

Prevalence of Diabetes and Incidence of Angiopathy in Patients with Chronic Viral Liver Disease

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Summary Patients with chronic liver disease (CLD) often develops glucose intolerance. We explored the prevalence of diabetes mellitus in viral CLD, and analyzed factors profoundly affecting the diabetic angiopathies. 229 CLD patients (124 chronic hepatitis and 105 liver cirrhosis) entered the study. The diagnosis of diabetes was made with the criteria by World Health Organization. Laboratory investigation included serum aspartate aminotransferase, alanine aminotransferase, albumin, fasting blood sugar, hemoglobin A1c (HbA1c), fasting immunoreactive insulin, and HOMA-R (FBS*IRI/405). The incidence of macro- and micro-angiopathy were also examined. Forty (17.5%) CLD patients were diagnosed diabetes, giving a significantly higher incidence than that of general cohort (5.3%) ($p < 0.001$). Among them, 12 (30%) had the triopathy, significantly lower than that in a matched group of diabetic patients without CLD (65%) ($p < 0.001$). Significantly increased levels of HbA1c and HOMA-R were observed in diabetic CLD with angiopathy compared with diabetic CLD without. Incidence of diabetes was increased in viral CLD patients. The rate of diabetic angiopathies in CLD, however, was relatively low, this could be explained by low coagulability in these patients. Poor control of hyperglycemia, partly due to insulin resistance, might explain the onset of angiopathy in diabetic CLD.

Key Words: hepatogenous diabetes, chronic liver disease, diabetes mellitus, insulin resistance, glucose intolerance

Introduction

Patients with chronic liver disease (CLD) are characterized by impaired glucose tolerance [1–4]. In particular, 50–80% of cirrhotic patients are glucose intolerant, and 10–20% of them develop diabetes mellitus (DM) [2, 5–11]. Insulin

resistance has been suggested as the major cause of such glucose intolerance in cirrhotic patients [12, 13]. The impact of hepatogenous DM [1, 3] has been recently reported to worsen long-term prognosis caused by hepatic failure [3, 6, 14]. Diabetic macroangiopathy (cardiac events, stroke, and peripheral arterial disease) as well as microangiopathy (retinopathy, neuropathy, and nephropathy) in cirrhotics were, however, relatively rare as compared to those in DM alone [14].

Reported studies as to the occurrence of diabetes in liver disease, however, employed mostly the alcoholic CLD [3, 5,

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15–18]. Alcohol damages the pancreas directly, leading to insufficient secretion of insulin. The association of hepatitis C virus infection with the development of DM has been also suggested [5, 7–9, 19]. However, incidence and significance of diabetic angiopathies in chronic viral liver disease have not yet been clarified.

We here conducted a study to elucidate the prevalence of DM and the incidence of diabetic macro- and microangiopathy in chronic viral liver disease, and to characterize the clinical background of those patients.

Materials and Methods

Patients

The subjects consisted of 229 patients with CLD aged 61 years (median, range 24–87 years) who were either hospitalized or followed-up at the outpatient clinic between January 2000 and March 2001. Of those patients, 124 (90 males and 34 females) were diagnosed as chronic hepatitis, and 105 (69 males and 36 females) were liver cirrhosis. The etiologies of liver disease were hepatitis B virus in 51 patients and hepatitis C in 178 patients. Clinical characteristics of the patients are given in Table 1.

Three hundred and forty five non-insulin dependent DM patients without CLD from our hospital were also included in this study as a disease-control group against diabetic CLD patients. Informed consent was obtained from each subject.

Methods

Diagnosis of chronic hepatitis or liver cirrhosis was based on liver biopsy, blood examination, and imagings such as ultrasound or computed tomography. The demographic data including age, sex, alcohol drinking, duration of liver disease, duration of diabetes, and family history of diabetes were collected. Body mass index (BMI) was calculated as body weight in kilograms divided by the square of height in meters (kg/m^2). Patients with autoimmune hepatitis, alcoholic hepatitis, Wilson's disease, hemochromatosis, drug-induced hepatitis, or hepatitis of unknown cause were excluded from the study.

Serum total bilirubin (T-Bil), aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin (Alb), fasting blood sugar (FBS), platelet count (Plt), triglyceride (TG), total cholesterol (T-cho), and urine protein were measured by standard methods. Severity of liver cirrhosis was graded by Child-Pugh classification [20]. Diabetes was diagnosed according to the current World Health Organization (WHO) criteria [21]. Mild glucose intolerance was not included in the diagnosis of diabetes. The presence of hypertension, or the development of hepatocellular carcinoma (HCC) was also recorded.

For CLD patients with diabetes, glycosylated hemoglobin (HbA1c) and fasting immunoreactive insulin (IRI) were measured. The insulin resistance was calculated on the basis of fasting plasma levels of glucose and insulin according to the HOMA model as follows [22]:

$$\text{Insulin resistance (HOMA-R)} = \text{fasting insulin } (\mu\text{U/ml}) \times$$

Table 1. Clinical characteristics of the 229 patients with chronic liver damage

Characteristic	Chronic hepatitis	Liver cirrhosis	<i>p</i> value*
No. of patients	124	105	
Age (years)	57 (24–78)	64 (32–87)	<i>p</i> <0.001
Gender (male/female)	90/34	69/36	ns
Etiology (HBV/HCV)	30/94	21/84	ns
No. with HCC	7 (6%)	49 (47%)	<i>p</i> <0.001
No. with Hypertension	15 (12%)	21 (20%)	ns
BMI (kg/m^2)	22.4 (16.7–32.4)	22.3 (14.5–32.2)	ns
T-Bil (mg/dl)	0.8 (0.4–1.1)	1.2 (0.4–2.6)	<i>p</i> <0.05
AST (IU/l)	49 (15–186)	68 (14–346)	<i>p</i> <0.001
ALT (IU/l)	57 (7–274)	56 (9–195)	ns
FBS (mg/dl)	102 (72–225)	92 (69–124)	<i>p</i> <0.01
Alb (g/dl)	4.1 (2.6–4.8)	3.6 (2.3–4.7)	<i>p</i> <0.001
PT (%)	84 (55–100)	70 (41–100)	ns
Plt ($\times 10^4/\mu\text{l}$)	17.0 (5.0–34.2)	11.8 (2.4–33.2)	<i>p</i> <0.001

Values are expressed as median (range). *by Mann-Whitney's *U* test or Fischer's exact probability test. Abbreviations used are; HBV, hepatitis B virus; HCV, hepatitis C virus; BMI, body mass index; HCC, hepatocellular carcinoma; T-Bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; FBS, fasting blood sugar; Alb, serum albumin; PT, prothrombin time; Plt, platelet count; ns, not significant.

fasting glucose (mg/dl)/405

In order to determine the presence of triopathy, the patients were further examined by ophthalmologists for retinopathic complications, and by the measurement of urinary trace albumin, blood urea nitrogen (BUN) and creatinine (Cr) for nephropathy. Neurological examinations on patellar tendon reflex and Achilles tendon reflex, and on paralysis of the feet were carried out for neuropathy. The CLD patients with diabetes were categorized into two groups: those with either of triopathy and those without triopathy.

The study protocol conformed to the ethical guideline of the 1975 Declaration of Helsinki as reflected in a prior approval by the institution's review board for human research [23].

Statistical analysis

The results are expressed as median and range. For statistical comparison between median values, Mann-Whitney's *U* test was used. Fisher's exact test was used to compare incidences. All statistical tests performed were two-tailed. Difference was considered significant when *p* value was less than 0.05. All analyses were performed using Stat View 5.0 for Macintosh (SAS Institute, Cary, NC).

Results

Forty patients with chronic liver disease (11 chronic hepatitis and 29 liver cirrhosis) were diagnosed diabetes

(Table 2). This incidence of diabetes in CLD (40/229, 17.5%) was significantly higher than that in an age- and sex-matched general cohort (5.3%) obtained from reference 1 ($p < 0.001$ by chi-square test). The incidence of DM in LC (29/105, 27.6%) was significantly higher than that in CH (11/124, 8.9%) ($p < 0.001$) (Table 2). In CH, all patients with DM were HCV-positive while no HBV(+)-CH patient presented DM ($p < 0.05$, Table 2). In contrast, such difference between HCV and HBV was not found in LC. There was no significant difference in clinical parameters, except FBS and HbA1c, between CLD patients with DM and those without DM.

Among 40 CLD patients with DM, 12 (30%) were complicated with diabetic triopathy (Table 3). This incidence in diabetic CLD was significantly lower than that in DM without CLD (225/345, 65%) ($p < 0.001$). Such difference was due to a significantly lower incidence of retinopathy in diabetics with CLD ($p < 0.05$). The incidence of neuropathy in diabetics with CLD tended to be also lower than those without CLD ($p = 0.06$), while the incidence of nephropathy was not different between both groups (Table 3). Only one patient (1/40, 2.5%) developed a major cardio-vascular event and cerebral infarction that is considered to result from hepatogenous diabetes.

Clinical characteristics of 40 diabetic CLD patients were compared with those of 345 diabetic patients without liver disease (Table 3). There was no significant difference in age, gender, BMI, and treatment modalities between the

Table 2. Incidence of diabetes mellitus in chronic liver damage

Characteristic	DM(-)	DM(+)	<i>p</i> value*
No. of patients	189 (82.5%)	40 (17.5%)	
Age	64 (24–87)	65 (53–77)	ns
Gender (male/female)	132/57	27/13	ns
CH/LC	113/76	11/29	$p < 0.001$
CH (HBV/HCV)	30/83	0/11	$p < 0.05$
LC (HBV/HCV)	16/60	5/24	ns
Child-Pugh classification (A/B/C)	44/25/7	16/9/4	ns
BMI (kg/m ²)	22.0 (14.5–32.2)	22.3 (16.9–32.4)	ns
No. with HCC	51 (27%)	13 (33%)	ns
AST (IU/l)	68 (15–346)	62 (21–154)	ns
ALT (IU/l)	56 (7–274)	51 (9–166)	ns
FBS (mg/dl)	92 (72–125)	148 (69–225)	$p < 0.01$
HbA1c (%)	4.8 (3.5–6.3)	6.8 (4.3–10.8)	$p < 0.01$
Alb (g/dl)	3.6 (2.3–4.8)	3.5 (2.3–4.7)	ns
Plt ($\times 10^4/\mu$ l)	11.8 (2.5–34.2)	9.9 (2.4–28.6)	ns

Values are expressed as median (range). *by Mann-Whitney's *U* test or chi-square test. Abbreviations used are; DM, diabetes mellitus; CH, chronic hepatitis; LC, liver cirrhosis; HBV, hepatitis B virus; HCV, hepatitis C virus; BMI, body mass index; HCC, hepatocellular carcinoma; AST, aspartate aminotransferase; ALT, alanine aminotransferase; FBS, fasting blood sugar; HbA1c, glycosylated hemoglobin; Alb, serum albumin; Plt, platelet count; ns, not significant.

Table 3. Clinical characteristics of diabetic CLD patients and diabetic patients without CLD

	DM without CLD	Diabetic CLD	<i>p</i> value*	
No. of patients	345	40		
Age (years)	60 (15–87)	65 (53–77)	ns	
Gender (male/female)	155/190	27/13	ns	
BMI (kg/m ²)	22.8 (16.2–31.8)	23.2 (16.9–32.4)	ns	
FBS (mg/dl)	120 (41–303)	148 (69–225)	ns	
HbA1c (%)	6.7 (4.2–12.0)	6.8 (4.3–10.8)	ns	
HOMA-R	8.3 (0.72–17.58)	6.9 (0.88–32.2)	ns	
Insulin	28 (3.1–63.0)	26 (4.4–110)	ns	
TG (mg/dl)	128 (33–430)	82 (33–233)	<i>p</i> <0.05	
T-cho (mg/dl)	195 (127–387)	141 (70–221)	<i>p</i> <0.001	
PT (%)	89 (77–96)	72 (40–100)	<i>p</i> <0.001	
Plt (×10 ⁴ /μl)	23.8 (12.8–33.4)	9.9 (2.4–28.6)	<i>p</i> <0.001	
Treatment				
	Diet	49 (14%)	10 (25%)	
	Drug	128 (37%)	17 (43%)	ns
	Insulin	168 (49%)	13 (32%)	
Triopathy		225 (65%)	12 (30%)	<i>p</i> <0.001
	Retinopathy	133 (39%)	8 (20%)	<i>p</i> <0.05
	Neuropathy	121 (35%)	8 (20%)	<i>p</i> =0.06
	Nephropathy	57 (17%)	4 (10%)	ns

Values are expressed as median (range). *by Mann-Whitney's *U* test or chi-square test. Abbreviations used are; DM, diabetes mellitus; CLD, chronic liver disease; BMI, body mass index; FBS, fasting blood sugar; HbA1c, glycosylated hemoglobin; HOMA-R, homeostasis model assessment; Alb, serum albumin; TG, triglyceride; T-cho, total-cholesterol; PT, prothrombin time; Plt, platelet count; ns, not significant.

two groups. While blood biochemical parameters such as FBS, HbA1c, HOMA-R, and IRI were similar, Plt, blood coagulation activity indicated by prothrombin time (PT), TG, and T-cho were significantly lower in diabetic CLD than in DM without CLD (Table 3).

Clinical characteristics of diabetic CLD patients with and without triopathy are shown in Table 4. Those with triopathy had a significantly longer morbidity period of diabetes (*p*<0.05) and received insulin injection at a higher rate (*p*<0.05) than diabetic CLD without triopathy.

Blood biochemical data in diabetic CLD patients with and without triopathy are given in Table 5. Significant difference was observed in HbA1c and HOMA-R between the two groups, suggesting hyperglycemia for a longer period and insulin resistance in the former group. No difference in liver function tests was observed between two groups.

Discussion

The incidence of diabetes as a complication of chronic liver disease is reported to be 13% in chronic alcoholic hepatitis and 14 to 63% in alcoholic liver cirrhosis [5, 9, 15–17]. However, there have been few reports as to the incidence of diabetes in viral liver disease [16].

Zein reported 25% of cirrhotic patients before transplantation had diabetes [16]. In our study, 8.9% of patients with chronic viral hepatitis and 27.6% of patients with viral liver cirrhosis were complicated with diabetes. Thus, significantly higher incidence of diabetes was observed in chronic liver disease.

There were a few differences between diabetic patients with liver disease (diabetic CLD) and authentic diabetic patients. The most pronounced was that, very few patients had a family history of diabetes in diabetic CLD (4/40, 10%), whereas more than 50% of the latter patients showed that. This is because diabetic state in CLD could be acquired secondary to liver disease *per se*, not due to genetic background as in most non-insulin dependent diabetes mellitus (NIDDM).

The pathogenesis of diabetes in liver disease is not fully understood. In alcoholic liver disease, reduced insulin secretion due to pancreatic damage could be the cause of impaired glucose metabolism. However, that may not be the case of diabetes in viral liver disease, because excess insulin secretion is observed after glucose loading in liver cirrhosis [24]. Glucose uptake into hepatocytes after glucose absorption is delayed due to decreased hepatocyte mass in CLD, leading to hyperinsulinemia. Subsequent continuous hyperinsulinemic

Table 4. Clinical characteristics of diabetic CLD patients with and without diabetic triopathy

Triopathy		(-)	(+)	<i>p</i> value*
No. of patients		28	12	
Age (years)		64 (53–77)	66 (57–77)	ns
Gender (male/female)		19/9	8/4	ns
Etiology	HBV/HCV	3/25	2/10	ns
CH/LC		7/21	4/8	ns
CH	HBV/HCV	0/7	0/4	ns
LC	HBV/HCV	3/18	2/6	ns
Child-Pugh classification	A/B/C	11/6/4	5/3/0	
BMI (kg/m ²)		23.4 (16.9–32.4)	23.1 (19.4–27.0)	ns
Duration of liver disease (years)		9 (2–19)	10 (4–19)	ns
Duration of DM (years)		5 (1–14)	8 (1–16)	<i>p</i> <0.05
Treatment	Diet	10 (36%)	0 (0%)	<i>p</i> <0.05
	Drug	11 (39%)	6 (50%)	
	Insulin	7 (25%)	6 (50%)	
Hypertension		7 (25%)	4 (33%)	ns
HCC		10 (36%)	4 (33%)	ns
Family history of DM		1 (3.6%)	3 (25%)	<i>p</i> <0.05

Values are expressed as median (range). *by Mann-Whitney's *U* test or chi-square test. Abbreviations used are; CLD, chronic liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; CH, chronic hepatitis; LC, liver cirrhosis; BMI, body mass index; DM, diabetes mellitus; HCC, hepatocellular carcinoma; ns, not significant.

Table 5. Biochemical analysis of diabetic CLD patients with and without diabetic triopathy

Triopathy		(-)	(+)	<i>p</i> value*
No. of patients		28	12	
FBS (mg/dl)		127 (69–257)	172 (110–266)	<i>p</i> <0.001
HbA1c (%)		6.3 (4.3–9.2)	7.6 (5.7–10.8)	<i>p</i> <0.05
Insulin (U/ml)		22 (4.5–33.0)	34 (9.3–69.1)	ns
HOMA-R		4.1 (0.88–9.49)	13.5 (3.1–32.2)	<i>p</i> <0.05
TG (mg/dl)		84 (33–205)	80 (39–233)	ns
T-cho		135 (70–221)	151 (94–216)	ns
T-Bil (mg/dl)		1.4 (0.4–4.9)	1.0 (0.7–1.4)	ns
AST (IU/l)		63 (21–154)	51 (24–97)	ns
ALT (IU/l)		54 (9–166)	47 (17–83)	ns
Alb (g/dl)		3.5 (1.8–4.7)	3.4 (2.4–4.3)	ns
PT (%)		72 (51–99)	81 (58–100)	ns
Plt ($\times 10^4/\mu$ l)		9.7 (2.4–28.6)	10.1 (3.9–18.8)	ns
CH		12.8 (10.1–28.6)	16 (8.1–18.8)	ns
LC		7.1 (2.4–15)	7.6 (3.9–14.6)	ns

Values are expressed as median (range). *by Mann-Whitney's *U* test or chi-square test. Abbreviations used are; CLD, chronic liver disease; FBS, fasting blood sugar; HbA1c, glycosylated hemoglobin; HOMA-R, homeostasis model assessment; TG, triglyceride; T-cho, total-cholesterol; T-Bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Alb, serum albumin; PT, prothrombin time; Plt, platelet count; CH, chronic hepatitis; LC, liver cirrhosis; ns, not significant.

state could eventually induce insulin resistance in the patients. Previous reports suggested that insulin resistance, characterized by both decreased glucose transport and decreased nonoxidative glucose metabolism in skeletal muscle, could be the cause of diabetes in liver cirrhosis [25]. In addition, glucose effectiveness, glucose metabolic pathway independent of insulin secretion, is also reduced in cirrhotic patients [4, 26].

A strong association between HCV infection and diabetes has been recently suggested. Mason reported that HCV infection and age were independent predictors of diabetes, and significantly higher prevalence of HCV infection, especially genotype 2a, was observed in diabetic patients as compared to non-diabetic hepatitis C patients [8]. Recognized diabetic factors such as age or obesity may increase the risk for type 2 diabetes in HCV-infected persons [27]. We have found higher incidence of DM in chronic hepatitis C than in chronic hepatitis B (Table 2), and also obesity tendency in chronic hepatitis C with DM compared to CH(C) without DM (BMI 25 ± 4 ; 22 ± 3 kg/m², $p=0.08$). Additional higher prevalence of diabetes was observed in liver cirrhosis as compared to that in chronic hepatitis. Furthermore, in contrast to CH, no difference was found in the incidence of DM between HBV-positive cirrhotics and HCV-positive ones. These observations suggest that severity of liver disease could increase by itself the risk of diabetes in CLD.

We showed significantly lower incidence of macro- and microangiopathy in patients with diabetic CLD than in authentic diabetic patients (Table 3), in a similar manner to ref [28]. As for macroangiopathy, there was only one patient (2.5%) with cerebral infarction who developed cardio-vascular event possibly attributable to diabetes in CLD group. Microangiopathy was observed in 12 patients (30%). Progressive retinopathy was observed in two patients who had a history of diabetes lasting 10 years and 8 years, respectively. There were two patients (5%) with diabetic neuropathy, who were on medication such as Epalrestat (Kinedak®). Positive trace albumin in urine, ophthalmologic abnormality, and neurological impairment were identified in other eight patients without any subjective symptom. Although the incidence of triopathy in diabetic CLD was significantly lower, the proportion of retinopathy, neuropathy, and nephropathy did not differ between diabetic CLD (2:2:1) and DM without CLD (2.3:2.1:1) (Table 3). Thus, the detection (or non-detection) of statistical significance for the difference in the incidence of each of triopathy between 2 groups (Table 3) may have depended solely on the size of the number of each event.

This study clarified that several factors might affect the occurrence of diabetic macro- and microangiopathy in CLD. First, significantly longer duration and frequent family history of diabetes were observed in CLD patients with diabetic triopathy as compared to those without triopathy. Poor

control of blood glucose level, indicated by high FBS and HbA1c, could also be a cause of diabetic triopathy. Interestingly, significantly higher level of HOMA-R was also observed in the group with diabetic triopathy, suggesting insulin resistance might have an impact as a factor for diabetic triopathy. Therefore, improvement of insulin resistance would be important to prevent diabetic angiopathy also in liver disease. Further prospective study is needed to find the relevance between diabetic angiopathy and insulin resistance in CLD patients.

Significant decreases in platelet count and PT were observed in CLD with diabetes as compared with authentic diabetic patients as shown in Table 3. It has been reported that increased platelet aggregation is associated with the development of diabetic complications, and strict blood sugar control could improve platelet aggregation and prevent triopathy [29]. Decreased production of coagulation factors from the liver might also help preventing intravascular coagulation promoted by hyperglycemia in diabetic state [30, 31], leading to a low rate of angiopathy in diabetic CLD patients.

It is difficult to avoid some limitations in this kind of clinical study. The limitation in this study is the lack of area under the curve (AUC) analysis of oral glucose tolerance test (OGTT), since AUC better estimates the grade of glucose intolerance in LC than HbA1c. This study was a retrospective cross-sectional study, and we could obtain only the diagnosis in the chart, but not the raw OGTT data to calculate AUC.

In conclusion, high incidence of diabetes was observed in viral CLD. Low intravascular coagulability may explain relatively lower rate of diabetic complication in CLD. However, poor control of hyperglycemia, partly due to insulin resistance, could contribute to the pathogenesis of angiopathy in diabetic CLD. Strict control of blood glucose and improvement of insulin resistance, therefore, should be directed in patients with diabetic CLD to help prevent diabetic angiopathy in those patients.

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