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The Risk Factor Analysis for Type 2 Diabetes Mellitus Patients with Nonalcoholic Fatty Liver Disease and Positive Correlation with Serum Uric Acid

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Abstract Recent years, we has witnessed a sharp increase in the complications of Type 2 diabetes mellitus (T2DM) with nonalcoholic fatty liver disease (NAFLD). Here we aimed to determine the risk factors for T2DM patients with NAFLD and the relationship of serum uric acid (SUA) in these complications. We performed retrospective analysis of 300 T2DM patients admitted into our hospital from April 2010 to January 2014. We divided the T2DM patients into two groups based on whether the patients also had NAFLD or not, Group A (without NAFLD, 155 cases) and Group B (with NAFLD, 145 cases). General information of the patients was collected and analyzed statistically. Meanwhile, we detected and compared the blood biochemistry, glucose, and fasting insulin (FINS), and further performed Logistic regression analysis and determined the risk factors in T2DM patients with NAFLD. Significantly higher BMI, waist circumference, hip circumference, WHR, systolic, and diastolic blood pressure were observed in T2DM patients with NAFLD than the patients without NAFLD, which were statistically different ($P < 0.05$). There were also significant higher levels of TC, TG, ALT, AST, GGT, and SUA in T2DM patients with NAFLD than those in patients without NAFLD, which

were statistically different ($P < 0.05$). Significantly higher levels of FPG, FINS, and HOMA-IR were observed in the T2DM patients with NAFLD than those without, which were statistically significant ($P < 0.05$). Logistic regression analysis also showed high BMI, WHR, TG, and SUA were independent risk factors in T2DM patients with NAFLD ($P < 0.05$). Meanwhile, SUA levels were positively correlated with BMI, W, H, WHR, hip circumference, waist circumference, TG, ALT, AST, GGT, FPG, FINS, and HOMA-IR, which were statistically significant ($P < 0.05$). The risk factors for T2DM patients with NAFLD are mainly BMI, WHR, TG, and SUA. Our findings provide clinical implications for the prevention and early diagnosis of T2DM patients with NAFLD.

Keywords NAFLD · T2DM · SUA · WHR

Introduction

Nonalcoholic fatty liver disease (NAFLD) manifests liver damages in response to metabolic stresses, which is closely related with genetic predisposition and insulin resistance (IR) [1]. With the ever-rising living standards, the incidence of NAFLD and diabetes mellitus (T2DM) also increases annually, which can be claimed to be the leading causes of chronic liver diseases. Meanwhile, NAFLD patients are often complicated with insulin resistance-related diseases, such as impaired glucose tolerance, hyperinsulinemia, hypertension, and lipid metabolism disorders. Previous studies have shown close correlations between T2DM and NAFLD, and T2DM has been considered as one of the most common risk factor for NAFLD [2]. Recently, serum uric acid (SUA) has received increasing attention in the NAFLD field, which is now considered as an

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independent risk factor in NAFLD [3–5]. However, little is known about SUA in NAFLD in the Chinese population. Here, we analyzed the risk factors in NAFLD patients with complication of T2DM, and explored if SUA is correlated with NAFLD and T2DM complications. Our results further elucidated the possible etiology of T2DM and NALFD complications, and provided clinical basis for the prevention and early diagnosis of these patients in the Chinese population.

Materials and Methods

Clinical Data

All information was collected from 300 patients admitted into our hospital for T2DM from the April 2010 and January 2014. The diagnosis of all NAFLD patients was in line with the Chinese Medical Association of Liver Diseases Society Standards (January 2010 revision), and the diagnosis of T2DM met the 2003 WHO criteria. There were 153 males and 147 female in the 300 cases in the study, aged 31–69 (mean 46.14 ± 8.11) years old. There were 155 cases (male 80 cases, female 75 cases) in the T2DM patients without NAFLD (Group A), the average age of who was 46.34 ± 11.23 years old. There were 145 patients (83 males, females 62 cases) of T2DM patients with NAFLD (Group B), the average age of who was 47.24 ± 12.54 years old. There was no statistical difference in gender or age between the two groups ($P > 0.05$).

Additionally, significantly higher BMI, waist circumference, hip circumference, and waist-hip ratio (WHR) were observed in the T2DM patients with NAFLD than those without, which were statistically different ($P < 0.05$). There were also significantly higher levels of systolic and diastolic blood pressures in the T2DM patients with NAFLD than those without, which were also statistically different ($P < 0.05$, Table 1).

Methods

All the patient information was recorded by designated persons, which included gender, age, drug use history, smoking and drinking history, T2DM history, past disease, and family history.

Rountine Measurement

Routine measurement of height, weight, waist circumference, hip circumference, body mass index (BMI), and waist-hip ratio (WHR) were recorded. BMI was calculated as weight (kg)/height^2 (m^2), waist-hip ratio (WHR) = waist/hip.

Table 1 General clinical data

Variables	Group A ($n = 155$)	Group B ($n = 145$)	P value/χ^2 value
Age	46.34 ± 11.23	47.24 ± 12.54	0.513
Gender			
Male	80 (51.6 %)	83 (57.2 %)	0.394
Female	75 (48.4 %)	62 (42.8 %)	
BMI	24.34 ± 3.21	28.31 ± 3.34	0.000
Waist	90.78 ± 9.93	100.74 ± 10.20	0.000
Hip	100.35 ± 8.78	104.87 ± 8.98	0.000
WHR	0.84 ± 0.06	0.94 ± 0.07	0.000
Blood pressure			
Systolic	129.34 ± 13.16	136.34 ± 12.48	0.000
Diastolic	80.78 ± 9.12	85.37 ± 9.96	0.000

Blood Biochemistry Parameters and Assays

The venous blood after 12 h fasting was analyzed using RILI 7600 automatic biochemical analyzer for total cholesterol (TC), triglyceride (TG), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ- glutamyl transferase (GGT), blood urea nitrogen (BUN), serum creatinine (Scr), and SUA. Bayer DCA2000 + Automatic glycosylated hemoglobin analyzer was used for HbA1C measurement.

Glucose Tolerance Test

Fasting plasma glucose (FPG) was measured in blood by RILI 7600 automatic biochemical analyzer and chemiluminescence was measured for fasting insulin (FINS) levels. Insulin resistance index HOMA model was used to calculate HOMA-IR = (FINS × FPG)/22.5.

Statistical Analysis and Graphing

All data were analyzed using SPSS17.0 statistical software. The data were expressed as mean ± standard deviation. Comparisons between groups were analyzed by independent samples t test. Correlation analysis was performed with Spearman correlation analysis. Multivariate analysis was performed with stepwise Logistic regression analysis, $P < 0.05$ was considered as statistically significant.

Results

Comparisons of Blood Biochemistry

In the aspect of blood lipids, the T2DM patients with NAFLD displayed significantly higher levels of TC, TG

Table 2 General biochemical data

Variables	Group A (n = 155)	Group B (n = 145)	P value
Blood lipids			
TC (mmol/L)	5.08 ± 1.11	5.34 ± 1.03	0.036
TG (mmol/L)	1.64 ± 1.17	2.34 ± 1.20	0.000
HDL-C (mmol/L)	1.16 ± 0.26	1.19 ± 0.23	0.292
LDL-C (mmol/L)	3.19 ± 0.85	3.24 ± 0.73	0.584
Liver function parameter			
ALT (U/L)	14.22 ± 5.12	21.45 ± 5.27	0.000
AST (U/L)	15.79 ± 4.48	19.24 ± 5.24	0.000
GGT (U/L)	16.89 ± 4.26	26.18 ± 6.03	0.000
Kidney function parameters			
BUN (mmol/L)	5.26 ± 1.03	5.41 ± 1.25	0.256
Ucr (μmol/L)	62.35 ± 4.71	62.18 ± 5.23	0.767
SUA (mmol/L)	281.78 ± 89.21	325.35 ± 79.94	0.000
Other parameters			
HbA$_{1C}$ (%)	8.21 ± 1.21	8.24 ± 1.15	0.826

Table 3 Comparison of glucose metabolism

Variables	Group A (n = 155)	Group B (n = 145)	P value
FPG (mmol/L)	4.52 ± 0.63	10.02 ± 3.99	0.000
FINS (μIU/L)	6.18 ± 1.81	12.23 ± 4.75	0.000
HOMA-IR	1.06 ± 0.29	1.52 ± 0.36	0.000

Table 4 Logistic regression analysis of risk factors for T2DM with NAFLD patients

Risk factors	OR	95 % CI	Regression coefficients	P value
BMI	4.81	1.03–1.19	1.27	0.031
WHR	7.90	1.35–3.51	0.56	0.023
TG	3.19	1.37–1.67	1.57	0.017
SUA	10.87	1.28–4.12	2.2	0.005

Table 5 Analysis of SUA with general clinical data

	BMI	W	H	WHR	Waist	Hip	Systolic blood pressure	Diastolic blood pressure
r	0.512	0.458	0.448	0.502	0.490	0.428	0.210	0.234
P	0.003	0.021	0.033	0.042	0.037	0.041	0.291	0.232

levels than those T2DM patients without NAFLD, the differences of which were statistically significant ($P < 0.05$). However, there was no difference in HDL-C, LDL-C in T2DM patients with or without NAFLD ($P > 0.05$).

For liver function parameters, significantly more elevated ALT, AST, and GGT levels were observed in the T2DM patients with NAFLD than those without, which were statistically significant ($P < 0.05$).

Among the kidney function parameter, there was higher level of SUA in the T2DM patients with NAFLD than those without, which was statistically significant ($P < 0.05$). But there was no statistical difference in BUN and Ucr ($P > 0.05$, Table 2).

Comparison of Glucose Metabolism

Significantly higher levels of FPG, FINS, and HOMA-IR were observed in the T2DM patients with NAFLD than those without, which were statistically significant ($P < 0.05$, Table 3).

Logistic Regression Analysis of Risk Factors for T2DM with NAFLD Patients

We used BMI, WHR, blood pressure, TC, TG, ALT, AST, GGT, SUA, FPG, FINS, and HOMA-IR as argument variables, and T2DM as the dependent variable to carry out the stepwise Logistic regression analysis. Our analysis found that BMI, WHR, TG, and SUA are the risk factors for T2DM patients with NAFLD ($P < 0.05$, Table 4).

Correlation Analysis

Further, we performed correlation analysis with SUA level. Our results showed that SUA level was positively correlated with BMI, W, H WHR, hip, waist, TG, ALT, AST, and GGT, which was statistically significant ($P < 0.05$, Tables 5 and 6). Among glucose parameters, SUA level was significantly correlated with FPG, FINS, and HOMA-IR, which was significantly meaningful ($P < 0.05$, Table 7).

Discussion

Fatty liver disease is an acquired disease by a variety of causes, which is closely related with lifestyles. Fatty liver disease is often clinically defined as alcoholic fatty liver and NAFLD. NAFLD is one of the most common chronic liver diseases clinically, which has been on the rise annually. Etiologies of NAFLD are quite complicated, whereas, lipid deposition, oxidative stress, and lipid peroxidation in the hepatocyte caused by IR, and lipid metabolism disorders are the major causes for NAFLD. To be more specific, the causes include fatty acid intake increase, increased hepatic synthesis of fatty acids, impaired liver functions of fatty acid catabolism and secretion of VLDL, the changes in necrotizing inflammation, etc. [6–10]. Accumulating evidence points to the close relationship between NAFLD

Table 6 Analysis of SUA with blood biochemical data

	TC	TG	HDL-C	LDL-C	ALT	AST	GGT	BUN	Ucr	HbA$_{1C}$
r	0.312	0.454	0.248	0.338	0.479	0.451	0.515	0.231	0.272	0.321
P	0.053	0.025	0.063	0.071	0.035	0.036	0.019	0.251	0.309	0.412

Table 7 Analysis of SUA with blood glucose

	FPG	FINS	HOMA-IR
r	0.549	0.489	0.482
P	0.006	0.017	0.026

and T2DM. NAFLD patients are susceptible to T2DM. Meanwhile, more and more T2DM patients also suffer from NAFLD [11–14]. At present, numerous studies have elucidated the risk factors for T2DM patients with NAFLD [15–17]. However, there was still few report about Chinese population. Our study aimed to compare the parameters of T2DM patients with or without NAFLD admitted into our hospital and determines the risk factors for T2DM patients with NAFLD.

Our results showed that T2DM patients with NAFLD displayed significantly higher BMI, waist, hip, WHR, systolic and diastolic blood pressure, TC, TG, ALT, AST, and GGT levels that those T2DM patients without NAFLD. Our results showed that T2DM patients with NAFLD presented a central obesity, liver enzyme abnormalities, abnormal lipid metabolism, and other clinical features, which is consistent with previous reports [13, 18]. In addition, FPG, FINS, and HOMA-IR in T2DM patients with NAFLD were statistically higher than those without NAFLD. This implied that T2DM patients with NAFLD suffered from severe glucose metabolism disorders, which could be due to the lipid disposition-induced hepatic IR impaired hepatic glucose export in the hepatocytes of T2DM patients with NAFLD. This in turn will aggravate glucose metabolism disorders [19].

Further Logistic regression analysis showed that high BMI, WHR, TG, and SUA are independent risk factors for T2DM with NAFLD. SUA level is mainly maintained by generation and excretion of uric acid. Previous study shows that SUA elevation is closely related with IR [20], and IR plays a central role in the metabolism disorders of the T2DM patients with NAFLD. Our results showed SUA levels in the T2DM patients with NAFLD was positively correlated with central obesity, abnormal liver enzymes, abnormal lipid metabolism, and glucose metabolism, which suggest the clinical importance of SUA in the T2DM patients with NAFLD. Elevated SUA level can be due to decreased insulin sensitivity leads to the increased metabolites of glucose, ribose-5-phosphate increased pyrophosphate, and eventually increase SUA generation [21].

In summary, T2DM patients with NAFLD suffered from multiple metabolism disorder. Our study also implied that SUA should be included for measurement in T2DM patients with NAFLD clinically, which is of great clinical importance for the prevention and early diagnosis of T2DM with NAFLD. Clinically, combined measures including weight loss and decrease in glucose and blood pressure can be useful for the prevention T2DM with NAFLD and improve the treatment.

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