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Risk factors and metabolic abnormality of patients with non-alcoholic fatty liver disease: Either non-obese or obese Chinese population

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ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) occurs not only in obese individuals but also in non-obese ones. The aim of this study was to focus on the association between NAFLD and metabolic events in a non-obese or obese Chinese population.
Methods: Data collected from subjects registered at Taichung Veterans General Hospital from January to December 2009 were analyzed. The exclusion criteria were alcoholics, chronic hepatitis B or C. Patients included in analyses were assigned to four groups according to sonography of their liver (normal or NAFLD), and body mass index (BMI) levels (non-obese if BMI < 25 kg/m^2 or obese if BMI ≥ 25 kg/m^2).
Results: There were 745, 208, 770 and 285 patients enrolled in four groups labeled non-obese normal liver (group A), non-obese NAFLD (group B), obese normal liver (group C) and obese NAFLD (group D), respectively. The highest ratio of metabolic syndrome existed in the group B (26.9%), followed by group A (11.7%), group D (10.9%) and finally the group C (5.2%). The positive association with NAFLD in non-obese individuals was significant in triglyceride (OR = 1.01; 95% CI: 1.01–1.02) and glucose (OR = 1.02; 95% CI: 1.01–1.03), while the positive association with NAFLD in obese subjects was only significant in triglyceride (OR = 1.01; 95% CI: 1.01–1.02). The positive association was most significant in all cases (adjusted OR = 2.41; 95% CI: 1.78–3.24), especially in non-obese individuals (OR = 2.81; 95% CI: 1.92–4.12).
Conclusions: Non-obese NAFLD subjects displayed a higher proportion of metabolic abnormality. Hyperlipidemia and hyperglycemia had the most positive strength association with NAFLD.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a clinicopathological condition characterized by lipid deposition in the hepatocytes, when there is an absence of excess alcohol intake [1,2]. Although the majority of NAFLD cases occur in obese or overweight individuals, there exists a smaller proportion of patients who develop NAFLD despite having a relatively normal body mass index (BMI). This condition is often referred to as lean or non-obese NAFLD [3,4]. One's BMI is considered an important parameter when evaluating the grade of obesity. Asians in general have shown a propensity to develop adverse metabolic clinical events when measured with a comparatively lower BMI [5,6]. The aim of this study was to focus on the strength of association between NAFLD and metabolic events, in a non-obese or obese Chinese population.

Methods

Data from subjects who were admitted to the Medical Screening Center at Taichung Veterans General Hospital was retrospectively collected from January to December 2009. The general data of enrolled patients, including age, gender, BMI, waist circumference, blood pressure, cholesterol, triglyceride, fasting glucose and glutamic pyruvic transaminase (GPT) levels were recorded. All patients underwent a liver ultrasound performed by experienced radiologists, and the findings of each case were recorded. The exclusion criteria included a history of a significant consumption of alcohol, chronic hepatitis B or C.

These patients were assigned to four groups according to individual ultrasound findings of their liver (normal liver or NAFLD), and BMI level (non-obese if BMI < 25 kg/m^2 or obese if BMI ≥ 25 mg/m^2).

Metabolic syndrome was diagnosed based on the 2005 International Diabetes Federation (IDF) criteria [7], with ethnicity specific values: central obesity (waist circumference ≥90 cm for men

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Table 1
The characteristics of enrolled individuals.

Characteristics	Non-obese normal liver ($n = 745$)	Non-obese NAFLD ($n = 208$)	P value	Obese normal liver ($n = 770$)	Obese NAFLD ($n = 285$)	P value	P value*
Age (yr)	52.0 ± 12.2	52.7 ± 12.0	0.45	53.9 ± 11.2	54.8 ± 11.1	0.25	0.05
Male	304 (40.8%)	102 (49.0%)	**0.03**	516 (67.0%)	200 (70.2%)	0.36	**0.01**
BMI (kg/m^2)	21.4 ± 1.8	23.8 ± 1.8	**0.01**	26.7 ± 2.2	26.5 ± 2.3	0.09	**0.01**
WC (cm)	73.9 ± 7.4	75.5 ± 7.8	**0.01**	87.4 ± 8.0	87.0 ± 8.5	0.51	**0.01**
Cholesterol (mg/dL)	199.4 ± 35.8	206.8 ± 37.8	**0.01**	202.4 ± 39.8	204.7 ± 37.4	0.69	0.67
TG (mg/dL)	127.2 ± 38.7	190.6 ± 55.2	**0.01**	125.8 ± 42.4	187.6 ± 63.4	**0.01**	0.78
Glucose (mg/dL)	93.9 ± 20.5	107.6 ± 32.3	**0.01**	95.6 ± 23.1	106.7 ± 28.2	**0.01**	0.73
ALT (U/L)	23.3 ± 15.0	37.8 ± 23.1	**0.01**	23.2 ± 17.9	37.2 ± 29.2	**0.01**	0.81
MetS	87 (11.7%)	56 (26.9%)	**0.01**	40 (5.2%)	31 (10.9%)	**0.01**	**0.01**

*: compare between non-obese NAFLD group and obese NAFLD group; ALT: alanine aminotransferase; BMI: body mass index; MetS: metabolic syndrome; TG: triglyceride; WC: waist circumference.

and ≥80 cm for women), combined with any two of the following four conditions, (1) triglyceride levels ≥150 mg/dL; (2) high-density lipoprotein (HDL) levels <40 mg/dL for men and <50 mg/dL for women; (3) fasting glucose levels >100 mg/dL; and (4) systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg.

Statistical analysis

Data were expressed as the standard deviation of mean for each of the measured parameters. Gender, positive ratio of metabolic syndrome and abnormal metabolic events are expressed as a percentage of the total number of patients. Statistical comparisons were made using Pearson's Chi-square test when analyzing the effects of gender, ratio of metabolic syndrome and each individual item. An independent Student's t test was used to analyze age, waist circumference and individual serum values. A P value below .05 was considered statistically significant. Multivariate Cox's regression was used to examine the strength of association between the associated risk factors and NAFLD, as shown by odds ratio (OR) with a 95% confidence interval (CI).

Results

Of the 2008 enrolled subjects in our study, 745 (37.1%), 208 (10.4%), 770 (38.3%) and 285 (14.2%) were categorized into the groups of non-obese normal liver (group A), non-obese NAFLD (group B), obese normal liver (group C) and obese NAFLD (group D), respectively. The patient's characteristics have been summarized in Table 1. The mean ages were similar among the four groups. Male predominance was significant in the group B when compared with the group A (49.0% vs. 40.8%, $P = 0.03$). The individuals in the group B had a significant higher BMI, waist circumference, cholesterol, triglyceride, glucose and ALT, than those in the group A ($P = 0.01$). Similarly, the subjects in the group D possessed significantly higher triglyceride, glucose and ALT than those in the group C. However, the difference in values of BMI, waist circumference and cholesterol were not significant between these two groups. For the individuals with NAFLD, there were no differences in cholesterol, triglyceride, glucose and ALT between group B and D. The highest ratio of metabolic syndrome existed in group B (26.9%), followed by group A (11.7%), group D (10.9%) and finally group C (5.2%). These differences were significant ($P = 0.01$).

The strength of the association between items including BMI, waist circumference, cholesterol, triglyceride and fasting glucose among non-obese cases is disclosed in Table 2. After adjustment for measured potential confounders, the positive association with NAFLD in non-obese individuals was significant in both triglyceride (adjusted OR = 1.01; 95% CI: 1.01–1.02) and glucose (adjusted OR = 1.02; 95% CI: 1.01–1.03). The strength of the association between metabolic events among obese cases is also shown in Table 2. After adjustment, the positive association with NAFLD in the obese group was only significant in triglyceride (adjusted OR = 1.01; 95% CI: 1.01–1.02).

Table 2
Odds ratios and 95% confidence interval of associated items with NAFLD.

Items	OR# (95% CI)
Non-obese cases	
Normal	1.00 (reference)
BMI	1.11 (0.98–1.25)
WC	1.00 (0.97–1.03)
Cholesterol	1.00 (0.99–1.00)
TG	1.01 (1.01–1.02)
Glucose	1.02 (1.01–1.03)
Obese cases	
Normal	1.00 (reference)
BMI	0.53 (0.13–2.14)
WC	0.95 (0.89–1.01)
Cholesterol	1.00 (0.99–1.00)
TG	1.01 (1.01–1.02)
Glucose	1.01 (0.99–1.03)

#: adjustment for age and gender; BMI: body mass index; WC: waist circumference; TG: triglyceride; OR: odds ratio; 95% CI: 95% confidence interval.

The positive ratio of events in metabolic syndrome between group B and D is displayed in Table 3. Patients in group B had a significantly higher ratio of metabolic syndrome (26.9% vs. 10.9%, $P = 0.001$), low HDL (24.0% vs. 15.1%, $P = 0.012$) and hypertension (8.2% vs. 2.1%, $P = 0.002$), than the subjects in group D. The strength of the association between metabolic syndrome and NAFLD is shown in Table 4. After adjustment for age and gender, the positive association was most significant in all cases (adjusted OR = 2.41; 95% CI: 1.78–3.24), in particular within the non-obese individuals (adjusted OR = 2.81; 95% CI: 1.92–4.12).

Discussion

The reported prevalence of NAFLD when defined by liver ultrasound ranged between 17% and 46% depending on the population [8]. In obese subjects, the incidence of NAFLD reaches as high as 60%–90%, while the prevalence of nonalcoholic steatohepatitis (NASH) and hepatic cirrhosis was 20%–25% and 2%–8%, respectively [9]. In 10% of non-obese Americans, NAFLD has also been found through the National Health and Nutrition Examination Survey III [10]. Evidence of a non-obese phenotype of NAFLD was first reported in Asian countries. In a study of 1444 non-obese subjects enrolled in Taiwan, China, 61 cases (4.2%) were diagnosed with NAFLD [11]. One study, including 786 clinic based medical check-up individuals in Korea, found 74 of the 460 non-obese cases (16%) to have NAFLD [12]. An additional study performed in India uncovered that 90 of all 1777 non-obese cases (5.1%) had NAFLD [13]. In