Low Incidence of Vascular Complications in Patients with Diabetes Mellitus Associated with Liver Cirrhosis as Compared with Type 2 Diabetes Mellitus

FUMIKADO FUJIWARA, MOTOTSUGU ISHII, HARUHITO TANEICHI, MASANORI MIURA, MAKIKO TOSHIHIRO, NORIKO TAKEBE, WATARU ISHIDA, YOSHIITO KANEKO, AKINOBU KATO,1 KAZUYUKI SUZUKI1 and JO SATOH

Department of Diabetes and Metabolism, and 1The First Department of Internal Medicine, School of Medicine, Iwate Medical University, Morioka, Japan


We compared clinical features and vascular complications of patients with diabetes mellitus associated with liver cirrhosis versus patients with type 2 diabetes mellitus. Subjects were 19 patients (LC-DM group) in whom diabetes was diagnosed after development of liver cirrhosis. Control consisted of 38 patients with type 2 diabetes (T2DM group) matched for sex, age, duration of diabetes, body mass index, treatment, and degree of glycemic control, which was determined by glycoalbumin. The LC-DM group had significantly more smokers, higher serum insulin levels, more insulin resistance calculated by homeostasis model assessment, lower blood counts (white and red blood cells, hemoglobin, and platelets), and lower serum levels of total cholesterol, triglyceride, low density lipoprotein cholesterol and lipoprotein (Lp)(a) than the T2DM group. The incidence of diabetic retinopathy and cerebrovascular disease was significantly lower in the LC-DM group compared to the T2DM group. Logistic regression analysis indicated that Lp(a) and the diabetes duration were significant predictors for the retinopathy, while Lp(a) was a significant predictor for the cerebrovascular complication. In diabetes associated with liver cirrhosis, the incidence of diabetic retinopathy and cerebrovascular disease is lower than in type 2 diabetes mellitus in this study, probably because of lower levels of serum Lp(a).

Type 2 diabetes mellitus is frequently complicated by microangiopathy, such as diabetic retinopathy and nephropathy (Skyler 1996), and by macroangiopathy, such as ischemic heart disease and cerebrovascular disease (Garber 2002). These vascular complications greatly affect the prognosis of diabetic patients (WHO Study Group 1995). Among patients with liver cirrhosis, 20-30% have been reported to have diabetes, and if borderline cases are included, over 80% have abnormal glu-
cose metabolism of hepatic etiology (Giampaolo et al. 1994). In these patients, the incidence of microangiopathy and macroangiopathy is thought to be low (Grant et al. 1949; Creed et al. 1995). However, as far as we know, there have previously been few detailed studies on the incidence, severity, or pathogenesis of vascular complications in patients with cirrhosis-associated diabetes.

To study the pathogenesis and the risk factors for the development of vascular complications in diabetes secondary to liver disease, we compared the micro- and macroangiopathy and clinical features of patients with diabetes associated with liver cirrhosis versus patients with type 2 diabetes mellitus.

**RESEARCH DESIGN AND SUBJECTS**

We studied 19 patients presented at the First Department of Internal Medicine or the Department of Diabetes and Metabolism of the Iwate Medical University Hospital from September 2003 to July 2004, in whom diabetes was diagnosed after liver cirrhosis developed, thus fulfilling the diagnosis of diabetes secondary to liver cirrhosis (Kuzuya et al. 2002), and who were being treated with diet or oral hypoglycemic agents (LC-DM group). The diagnosis of diabetes was made according to the diagnostic criteria of WHO (Alberti and Zimmet 1998). The etiology of cirrhosis was type C hepatitis virus (including those with alcohol use) in 12 patients, type B hepatitis virus in 1 patient, alcoholic in 4 patients, and idiopathic in 2 patients. The patients with cirrhosis of grade A or grade B according to the Child-Pugh classification were eligible for this study. 14 patients had grade A, and 5 patients had grade B. Patients with decompensated cirrhosis (grade C) were excluded. Patients with clinical stage I of hepatocellular carcinoma were also included (4 patients).

The control group consisted of 38 patients with type 2 diabetes (T2DM group) who were selected randomly from 266 patients admitted to the hospital during the same period for the treatment of diabetes mellitus, by matching for type of therapy, sex, age, duration of diabetes, degree of glycemic control and body mass index (BMI) in order of these variables described. Duration of diabetes was determined based on the medical record, e.g., onset of glucosuria or hyperglycemia by annual medical check, onset of symptoms such as thirst, polyuria and polydipsia, or date of diagnosis. Because patients with cirrhosis have reduced red blood cell survival due to hypersplenism and thus show low hemoglobin A1c (HbA1c) (Nomura et al. 1986), the degree of glycemic control was determined by glycoalbumin (GA) (Cohen and Clements 1999) rather than by HbA1c. Variation of HbA1c of each patient in the both LC-DM and T2DM groups was approximately within ±10% in the recent several years.

For all subjects in both groups, blood was obtained after fasting for 12 hours or longer to measure by the Central Laboratory in our hospital, and compare blood cell count, fasting plasma glucose (FPG) level, fasting insulin (immunoreactive insulin: IRI) level, HbA1c, GA, total cholesterol (TC), triglyceride (TG), high density lipoprotein-cholesterol (HDL-C) and low density lipoprotein-cholesterol (LDL-C). Lipoprotein (a) (Lp[a]), remnant-like particle cholesterol (RLP-C), and adipokines such as leptin and plasminogen activator inhibitor-1 (PAI-1), considered associated with atherosclerosis, were measured by SRL Co. (Tokyo).

As an index of insulin resistance, the homeostasis model assessment of insulin resistance (HOMA-IR) (HOMA-IR = fasting blood glucose (mg/100 ml) × fasting insulin level (μU/ml) / 405) was used (Matthews et al. 1985).

To evaluate the extent of atherosclerosis, systolic blood pressure and diastolic pressure were measured, while Form PW/ABI (Colin Medical Technology Co., Aichi) was used to measure the pulse wave velocity (PWV), which is an index of atherosclerosis, and the ankle brachial index (ABI), which is an index of obstructive arteriosclerosis in the lower extremities. Risk for cerebrovascular disease was evaluated by measuring the intima-media thickness (IMT) of carotid artery by ultrasonography (LOGIQ 500, GE Yokogawa Medical systems Co., Tokyo), while the risk for ischemic heart disease was determined by measuring the coronary artery calcification score (CAC score) by multi detector-row helical computed tomography (MDCT) (Aquilion TSX-101A, TOSHIBA Medical systems Co., Tochigi). In addition, visceral and subcutaneous abdominal fat was measured by cross-sectional computed tomography (CT) scan using Multislice CT (Aquilion 16, Toshiba, Tokyo) at the navel level. Visceral fat area (VFA) and subcutaneous fat area (SFA) were identified with threshold attenuation values between −150 to 0 Hounsfield unit, and delineated by the Multislice CT. Fatty liver was determined by CT attenuation, and clinical fatty liver was defined as < 0.9 of the ratio of liver/spleen (L/S) CT num-
For the evaluation of microangiopathy, an ophthalmologist examined diabetic retinopathy, while diabetic nephropathy was diagnosed based on microalbuminuria of 20 mg/day or greater. For the evaluation of macroangiopathy, cerebrovascular and cardiovascular events were determined. Cerebrovascular events were defined as transient ischemic attacks and stroke, while cardiovascular events were defined as myocardial infarction, asymptomatic myocardial ischemia, angina, and cardiac death (Chiasson et al. 2002).

The values are expressed as the median (in quartiles). The difference between the two groups was tested by the Mann-Whitney’s U-test and the independence was tested by Fisher’s exact probability test. Factors affecting the incidence of vascular complications were tested by the logistic regression analysis. Macintosh Stat View 5.0 (SAS Institute Inc.) was used, and < 5% was considered to be significant.

RESULTS

Clinical characteristics of the two groups

Table 1 compares the clinical characteristics of the LC-DM group versus the T2DM group. Because the T2DM group was randomly selected essentially to match the LC-DM group for sex, age, duration of diabetes mellitus, BMI, and treatment, there were no significant differences in these parameters between the 2 groups. There were also no significant differences between the 2 groups for systolic blood pressure or diastolic blood pressure. There were significantly more smokers in the LC-DM group (11 / 19) as compared with those in the T2DM group (10 / 38) (p < 0.05).

As shown in Table 3, blood count showed that the LC-DM group had significantly lower white blood cell count (p < 0.0001), red blood cell count (p = 0.0001), hemoglobin (p < 0.05), and platelet count (p < 0.0001). On the other hand, there were no differences between the groups for adipocytokines (leptin and PAI-I), distribution of adipose tissue (VFA and SFA), CAC score, IMT, ABI, and PWV which are related to atherosclerosis (Table 2). Although not shown in the Table, there were no significant differences in CT liver/spleen ratio (L/S ratio). However, spleen CT number was significantly higher in the LC-DM group (51.5 Hounsfield unit) compared to the T2DM group (48.2 Hounsfield unit) (p < 0.05).

Comparison of glucose and lipid metabolism

Table 3 compares the glucose and lipid metabolism. The GA level did not differ between the groups because the control chosen had been essentially matched. Compared to the T2DM group, the LC-DM group had significantly lower fasting plasma glucose (p < 0.01) and HbA1c (p < 0.0001), while fasting insulin level (p < 0.0001) and HOMA-R (p < 0.001) were significantly higher.

Data on lipid metabolism showed that compared to the T2DM group, the LC-DM group had significantly lower VLDL, LDL, and TG, and higher HDL (p < 0.0001). There were no significant differences in VFA and SFA.

Table 1. Clinical characteristics of patients

<table>
<thead>
<tr>
<th></th>
<th>LC-DM group</th>
<th>T2DM group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M / F)</td>
<td>13 / 6</td>
<td>26 / 12</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64 (53 - 71)</td>
<td>65 (58 - 71)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.8 (22.2 - 26.5)</td>
<td>24.5 (22.3 - 27.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Duration (years)</td>
<td>3.0 (1.0 - 8.3)</td>
<td>5.0 (2.0 - 13.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>126 (118 - 140)</td>
<td>134 (120 - 149)</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>72 (70 - 78)</td>
<td>78 (70 - 84)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking (+ / −)</td>
<td>11 / 8</td>
<td>10 / 28</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>(Diabetes treatment)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>8 / 19</td>
<td>16 / 38</td>
<td>NS</td>
</tr>
<tr>
<td>OHA</td>
<td>11 / 19</td>
<td>22 / 38</td>
<td>NS</td>
</tr>
</tbody>
</table>

Median, interquartile range.
significantly lower TC (p < 0.05), TG (p < 0.05), LDL-C (p = 0.0002), and Lp(a) (p < 0.0001). There were no significant differences in HDL-C, TG/HDL-C ratio, or RLP-C (Table 3).

Comparison of incidence of vascular complications between the groups and analysis of affecting factors

Fig. 1 shows microangiopathic and macroangiopathic complications in the LC-DM group and the T2DM group. With respect to microangiopathy, the incidence of diabetic retinopathy was significantly lower in the LC-DM group (3 / 19, 16%) compared to the T2DM group (20 / 38, 53%) (p < 0.01). The retinopathy of the LC-DM group was in the earlier stage than that of the T2DM group, although the difference was not significant. There was no significant difference in the incidence of diabetic nephropathy. With respect to macroangiopathy, the incidence of cerebrovascular complications was significantly lower in the LC-DM group (0 / 19, 0%) compared to the
Diabetic Complications in Diabetes with Liver Cirrhosis

T2DM group (9 / 38, 31%) (p < 0.05), in which all 9 events were cerebral infarction. There were no significant differences in the incidence of ischemic heart disease, ischemic changes on electrocardiogram (ECG) and calcifications in the aortic arch on chest x-ray, and in the incidence of family history of diabetes mellitus, cerebrovascular disease and ischemic heart disease between the two groups.

Logistic regression analysis indicated that the duration of diabetes mellitus and Lp(a) were the significant independent factors for the diabetic retinopathy (Table 4), while the Lp(a) was a significant independent factor for cerebrovascular complication (Table 5) in LC-DM group. On the other hand, none of independent variables was obtained in T2DM group.

DISCUSSION

In this study, we compared vascular complications between patients with diabetes associated with liver cirrhosis and those with type 2 diabetes, and found that incidence of diabetic retinopathy and cerebrovascular diseases were significantly lower in the former than those in the latter. The low serum Lp(a) was the independent factor af-

Table 4. Logistic regression analysis for diabetic retinopathy

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Odds ratio</th>
<th>95%CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic duration (years)</td>
<td>1.133</td>
<td>1.026 ~ 1.251</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Platelet (× 10⁴ mm⁻³)</td>
<td>1.025</td>
<td>0.934 ~ 1.126</td>
<td>NS</td>
</tr>
<tr>
<td>F-IRI (μU/ml)</td>
<td>1.016</td>
<td>0.994 ~ 1.039</td>
<td>NS</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>0.846</td>
<td>0.551 ~ 1.298</td>
<td>NS</td>
</tr>
<tr>
<td>TG (mg/100 ml)</td>
<td>0.999</td>
<td>0.992 ~ 1.006</td>
<td>NS</td>
</tr>
<tr>
<td>Lp(a) (mg/100 ml)</td>
<td>1.027</td>
<td>1.005 ~ 1.049</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

dependent variable: diabetic retinopathy.
fecting the low incidence of the vascular complications in the diabetic patients with liver cirrhosis.

Diabetes associated with liver diseases such as chronic hepatitis and liver cirrhosis is classified as “diabetes due to other specific mechanisms or diseases” in the classification and diagnostic criteria of diabetes mellitus by Japan Diabetes Society published in 2002 (Kuzuya et al. 2002). Liver plays a central role as a regulator of blood glucose through the uptake and release of glucose. Cirrhosis-associated diabetes is thought to be a type of secondary diabetes, and the pathogenesis has been reported to involve a decrease in the number of hepatic parenchymal cells due to interstitial fibrosis, resulting in decreased glucokinase activity, glycogen synthesis, gluconeogenesis and ability to degrade insulin, as well as impaired utilization of insulin due to the porto-systemic shunt (Sotaniemi and Keinanen 1985). There are also reports on significant insulin resistance in the peripheral tissues and the liver (Petrides and DeFronzo 1989).

Chronic hyperglycemia, diabetes duration and hypertension are predominant risk factors for diabetic microangiopathy such as retinopathy, nephropathy and neuropathy (Skyler 1996), while, in addition to these, sex, age, smoking, insulin resistance and dyslipidemia are also strong risk factors for macroangiopathy (Garber 2002). To compare the vascular complications, we adjusted the background factors such as sex, age, diabetes duration and glycemic control between the groups. Therefore, there were no differences in these risk factors as well as blood pressure between the two groups. However, there were significant differences in other risk factors between the two groups, e.g., fasting plasma insulin, HOMA-IR and incidence of smoking were much higher in the LC-DM group, whereas TC, TG, LDL-C, and Lp(a) were much lower in the LC-DM group. Although CT L/S ratio as an indicator of fatty liver was normal in the two groups, spleen CT number was also significantly higher in the LC-DM group, probably because of portal hypertension in the LC-DM group.

Fasting hyperinsulinemia, a characteristic of diabetes associated with liver cirrhosis, indicates the insulin resistance in the LC-DM, which is a risk factor of macroangiopathy (DeFronzo and Ferrannini 1991). In addition, diabetic patients with liver cirrhosis usually have post-prandial hyperglycemia which is also involved in the development and the progression of diabetic complications, particularly macroangiopathy (Hanefeld et al. 1996; Bonora and Muggeo 2001). Furthermore, there were more smokers in our patients with liver cirrhosis. Thus, although the LC-DM group had more risk factors for macroangiopathy, there were no significant differences in the degree of atherosclerosis evaluated by CAC score, IMT, ABI and PWV. However, as a whole, there were significantly fewer incidences of the retinopathy and cerebrovascular disease in the LC-DM group. This may be due to the protective effects on vascular complications of the low serum level of lipids such as TC, TG, LDL-C and Lp(a), decreased coagulation function and thrombocytopenia associated with liver cirrhosis. Among these factors, low serum Lp(a) was the independent predictor for low incidence of the retinopathy and cerebro-

### Table 5. Logistic regression analysis for cerebrovascular disease

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic duration (years)</td>
<td>0.975</td>
<td>0.920 – 1.035</td>
<td>NS</td>
</tr>
<tr>
<td>Platelet (× 10⁴ mm³)</td>
<td>0.970</td>
<td>0.827 – 1.137</td>
<td>NS</td>
</tr>
<tr>
<td>F-IRI (μU/ml)</td>
<td>1.005</td>
<td>0.870 – 1.160</td>
<td>NS</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>1.448</td>
<td>0.845 – 2.480</td>
<td>NS</td>
</tr>
<tr>
<td>TG (mg/100 ml)</td>
<td>0.985</td>
<td>0.952 – 1.020</td>
<td>NS</td>
</tr>
<tr>
<td>Lp(a) (mg/100 ml)</td>
<td>1.023</td>
<td>1.001 – 1.047</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

Dependent variable: cerebrovascular disease.
vascular disease.

Lp(a) is an LDL-like lipoprotein whose concentration in plasma is correlated with atherosclerosis. The characteristic protein component of Lp(a) is apolipoprotein(a) which is disulphide-linked to apolipoprotein B-100. Apolipoprotein(a) complementary DNA is very similar to human plasminogen (McLean et al. 1987). Amino acid sequence of apolipoprotein(a) is homologous to plasminogen, but has inactive protease domain (Eaton et al. 1987). Because of this structural/functional homology and enzymatic inactivity, Lp(a) competes with plasminogen for binding to fibrin and impairs, thereby, fibrinolysis and pericellular proteolysis. High concentrations of Lp(a) in plasma may, therefore, represent a potential source of antifibrinolytic activity (Angles-Cano et al. 2001). It is also thought that through the suppression by Lp(a) of the activity of transforming growth factor-β (TGF-β), which has the potential to inhibit the proliferation of endothelial cells and smooth muscle cells, there is increased proliferation of the vascular endothelial cells and smooth muscle cells (Miyata et al. 1995), resulting in the progression of atherosclerosis.

For these reasons, Lp(a) is a known independent risk factor for ischemic heart disease (Rhoads et al. 1986; Murakami et al. 1998), and is also a risk factor for cerebrovascular infarction in the region of the cortical branch (Murai et al. 1986). It is interesting to note that none of our diabetic patients with liver cirrhosis had cerebrovascular events, whereas 31% patients of the T2DM group had cerebral infarction. There is a report on relationship between low Lp(a) level and reduced risk for vascular atheromatosis in patients with alcoholic liver disease (Ricciardi et al. 1994). There are also reports that high Lp(a) levels in the blood is associated with the development and progression of diabetic retinopathy (Suehiro et al. 2002) and nephropathy in diabetic patients (Hernandez et al. 1997) and that there exists a correlation between the severity of diabetic retinopathy and Lp(a) (Makino 1987). The similar results were reported on the low prevalence of micro- and macroangiopathy in cirrhosis with diabetes, but the authors thought that it was partly due to short-duration of diabetes (Marchesini et al. 1999). In our data, the patients of the LC-DM group had low incidence of the retinopathy, and an earlier stage of retinopathy as compared to those of the T2DM group, although the difference was not significant probably because of small number of patients analyzed. By the Logistic regression analysis, in addition to Lp(a), the duration of diabetes was also independent factor for the retinopathy. Although there was no difference in the diabetes duration between the two groups, it could not be denied a possibility that the diabetes duration was underestimated in T2DM group, as well as LC-DM group, because of asymptomatic or undiagnosed stage of diabetes.

Factors determining Lp(a) levels in the blood are considered to be 90% genetic and 10% environmental (Boerwinkle 1992). Serum Lp(a) concentrations are reduced in liver cirrhosis (Malaguarnera et al. 1996). In this study, the LC-DM group showed significantly lower Lp(a) levels compared to the T2DM group, and in the LC-DM group, the median Lp(a) level was 3.0 mg/100 ml in patients with grade A cirrhosis according to the Child-Pugh classification and 1.0 mg/100 ml in grade B patients, suggesting that in cirrhotic patients, the mechanism underlying the decrease in Lp(a) is due to decreased hepatic function, resulting in decreased synthesis of Lp(a) in the liver.

In summary, although the diabetic subjects with liver cirrhosis were associated with insulin resistance and hyperinsulinemia, risk factors for vascular complications, the incidence of diabetic retinopathy and cerebrovascular disease were significantly lower in these patients than in the patients with type 2 diabetes mellitus in this study. This is probably due to the lower levels of serum lipids such as Lp(a) because of a decreased liver function.

**Acknowledgements**

This research was supported in part by a Grant-in-Aid for Scientific Research (C) (15590926) from The Ministry of Education, Science, Sports and Culture of Japan (to JS), and a research grant from Iwate Prefecture. This work was also supported by MEXT: HAITEKU (2004-2008).
References


