JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

Assessment of the relationship between non-alcoholic fatty liver disease and diabetic complications

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Keywords
Diabetic complication, Non-alcoholic fatty liver disease, Type 2 diabetes

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J Diabetes Investig 2016; 7: 889–894

doi: 10.1111/jdi.12518

ABSTRACT

Aims/Introduction: Non-alcoholic fatty liver disease (NAFLD) is a metabolic disorder of the liver. The relationship between NAFLD and type 2 diabetes remains largely unknown. The aim of the present study was to determine the incidence of complications arising from the interaction between NAFLD and type 2 diabetes.

Materials and Methods: A total of 212 individuals with type 2 diabetes were included in the study. The presence of NAFLD was determined in individuals using abdominal ultrasonography for the diagnosis of fatty liver disease. Patients were divided into three groups based on the duration of diabetes and NAFLD diagnosis. Type 2 diabetes patients were placed in group A; patients with type 2 diabetes longer than NAFLD were placed in group B; and patients with NAFLD longer than type 2 diabetes were placed in group C. All individuals had undergone electrocardiogram, blood pressure measurements, and thorough medical history and physical examinations (Doppler ultrasound, electrophysiology, fundoscopy, cardiac computed tomography). Laboratory measurements included fasting blood glucose, glycated hemoglobin, oral glucose tolerance test, liver and renal function, lipid profile, and urinary albumin excretion.

Results: Compared with groups A and B, the patients of group C showed a higher prevalence of significant coronary artery disease and hypertension ($P < 0.05$). Compared with groups A and B, the patients of group C showed a lower prevalence of diabetic retinopathy and diabetic peripheral neuropathy ($P < 0.05$). There was no significant difference in the prevalence of diabetic nephropathy among the three groups ($P > 0.05$).

Conclusions: NAFLD combined with type 2 diabetes is associated with the presence of significant coronary artery disease and hypertension.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a fatty liver disease where fat is deposited in the liver independent of excessive alcohol use[1]. Epidemiological surveys have shown that NAFLD has become a serious public health problem in China and elsewhere in Asia[2–5]. NAFLD represents a spectrum starting from fatty liver, to fatty liver with inflammation, to evidence of damage to hepatocytes and can progress to cirrhosis or, in the most extreme form of NAFLD, can progress to cirrhosis and hepatocellular carcinoma. NAFLD is also present in a high proportion (range 50–75%) of patients affected by type 2 diabetes[6,7]. A number of studies have shown that NAFLD is strictly related to type 2 diabetes[8–11].

The majority of previous studies have shown that NAFLD is the best predictor of type 2 diabetes complications. A previous study suggests that NAFLD might be linked to the increased incidence of chronic kidney disease and cardiovascular disease[12]. Cross-sectional studies showed that NAFLD is strongly associated with increased carotid intima-media thickness and increased coronary artery calcium score[13–16]. NAFLD is also associated with early left ventricular diastolic dysfunction and decreased myocardial perfusion in patients with type 2 diabetes[17]. NAFLD also appears to be associated with an increased

Received 20 November 2015; revised 20 February 2016; accepted 15 March 2016

prevalence and incidence of chronic kidney disease among patients with type 2 diabetes[18]. The majority of the aforementioned studies on the association between NAFLD and diabetic complications did not distinguish the temporal sequence of NAFLD and type 2 diabetes. Theoretically, NAFLD combined with type 2 diabetes might reflect the coexistence of underlying metabolic syndrome risk factors. Alternatively, type 2 diabetes combined with NAFLD might reflect the longer duration of type 2 diabetes and associated complications.

The purpose of the present study was to explore differences in complications when NAFLD developed with pre-existing type 2 diabetes and when type 2 diabetes developed with pre-existing NAFLD.

MATERIALS AND METHODS

During the period from April 2014 to May 2015, 212 individuals from the Metabolic Disease Hospital, Tianjin Medical University, were recruited to the present observational study. Data were collected retrospectively, and the approval of the ethical committee was obtained. This study conforms to the provisions of the Declaration of Helsinki. All participants provided written informed consent before participation. Study groups included individuals who did not consume alcohol or consumed alcohol such that their intake of ethanol was less than 20 g/day. People with positive serology for hepatitis B or C or who had a history of chronic liver disease were excluded from the study. Patients with NAFLD did not receive any medical treatment to prevent liver injury before they were recruited to this study. Investigators decided on the treatment for type 2 diabetes, hypertension, coronary artery disease (CAD) and other internal disease that were in the best interests of their patients.

Patients were divided into three groups based on the presence of NAFLD, diagnosed by abdominal ultrasonography to identify fatty liver disease and the duration of diabetes. Patients with type 2 diabetes were placed in group A; if the duration of type 2 diabetes was longer than NAFLD, the patients were placed in group B; and if the duration of NAFLD was longer than type 2 diabetes, the patients were placed in group C. All individuals had undergone an electrocardiogram, blood pressure measurements and physical examinations (Doppler ultrasound, electrophysiology, funduscopy, cardiac computed tomography), and had provided a thorough medical history. Laboratory measurements included fasting blood glucose, glycated hemoglobin, an oral glucose tolerance test, liver and renal function, lipid profile, and urinary albumin excretion.

Diabetic macrovascular complications included CAD and hypertension. Significant CAD was defined when stenosis was detected in ≥50% of the lumen diameter of a major coronary artery, including the left main coronary artery, left anterior descending artery or its first diagonal branch, left circumflex artery or its first obtuse marginal branch, and right coronary artery according to cardiac computed tomography. Essential hypertension was defined according to the European Society of Hypertension/European Society of Cardiology 2007 guidelines as office sitting systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg measured by mercury sphygmomanometer, at rest in a sitting position in at least three separate casual measurements.

Diabetic microvascular complications included diabetic nephropathy, diabetic retinopathy and diabetic peripheral neuropathy. Diabetic nephropathy was defined as positive persistent proteinuria for at least three consecutive readings per year. Diabetic retinopathy was diagnosed as the presence of retinal hemorrhage, exudates or macular edema. Diabetic peripheral neuropathy was diagnosed as the presence of persistent numbness, paresthesia, a decreased sense of vibration or a failure to elicit a knee and/or ankle jerk.

Statistical analysis

Continuous variables are shown as the mean and standard deviation, and categorical variables as percentage. Differences in demographic and clinical variables between groups were compared using χ^2 analysis for categorical variables and Student's *t*-test for continuous variables. Analysis of covariance was used to adjust for sex and smoking history for the potential confounding effect of covariates in multivariate analysis. $P < 0.05$ was considered statistically significant.

RESULTS

Clinical and laboratory characteristics of participants

Overall, 69 participants were included in group A (type 2 diabetes without NAFLD); 62 participants were included in group B (type 2 diabetes combined with NAFLD); and 81 participants were included in group C (NAFLD combined with type 2 diabetes). Furthermore, 143 participants (67.5%) of the diabetes patients had NAFLD. Baseline clinical and biochemical characteristics of groups A, B and C are shown in Table 1. The patients with type 2 diabetes combined with NAFLD (group B) generally had a duration of type 2 diabetes longer than 8 years. The NAFLD combined with type 2 diabetes (group C) generally had NAFLD for longer than 10 years. Compared with group A, groups B and C had higher body mass indexes and waist-to-hip ratios, and higher levels of triglycerides, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase, diastolic blood pressure and uric acid (Table 1; $P < 0.05$). There were no significant differences in sex, smoking history, family history of diabetes, CAD and hypertension, systolic pressure, glucose control, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, blood urea nitrogen, creatinine, endogenous creatinine clearance rate, microalbuminuria or urine total protein in the three groups (Table 1; $P > 0.05$).

Incidences of diabetic complications in the three groups

As shown in Table 2, there was no significant difference in the incidence of significant coronary artery disease and hypertension between group A and group B ($P > 0.05$). However, compared with groups A and B, group C had a higher prevalence

Table 1 | Clinical and laboratory characteristics of study participants

Variables	Group A (n = 69)	Group B (n = 62)	Group C (n = 81)
Age (years)	56.74 ± 11.51	51.81 ± 9.47†	52.49 ± 10.55†
Sex, male (%)	55.1	48.4	64.2
Smoking (%)	43.5	38.7	50.6
Family history of T2DM (%)	53.6	67.7	64.2
Family history of hypertension (%)	29.0	25.8	38.3
Family history of CAD (%)	15.9	20.9	16.0
Duration of T2DM (years)	9.65 ± 7.67	8.32 ± 5.84	5.01 ± 5.15†*
Duration of NAFLD (years)		3.09 ± 4.02	10.05 ± 6.97*
SBP (mmHg)	125.29 ± 15.72	128.23 ± 12.38	130 ± 14.23
DBP (mmHg)	73.99 ± 12.62	79.19 ± 7.37†	79.81 ± 8.46†
BMI (kg/m^2)	23.75 ± 3.78	27.87 ± 3.63†	28.82 ± 3.50†
WHR	0.89 ± 0.05	0.93 ± 0.05†	0.97 ± 0.06†
Blood glucose (mmol/L)	9.11 ± 2.43	9.82 ± 2.29	9.20 ± 2.25
HbA1c (%)	9.23 ± 2.52	9.03 ± 1.73	9.03 ± 2.10
TG (mmol/L)	1.26 ± 0.60	2.41 ± 2.08†	2.21 ± 1.55†
TC (mmol/L)	4.64 ± 0.89	4.99 ± 1.29	4.88 ± 0.97
HDL-c (mmol/L)	1.24 ± 0.29	1.20 ± 0.23	1.18 ± 0.23
LDL-c (mmol/L)	2.91 ± 0.71	3.17 ± 0.94	2.99 ± 0.79
ALT (U/L)	17.20 ± 8.01	24.18 ± 12.53†	17.20 ± 8.01†
AST (U/L)	16.74 ± 5.08	22.57 ± 15.69†	24.57 ± 19.24†
γ-GT (U/L)	21.35 ± 18.75	38.3 ± 28.91†	47.17 ± 38.02†
BUN (mmol/L)	5.93 ± 2.09	5.15 ± 1.33	5.52 ± 1.47
Cr (μmol/L)	64.42 ± 28.31	61.78 ± 14.67	65.27 ± 14.76
Ccr	117.33 ± 36.35	113.88 ± 22.64	112.35 ± 28.70
UA (μmol/L)	268.32 ± 81.83	309.88 ± 78.37†	334.37 ± 104.03†
UMA (mg/24 h)	43.14 ± 70.84	53.91 ± 79.46	35.51 ± 59.13
UTP (g/24 h)	0.20 ± 0.36	0.25 ± 0.45	0.14 ± 0.18

Data are expressed as the mean ± standard deviation. †P < 0.05 vs group A. *P < 0.05 vs group B. γ-GT, gamma-glutamyltransferase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CAD, coronary artery disease; Ccr, endogenous creatinine clearance rate; Cr, creatinine; DBP, diastolic blood pressure; HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride; UA, uric acid; UMA, microalbuminuria; UTP, urine total protein; WHR, waist-to-hip ratio.

Table 2 | Incidence of diabetic complications in the three groups

Group	CAD	Hypertension	DR	DN	DPN
A (n = 69)	69 (25)	69 (28)	69 (26)	69 (19)	69 (45)
B (n = 62)	62 (23)	62 (28)	62 (31)	62 (20)	62 (35)
C (n = 81)	81 (40)†*	81 (48)†*	81 (23)†*	81 (17)	81 (32)†*

†P < 0.05 vs group A. *P < 0.05 vs group B. CAD, coronary artery disease; DN, diabetic nephropathy; DPN, diabetic peripheral neuropathy; DR, diabetic retinopathy.

of significant coronary artery disease and hypertension (Table 2; P < 0.05). These differences remained significant after adjustment for sex and smoking history. Compared with groups A and B, group C had a lower prevalence of diabetic retinopathy and a lower prevalence of diabetic peripheral neuropathy (Table 2; P < 0.05). There was no significant difference in the incidence of diabetic nephropathy among the three groups (Table 2; P > 0.05).

DISCUSSION

In the present study, the NAFLD combined with type 2 diabetes group had a higher prevalence of significant CAD and hypertension than the type 2 diabetes combined with NAFLD group and the type 2 diabetes-alone group. These results suggest that the presence of type 2 diabetes in NAFLD patients was more important in predicting the risk of macrovascular diseases, such as significant CAD and hypertension.

NAFLD is a very common disease that is strongly linked to metabolic syndrome and its components: insulin resistance, obesity, hypertension, diabetes mellitus and hypertriglyceridemia. In recent years, an association between type 2 diabetes and NAFLD has been reported. Several studies suggest that NAFLD promotes type 2 diabetes, and is an independent determinant of cardiovascular disease[19]. NAFLD is a complex disease with clinical and therapeutic implications beyond liver disease. The present results suggest that compared with the type 2 diabetes-alone group, both the NAFLD combined with type 2 diabetes group and the type 2 diabetes combined with

NAFLD group had higher levels of body mass index, waist-to-hip ratios, triglycerides, alanine aminotransferase, aspartate aminotransferase and gamma-glutamyl transpeptidase, which is in agreement with most previous studies[20–22]. In addition, the present findings suggest that the NAFLD combined with type 2 diabetes group had the highest levels of uric acid. This agrees with an earlier Chinese cross-sectional study in which Xie *et al.*[23] reported that elevated serum uric acid was significantly associated with NAFLD. Given the strong link between NAFLD and type 2 diabetes, the present study investigated the relationship between NAFLD and diabetic complications.

We report that 67.5% of the diabetes patients had NAFLD, which supports the results of studies showing NAFLD prevalence in the 50–75% range in diabetes patients[6,7]. Previous studies did not distinguish the temporal sequence of NAFLD and type 2 diabetes. Our findings suggest that 56.6% of the diabetes combined with NAFLD patients had NAFLD of longer duration than the duration of diabetes. Furthermore, 43.4% of the diabetes combined with NAFLD patients had diabetes of longer duration than NAFLD. The characteristics of the different temporal sequence of NAFLD and type 2 diabetes have not previously been investigated. The present findings suggest that patients with type 2 diabetes combined with NAFLD generally had type 2 diabetes of longer than 8 years' duration. The patients with NAFLD combined with type 2 diabetes generally had NAFLD of longer than 10 years in duration. NAFLD shares many risk factors with atherosclerosis, including obesity, diabetes and hypertension[24]. These differences in the duration of NAFLD and diabetes might have different effects on outcomes.

Our studies suggest that the NAFLD combined with type 2 diabetes group had a higher prevalence of significant CAD than the type 2 diabetes combined with NAFLD group and the type 2 diabetes-alone group. Previous studies reported that NAFLD is a predictor of cardiovascular events[24]. Fat deposition in NAFLD is considered to increase free fatty acids that lead to CAD by causing low-grade inflammation[25]. NAFLD also promotes the development of type 2 diabetes, and enhances cardiovascular risk through the contribution to hepatic/systemic insulin resistance and atherogenic dyslipidemia[18]. According to the results of our studies, the NAFLD combined with type 2 diabetes group had a higher prevalence dyslipidemia and more serious insulin resistance[26]. Thus, the NAFLD combined with type 2 diabetes group had a higher prevalence of significant CAD. Our studies found that the NAFLD combined with type 2 diabetes group had a higher prevalence of hypertension than the type 2 diabetes combined with NAFLD group and the type 2 diabetes-alone group. In addition, our findings suggest that the NAFLD combined with type 2 diabetes group had the highest level of diastolic blood pressure. The results of Shengjie Wu *et al.*[27] suggest that increased levels of systolic blood pressure within the normal range are associated with significantly elevated risk for NAFLD. Aneni *et al.*[28] reported that controlling blood pressure among non-obese hypertensive patients might be beneficial in preventing or limiting NAFLD. Sung *et al.*[29] found that the development of fatty liver is associated with an increased risk for hypertension. These studies and the present results suggest that NAFLD might be linked to the increased incidence of hypertension. These links between NAFLD and hypertension could occur through multiple mechanisms. Luminita *et al.*[30] reported that the prevalence of NAFLD was significantly higher in the altered dipping status of hypertension (non-dipper, reverse-dipper and extreme-dipper), which had higher insulin resistance. This suggests that insulin resistance could be the pathogenic link between NAFLD and blood pressure. In addition, the dysregulation of the renin–angiotensin system in NAFLD might lead to the development of hypertension, through a mechanism of hepatic inflammation and fibrosis[31]. Hye Huh *et al.*[32] found that the fatty liver index might be useful for identifying NAFLD patients at high risk for incident hypertension in clinical practice. Therefore, in patients with NAFLD, evaluation for type 2 diabetes could potentially identify those patients at high risk for cardiovascular disease and hypertension.

Our studies suggest that the NAFLD combined with type 2 diabetes group had a lower prevalence of diabetic peripheral neuropathy and diabetic retinopathy than the type 2 diabetes combined with NAFLD group and the type 2 diabetes-alone group. However, the short duration of diabetes in these patients compared with the other groups might be the reason for this. We observed a trend toward decreasing diabetic nephropathy in the NAFLD combined with type 2 diabetes group compared with the type 2 diabetes combined with NAFLD group and the type 2 diabetes-alone group. However, there was no significant difference in the incidence of diabetic nephropathy among the three groups. Previous studies have shown negative correlations between the prevalence of NAFLD and the duration of diabetes, diabetic retinopathy, diabetic peripheral neuropathy, and diabetic nephropathy[33]. Kim *et al.*[34] reported that NAFLD was inversely associated with the prevalence of diabetic retinopathy and nephropathy in Korean patients with type 2 diabetes, and was not associated with diabetic neuropathy. The findings of our studies were similar to those of these studies. In contrast, Targher *et al.* showed that NAFLD is associated with an increased prevalence of chronic kidney disease and proliferative/laser-treated retinopathy in type 2 diabetic individuals[35]. These conflicting results might be a result of differences in the characteristics of the study participants. Targher *et al.*[35] found that glycated hemoglobin was higher in type 2 diabetes with NAFLD than in those without NAFLD. However, they did not distinguish the temporal sequence of NAFLD and type 2 diabetes, so these discrepancies might be due in part to the temporal sequence of NAFLD and type 2 diabetes. We should enlarge our sample size to validate the present results.

Our study had several limitations. First, this was a cross-sectional analysis and could not determine causal relations. We could further develop prospective studies into NAFLD and type 2 diabetes. Second, there was an absence of liver biopsies, which are the gold standard for the diagnosis of pure fatty liver

and non-alcoholic steatohepatitis. This factor prevented a detailed analysis of the association between the different types of NAFLD and diabetic complications.

Despite these limitations, these results suggest that NAFLD combined with type 2 diabetes is positively associated with significant coronary artery disease and hypertension, and is inversely associated with diabetic peripheral neuropathy and diabetic retinopathy. Our studies here might provide a new view of NAFLD, and new evidence on the different temporal sequence of NAFLD and type 2 diabetes with different diabetic complications.

ACKNOWLEDGMENTS

No funding was obtained from pharmaceutical companies to carry out this study. All authors were involved in the data collection and analysis.

DISCLOSURE

The authors declare no conflict of interest.

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