.19	5.10 ± 1.13	<0.001
At 6 months after LT	7.63 ± 1.90	5.17 ± 0.64	<0.001
BMI			
At transplantation	22.6 ± 2.0	22.2 ± 3.3	0.676
At 3 months after LT	21.7 ± 1.9	21.3 ± 2.9	0.710
At 6 months after LT	24.3 ± 1.6	23.1 ± 2.9	0.051
Anti-IL2 receptor antibody induction	7	32	0.699
Tacrolimus level (ng/ml)			
At 1 month after LT	9.97 ± 2.7	8.23 ± 2.8	0.005
At 3 months after LT	8.13 ± 1.7	7.30 ± 1.9	0.043
At 6 months after LT	6.08 ± 1.4	5.80 ± 1.8	0.511

BMI, body mass index; HBV, hepatitis B virus; LT, liver transplantation; MELD, model for end-stage liver disease; NODM, new-onset diabetes mellitus.
*Included patients treated with antidiabetic medicine.

In the current study, we aim at determining whether donor or recipient diabetes-susceptibility gene (*TCF7L2*) variations contribute to the development of NODM after LT, and also to identify the potential risk factors of NODM in a Han Chinese population.

Patients and methods

Patients

A total of 125 patients undergoing primary LT between November 2006 and July 2009 at the First Affiliated Hospital, Zhejiang University School of Medicine, China were enrolled. We excluded patients with a known history of diabetes, less than 6-month follow-up time or developing acute rejection. The mean age of recipients at transplantation was 47.8 ± 10.5 years (range: 18–70 years) and there were 107 males and 18 females. The main clinical characteristics of the study population are summarized in Table 1. No patient had a family history of diabetes. The causes of liver diseases were hepatitis B virus (n = 104), alcohol (n = 7), hepatitis C virus (n = 5), drug (n = 4), primary biliary cirrhosis (n = 3), sclerosing cholangitis (n = 1), and autoimmune hepatitis (n = 1). Lamivudine combined with low-dose intramuscular hepatitis B immunoglobulin therapy was applied in patients with hepatitis B virus-related liver disease [20]. All patients were routinely followed-up at the outpatient clinic and the mean follow-up time was 31 ± 17 months (range: 6–61 months). Immunosuppressive regimen was triple therapy incorporating tacrolimus, mycophenolate, and steroid (methylprednisolone, 1 g on the first day, and prednisolone, 20 mg tapered to zero within the first 3 months), which was previously reported [1].

Ethics statement

Informed consent was obtained from all donors and recipients. Each organ donation or transplant was approved by the Institutional Review Board, First Affiliated Hospital, Zhejiang University, strictly under the guidelines of the Ethics Committee of the hospital, the current regulation of the Chinese Government, and the Declaration of Helsinki. No donor livers were harvested from executed prisoners.

Data collection

The following data were recorded for the study population: age, gender, cold ischemia time, donor liver steatosis, primary liver disease, co-morbidities (e.g., hepatic encephalopathy, hepatorenal syndrome, ascites), body mass index