Observational Study

Risk factors associated with nonalcohol fatty liver disease and fibrosis among patients with type 2 diabetes mellitus

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Abstract

Type 2 diabetes mellitus (T2DM) is closely related to hepatic steatosis and fibrosis. The aim of this study was to analyze the occurrence of hepatic steatosis and fibrosis in patients with T2DM and to explore the risk factors.

A total of 629 patients with T2DM were enrolled. Liver stiffness value (LSV) and controlled attenuation parameters (CAP) were measured using Fibroscan. Liver fibrosis was diagnosed when LSV was greater than 7.4 kPa, and advanced liver fibrosis was diagnosed when LSV was greater than 10.6 kPa. Hepatic steatosis diagnosis was made when CAP value was greater than 238 dB/m. Demographic information, physical examination data, and laboratory tests results were collected. The 629 patients were classified into 2 groups by the liver fibrosis and liver steatosis, and then the difference was analyzed.

Among patients enrolled, 231 patients were diagnosed as liver fibrosis. The age of the patients in the fibrosis group was significantly greater than that in the non-fibrosis group, and similar trends were observed in the waist–hip ratio (WHR), systolic blood pressure, and diastolic blood pressure. The proportion of smoking and alcoholic consumption was significantly lower in patients with non-fibrosis group. A total of 426 patients were diagnosed with liver steatosis. Body mass index (BMI), WHR, systolic blood pressure, and diastolic blood pressure in patients with steatosis were significantly higher than those in non-steatosis group. We observed that the LSV ($P = .042$) and CAP value ($P < .001$) are positively correlated with metabolic syndrome components in T2DM patients. Older age (OR = 1.099, $P = .001$), high BMI (OR = 1.088, $P = .003$), low platelet level (OR = 0.996, $P = .014$), and smoking (OR = 1.653, $P = .013$) were independent risk factors of liver fibrosis among T2DM patients. High BMI (OR = 1.369, $P < .001$), high diastolic blood pressure (OR = 1.048, $P < .001$), and high gamma glutamyl transpeptidase (OR = 1.018, $P = .009$) were independent risk factors for liver steatosis among T2DM patients.

This study suggested risk factors screening of liver fibrosis and steatosis. Timely intervention should be taken into consideration among high risk patients to prevent progress liver diseases.

Abbreviations: BMI = body mass index, CAP = controlled attenuation parameters, GGT = gamma glutamyl transpeptidase, LSV = liver stiffness value, NAFLD = nonalcoholic fatty liver disease, PLT = platelet levels, T2DM = type 2 diabetes mellitus, WHR = waist–hip ratio.

Keywords: liver fibrosis, liver steatosis, nonalcoholic hepatitis, risk factors, T2DM

1. Introduction

The prevalences of obesity and type 2 diabetes mellitus (T2DM) are gradually increasing.[1,2] It is estimated that 2.9 million people were diagnosed with diabetes and 90% of them belonged to T2DM.[3] Patients diagnosed with T2DM can develop a wide range of complications and their life expectancy can be reduced by an average of 10 years.[4] T2DM is not only associated with atherosclerosis, cardiovascular diseases, chronic kidney diseases, and cancer, but also a wide spectrum of chronic liver diseases. T2DM associated liver disease is thought to be nonalcoholic fatty liver disease (NAFLD) while long-term nonalcoholic hepatitis is similar to chronic viral hepatitis and is ultimately able to lead to liver fibrosis, cirrhosis, and even end-stage liver diseases.[3,5]

NAFLD, featured by hepatocytes steatosis, is the manifestation of metabolic syndromes of the liver.[4,6] Furthermore, NAFLD can result from the metabolic stress induced by liver injury. NAFLD is also closely related to insulin resistance and genetic predisposition.[2] NAFLD includes liver steatosis, nonalcoholic steatohepatitis, liver fibrosis, liver cirrhosis, and hepatocellular carcinoma.[7,8] It was reported that the majority of patients with T2DM manifested with liver metabolic problems. Early screening and diagnosis of T2DM-related liver steatosis and liver fibrosis could improve the long-term prognosis of patients.[4] However, the risk factors for the occurrence of liver steatosis and liver fibrosis in patients with T2DM remain unknown.

In this study, patients with T2DM were enrolled and their liver conditions were evaluated. Risk factors for liver steatosis and liver fibrosis were explored. This study will provide clinical

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evidence for screening and early diagnosis of liver injury in T2DM patients.

2. Methods

2.1. Subjects

A total of 629 T2DM patients were enrolled. According to recommendations from American Diabetes Association,[3] T2DM were diagnosed if: fasting plasma glucose ≥7.0 mmol/L, or 2-hour plasma glucose ≥11.1 mmol/L during an oral glucose tolerance test, or glycated hemoglobin ≥6.5% and a random plasma glucose ≥11.1 mmol/L. Metabolic syndromes in our study were defined according to the International Diabetes Federation recommendation.[9] The components of metabolic syndromes are as follows: male abdominal circumference >90 cm or female abdominal circumference >80 cm; blood pressure ≥130/85 mm Hg; previous diagnosis of type 2 diabetes or fasting blood glucose level ≥5.6 mmol/L; and triglyceride levels >1.7 mmol/L or male high-density lipoprotein <1.03 mmol/L, female high-density lipoprotein <1.29 mmol/L. Patients were excluded if serological testing suggested that patients were infected with hepatitis B virus/hepatitis C virus or other underlying autoimmune hepatitis, or patients had severe alcohol dependence (alcohol consumption >30 g/day),[10] or patients were using drugs that can induce liver steatosis, such as cortisol, estrogen, and methotrexate.

This study protocol followed the ethical guidelines of the Declaration of Helsinki amended in 2008 and was approved by the Ethics Committee of People's Hospital of Xinjiang Uygur Autonomous Region.

2.2. Fibroscan test

Liver stiffness value (LSV) and controlled attenuation parameters (CAP) were assessed using Fibroscan (Echosens, Paris, France) by 2 professionally trained technicians according to the manufacturer's handbook. LSV were expressed by kilopascals (kPa) and CAP by decibels per meter (dB/m).

According to manufacturer's handbook, the LSV were considered reliable only when the procedures had at least 10 valid measurements and a success rate of >60% with an interquartile range to median ratio <0.3. CAP was measured according to the same criteria used for LSV and by the same signals, ensuring that one obtained a liver ultrasonic attenuation simultaneously and in the same volume of liver parenchyma as the LSV. The final CAP value was the median of individual measurements.

The METAVIR scoring system is a system for assessing the degree of liver fibrosis (F0 to F4). Hepatic fibrosis is indicated when the score is greater than or equal to F1. Progressive liver fibrosis is indicated when the score is greater than or equal to F2. According to studies published previously, liver fibrosis ≥F1 was diagnosed when LSV >7.4 kPa, and liver fibrosis ≥F2 was diagnosed when LSV >10.6 kPa.[11–13] Nonalcohol fatty liver disease was diagnosed when CAP value >238 dB/m, according to previously reported recommendations.[7,14]

2.3. Patient information collection

Demographic information, including age, gender, the medical history of T2DM, smoking history, and drinking history, was collected. Physical examination data including height, weight, and waistline was recorded. Blood pressures were measured after Fibroscan test. Laboratory tests, including platelet levels (PLT), serum aspartate aminotransferase, and alanine aminotransferase, were assessed according to standard procedures. These laboratory results were obtained by standard automated techniques within 14 days of the Fibroscan test.

2.4. Statistical analysis

Continuous variables were expressed as mean ± standard deviation. Categorical variables were expressed as percentages. χ^2 test and t test were used to detect whether the differences between the 2 groups were statistically significant. Multivariate logistic correlation analysis was used to explore the risk factors associated with liver steatosis and liver fibrosis. Data analysis and quality control were performed using SPSS for windows (version 13.0, Chicago, Illinois).

3. Results

3.1. Demographics and clinical characteristics

Among the 629 patients enrolled, 231 were diagnosed with fibrosis. Patients in fibrosis group were significantly older than those in non-fibrosis group. In addition, the waist–hip ratio (WHR), systolic blood pressure, and diastolic blood pressure in fibrosis group were higher than those in non-fibrosis group. The platelet count was significantly greater in non-fibrosis group compared with fibrosis group. As shown in Table 1, the proportions of patients who smoke and consume alcohol in non-fibrosis group were significantly smaller than those in fibrosis group. Patients with liver steatosis had significantly higher body mass index (BMI), WHR, systolic, and diastolic blood pressure compared with those without liver steatosis. The level of gamma glutamyl transpeptidase (GGT) in patients with steatosis was significantly higher than that in patients without steatosis (25.41 ± 16.65 vs 29.23 ± 17.61, P = .011, Table 2).

The LSV and CAP values in T2DM patients with different smoking and alcohol consumption status were compared. The result showed that LSV was significantly higher in patients with a history of smoking and alcohol consumption (P = .005), whereas CAP value did not show significant between-group difference (Table 3).

Table 1

Demographics and clinical characteristics in T2DM with or without liver fibrosis.

Variables	Liver fibrosis	Non-fibrosis	P value
Sex, M/F	205/26	368/30	.115
Age, y	47.07 ± 12.20	43.02 ± 11.10	<.001
BMI	26.58 ± 4.17	25.97 ± 6.99	.227
WHR	0.94 ± 0.06	0.92 ± 0.59	.015
SBP, mm Hg	131.19 ± 14.34	128.65 ± 13.39	.027
DBP, mm Hg	84.27 ± 10.09	82.16 ± 10.12	.013
ALT	30.39 ± 17.14	30.70 ± 18.88	.844
AST	24.93 ± 13.23	23.91 ± 12.83	.352
PLT	235.43 ± 70.72	253.21 ± 53.06	.001
GGT	28.55 ± 16.44	27.65 ± 17.95	.548
Smoking, Y/N	93/138	120/278	.010
Alcohol consumption, Y/N	87/144	110/288	.009
Hyperuricemia, Y/N	51/180	76/322	.369

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, DBP = diastolic blood pressure, GGT = gamma glutamyl transpeptidase, PLT = platelet levels, SBP = systolic blood pressure, T2DM = type 2 diabetes mellitus, WHR = waist–hip ratio.

Table 2

Demographics and clinical characteristics in T2DM with or without liver steatosis.

Variables	Liver steatosis	Non-steatosis	P value
Sex, M/F	381/45	192/11	.036
Age, y	44.03 ± 11.57	45.58 ± 11.87	.011
BMI	26.83 ± 4.22	24.86 ± 8.74	<.001
WHR	0.94 ± 0.06	0.92 ± 0.05	<.001
SBP, mm Hg	131.28 ± 14.08	125.92 ± 12.45	<.001
DBP, mm Hg	84.47 ± 10.17	79.63 ± 9.32	<.001
ALT	31.43 ± 17.81	28.68 ± 19.12	.092
AST	23.97 ± 11.95	25.01 ± 15.12	.274
PLT	247.89 ± 62.64	244.45 ± 56.06	.484
GGT	29.23 ± 17.61	25.41 ± 16.65	.011
Smoking, Y/N	143/283	69/134	.884
Alcohol consumption, Y/N	137/289	59/144	.456
Hyperuricemia, Y/N	94/332	34/169	.095

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, DBP = diastolic blood pressure, GGT = gamma glutamyl transpeptidase, PLT = platelet levels, SBP = systolic blood pressure, T2DM = type 2 diabetes mellitus, WHR = waist–hip ratio.

3.2. Liver fibrosis and steatosis in T2DM patients with components of metabolic syndromes

To further explore the relationship between liver injury and T2DM, we analyzed the relationship between the occurrence of metabolic syndromes and LSV and CAP values. The findings showed that LSV and CAP values were positively related with the frequencies of metabolic syndromes in patients with T2DM. According to the cut-off value of 7.4 kPa for liver fibrosis (F1), and the cut-off value of 10.6 kPa for advanced liver fibrosis (F2), we found that the numbers of components of metabolic syndromes were higher in patients with fibrosis and advanced liver fibrosis, as compared with those without liver fibrosis (P = .019, Table 4).

3.3. Risk factors associated with liver fibrosis in patients with T2DM

Univariate and multivariate analyses were conducted to explore the risk factors associated with liver fibrosis in patients with T2DM (Table 5). Univariate analysis showed that age, high BMI, high WHR, high systolic pressure, high diastolic blood pressure, low PLT level, smoking, and alcohol consumption were the risk factors for liver fibrosis in patients with T2DM. Multivariate analysis showed that only age (OR = 1.029, P = .001), high BMI (OR = 1.088, P = .003), smoking (OR = 1.653, P = .013), and low PLT (OR = 0.996, P = .013) were the independent risk factors for liver fibrosis in patients with T2DM.

Table 4

Liver fibrosis and steatosis among T2DM with component of metabolic syndromes.

	Number of metabolic syndrome component				
	1	2	3	4	P value
METAVIR					.019
F0	145	179	66	8	
F1–F2	26	46	21	5	
>F2	31	62	33	7	
LSM	7.96 ± 8.97	9.16 ± 9.59	10.61 ± 10.65	12.44 ± 8.24	.042
CAP	239.33 ± 55.81	265.44 ± 57.19	269.35 ± 56.62	278.55 ± 60.57	<.001

CAP = controlled attenuation parameters, LSV = liver stiffness value, T2DM = type 2 diabetes mellitus.

3.4. Risk factors associated with liver steatosis in patients with T2DM

The risk factors associated with liver steatosis in T2DM patients were also analyzed (Table 6). Univariate analysis indicated that female gender, high BMI, high WHR, high systolic pressure, high diastolic blood pressure, and high GGT were the risk factors for liver steatosis in patients with T2DM. Multivariate analysis showed that only high BMI (OR = 1.369, P < .001), high diastolic blood pressure (OR = 1.048, P < .001), and high GGT (OR = 1.018, P = .009) were independent risk factors associated with liver steatosis in patients with T2DM.

4. Discussion

The incidence of T2MD, accompanied with NAFLD, has been increasing with the changes of people's life styles.[1] NAFLD is a liver complication often present in patients with T2DM. Previous epidemiological report showed that NAFLD was currently the most common cause of chronic liver diseases in western countries.[15] In recent years, studies confirmed that NAFLD is a multisystem disease that affects multiple organs, including hepatic, cardiovascular, and cerebrovascular systems.[1,16] Therefore, early detection of liver steatosis and liver fibrosis can improve the long-term prognosis of patients with T2DM.

Although liver biopsy is the gold standard for assessing hepatic fibrosis and steatosis, biopsy procedures can cause certain complications and the fatality rate of biopsy is about 0.05%.[17] Also, it is difficult to perform liver biopsy in a large population in clinical practice. Therefore, developing a more practical clinical strategy to detect the risk factors for liver steatosis and fibrosis in patients with T2DM is very important. In our study, Fibroscan and other routine clinical laboratory tests were used to detect the risk of liver injury in T2DM patients.

T2DM, a component of metabolic syndrome, has been shown to be closely associated with liver fibrosis.[18] However, the

Table 3

Liver fibrosis and steatosis among T2DM with different behavioral characteristics.

Behavioral characteristic	Status				
Smoking	No	Yes	No	Yes	
Alcohol consumption	No	No	Yes	Yes	P value
LSM	8.02 ± 7.25	9.49 ± 12.07	10.99 ± 10.02	11.23 ± 14.91	.005
CAP	253.32 ± 56.03	257.05 ± 60.19	259.22 ± 57.21	268.76 ± 50.16	.428

CAP = controlled attenuation parameters, LSV = liver stiffness value, T2DM = type 2 diabetes mellitus.

Table 5

Risk factors associated with liver fibrosis among patients with T2DM.

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P value
Sex,	0.643	0.370–1.117	.117			
Age	1.030	1.016–1.045	<.001	1.029	1.013–1.047	.001
BMI	1.051	1.047–1.092	.015	1.088	1.030–1.150	.003
WHR	1.563	1.043–2.342	.030			
SBP	1.013	1.001–1.025	.027			
DBP	1.021	1.004–1.037	.013			
ALT	0.999	0.990–1.008	.844			
AST	1.006	0.993–1.019	.351			
PLT	0.995	0.992–0.998	.001	0.996	0.993–0.999	.014
GGT	1.003	0.993–1.013	.556			
Smoking,	1.561	1.112–2.191	.010	1.653	1.112–2.457	.013
Alcohol consumption	1.582	1.120–2.234	.009			
Hyperuricemia	1.200	0.806–1.789	.369			

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, CI = confidence interval, DBP = diastolic blood pressure, GGT = gamma glutamyl transpeptidase, OR = odds ratio, PLT = platelet levels, SBP = systolic blood pressure, T2DM = type 2 diabetes mellitus, WHR = waist–hip ratio.

relationship between the number of metabolic syndrome components in T2DM patients and liver injury has not been reported. According to our study, the LSV and CAP values were positively correlated with the number of metabolic syndrome components in T2DM patients. The result suggests that screening of liver fibrosis and steatosis should be performed in T2DM patients who have multiple components of metabolic syndrome. A timely behavioral and drug intervention should also be taken into consideration.

Our study confirmed that older age, high BMI, smoking, and low PLT levels are independent risk factors for liver fibrosis in patients with T2DM. Consistently, older age and low PLT level have also been reported to be associated with liver fibrosis.[19–22] Furthermore, our study found that high BMI and smoking can promote liver fibrosis in patients with T2DM, which is in accordance with previous studies showing that smoking can aggravate liver fibrosis in patients with primary biliary cirrhosis.[23] Another study reported that smoking could lead to activation of the apoptotic pathway in hepatocyte, leading to liver injury.[24,25] In addition, smoking could also promote the progress of liver fibrosis by activating Kuffer cells and stimulating

the expression of cytokines.[26] According to our study, smoking is an independent risk factor for hepatic fibrosis in patients with T2DM. Therefore, it is necessary to help T2DM patients to quit smoking. Possible approaches include smoking behavior treatment, smoking cessation counseling, intervention of the trigger of smoking, and avoidance of high-risk situations for smoking.

Our study also found that T2DM patients with high body weight, high diastolic blood pressure, and high GGT were more likely to develop liver steatosis. GGT, a thiol-containing mitochondrial enzyme, is one of the key enzymes responsible for glutathione metabolism.[27] A recent study reported that GGT is closely related with cardiovascular disease.[28] An Australian study also confirmed that GGT is significantly associated with central obesity.[29] Our study found that GGT level was significantly higher in T2DM patients with liver steatosis compared with those without liver steatosis. The result suggested that GGT could serve as a biomarker for liver steatosis in T2DM patients. A study in South Korea explored the relationship between liver enzymes and NAFLD. The results showed that NAFLD was closely related to GGT level, and the level of GGT was also positively correlated with diabetes and cardiovascular

Table 6

Risk factors associated with liver steatosis among patients with T2DM.

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P value
Sex	0.488	0.247–0.964	.039			
Age	0.989	0.975–1.003	.120			
BMI	1.181	1.110–1.257	<.001	1.369	1.252–1.517	<.001
WHR	1.453	1.219–2.379	<.001			
SBP	1.031	1.017–1.045	<.001			
DBP	1.053	1.033–1.073	<.001	1.048	1.023–1.074	<.001
ALT	1.008	0.999–1.018	.092			
AST	0.994	0.981–1.007	.368			
PLT	1.001	0.998–1.004	.510			
GGT	1.013	1.002–1.024	.017	1.018	1.004–1.031	.009
Smoking	0.974	0.684–1.387	.884			
Alcohol consumption	1.149	0.798–1.655	.456			
Hyperuricemia	1.450	0.936–2.246	.096			

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, CI = confidence interval, DBP = diastolic blood pressure, GGT = gamma glutamyl transpeptidase, OR = odds ratio, PLT = platelet levels, SBP = systolic blood pressure, T2DM = type 2 diabetes mellitus, WHR = waist–hip ratio.

risks.[30,31] The relationship between hepatic steatosis and steatohepatitis has been widely acknowledged.[1] Steatohepatitis will increase the risk of liver fibrosis, cirrhosis, and hepatocellular carcinoma. Based on our results, patients with T2DM should be screened for hepatic steatosis, especially overweight patients with high level of GGT and high diastolic blood pressure. Timely interventions should be taken into consideration for these patients.

Our study has some limitations. The sample size is relatively small and patients were enrolled in a single center. A multicenter controlled randomized study is warranted to validate the findings of our study.

Author contributions

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