Lean-non-alcoholic fatty liver disease increases risk for metabolic disorders in a normal weight Chinese population

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Abstract

AIM: To study the prevalence and clinical biochemical, blood cell and metabolic features of lean-non-alcoholic fatty liver disease (lean-NAFLD) and its association with other diseases.

METHODS: Demographic, biochemical and blood examinations were conducted in all the subjects in this study. We classified the subjects into four groups according to their weight and NAFLD status: lean-control, lean-NAFLD [body mass index (BMI) < 24 kg/m²], overweight-obese control and overweight-obese NAFLD. One-way analysis of variance (ANOVA) was used to compare the means of continuous variables (age, BMI, blood pressure, glucose, lipid, insulin, liver enzymes and blood cell counts) and the χ² test was used to compare the differences in frequency of categorical variables (sex, education, physical activity, smoking, alcohol consumption and prevalence of hypertension, hyperlipidemia, diabetes, metabolic syndrome central obesity and obesity). Both univariate and multivariate logistic regression models were adopted to calculate odds ratios (ORs) and predict hyperlipidemia, hypertension, diabetes and metabolic syndrome when we respectively set all controls, lean-control and overweight-obese-control as references. In multivariate logistic regression models, we adjusted potential confounding factors, including age, sex, smoking, alcohol consumption and physical activity.

RESULTS: The prevalence of NAFLD was very high in China. NAFLD patients were older, had a higher BMI, waist circumference, blood pressure, fasting blood glucose, insulin, blood lipid, liver enzymes and uric acid than the controls. Although lean-NAFLD patients had lower BMI and waist circumference, they had significantly higher visceral adiposity index than overweight-obese controls. Lean-NAFLD patients had comparable triglyceride, cholesterol and low-density lipoprotein cholesterol to overweight-obese NAFLD patients. In blood cell examination, both lean and overweight-obese NAFLD was companied by higher white blood cell count, red blood cell count, hemoglobin and hematocrit value. All NAFLD patients were at risk of hyperlipidemia, hypertension, diabetes and metabolic syndrome (MetS). Lean-NAFLD was more strongly associated with diabetes (OR = 2.47, 95%CI: 1.14-5.35), hypertension (OR = 1.72, 95%CI: 1.00-2.96) and MetS (OR = 3.19, 95%CI: 1.17-4.05) than overweight-obese NAFLD (only OR for MetS was meaningful: OR = 1.89, 95%CI: 1.29-2.77). NAFLD patients were more likely to have central obesity (OR = 1.97, 95%CI: 1.38-2.80), especially in lean groups (OR = 2.17, 95%CI: 1.17-4.05).

CONCLUSION: Lean-NAFLD has unique results in de-
Non-alcoholic fatty liver disease (NAFLD) has become an important public health issue because of its high prevalence\[1\]. It has been estimated that its prevalence varies between 20% and 30% in developed countries and Middle East\[2\]. Japan, China and India subcontinent have a similar prevalence (20%-30% in Japan, 15%-30% in China and 16%-32% in the Indian subcontinent)\[3\]. NAFLD is a hepatic manifestation of metabolic syndrome (MetS) and its long-term prognoses include non-alcoholic steatohepatitis (NASH), liver cirrhosis, even hepatocellular carcinoma (HCC)\[4\]. Patients with NAFLD are more likely to have insulin resistance (IR), abnormal glucose metabolism and higher risk for the development of diabetes\[5\]. It is an independent risk factor for chronic diseases, such as cardiovascular and renal diseases\[6\], and it is also associated with colorectal disease, atrial fibrillation and hypothyroidism\[7,9\].

Obesity is strongly associated with many metabolic diseases\[10\], including NAFLD, and bariatric surgery is recommended as a promising treatment\[11\]. However, NAFLD can also be observed in non-obese individuals and has its own metabolic characteristics, such as higher transaminase and insulin levels, less insulin sensitivity than non-obese controls; lower fasting glucose, less advanced necro-inflammatory activity and fibrosis compared with obese-NAFLD\[12\]. The prevalence of NAFLD in non-diabetic, non-obese adults was 23.4% (16.1% in the normal-weight group and 34.4% in the overweight group) in the study of Kim et al\[13\]. The prevalence varied from 15% to 21% in non-obese Asians [body mass index (BMI) < 25]\[14\]. NAFLD can be considered as an early predictor of metabolic disorders and a major cause of cryptogenic liver disease in normal-weight population\[12,13\]. Chinese people have lower BMI, but have a similar prevalence of NAFLD with Western people\[13,15\]. We suspected that lean-NAFLD is more serious in China and has different clinical characteristics.

The lack of knowledge of the prevalence and characteristics of lean-NAFLD in the Chinese population prompted us to conduct this study to: (1) define the prevalence and characterize the clinical biochemical, blood cell and metabolic features of lean-NAFLD; and (2) clarify the association between lean-NAFLD and chronic diseases, including diabetes, hypertension, hyperlipidemia and MetS.

**MATERIALS AND METHODS**

**Ethics**

The Ethics Committee of Harbin Medical University approved this study. Written Informed Consent was obtained from all participants.

**Subjects**

We randomly selected 2000 subjects who received annual physical examinations at Physical Examination Center of the Second Affiliated Hospital of Harbin Medical University from February 2012 to May 2013. The exclusion criteria were as follows: previous/current excessive alcohol intake (male ≥ 20 g/d; female ≥ 10 g/d), hepatitis, malignancies, pregnancy, long-term use of estrogens, tamoxifen, or corticosteroids, and absence of any of the anthropometric measurement, or laboratory analysis. Finally, 1779 adults aged 20-70 years were included.

**Measurements**

Each of these subjects was interviewed privately by trained interviewers, to complete a questionnaire that included questions regarding name, age, gender, education level, history of disease, drug or tobacco use, physical activity status and alcohol consumption. Smoking was defined as never, ≤ 1 cigarettes/d, ≤ 10 cigarettes/d, ≤ 20 cigarettes/d, and > 20 cigarettes/d; physical activity intensity was categorized into three groups: none, without any regular hard physical activity; moderate, having hard physical activity at least once a week regularly; and vigorous, having hard physical activity (leisure time or occupational) at least three times a wk. Alcohol consumption was calculated by the amount of alcohol drinks multiplied by the frequency.

Current weight, height and fat mass (FM) were measured using the electric impedance method with a body fat mass analyzer (ioi 353; Janex Medical, Seoul, Korea), with the examinees minimally clothed and wearing no socks. Weight and FM were recorded to the nearest 0.1 kg and height was measured in a standing position to the nearest 0.1 cm. BMI was calculated as weight in kilograms divided...
by height in meters squared. Waist circumference (WC) was measured at the umbilical level, using un-stretchable tape meter, without any pressure to body surface, and was recorded to the nearest 0.1 cm. A well-trained examiner measured all anthropometric indices. A qualified physician measured their blood pressure twice, and there was at least a 30-s interval between these two separate measurements, and thereafter the mean of the two measurements was recorded as definitive blood pressure.

**Laboratory analysis**

Blood samples were taken after > 10 h overnight fasting. A complete blood count was measured using an automated laser-based hematology analyzer (Sysmex XE-2100, Kobe, Japan). Hemoglobin (HGB), red blood cell count (RBC), hematocrit value (HCT), white blood cell count (WBC) and its subtypes-neutrophils (NEUT), lymphocytes (LYMPH), monocytes (MONO), eosinophils (EO), basophils (BASO) were all recorded. The biochemical indicators detected included fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transferase (GGT), alkaline phosphatase (ALP), serum creatinine (CRE), blood urea nitrogen (BUN) and serum uric acid (UA). All of these variables were determined using a ROCHE Modular P800 Automatic Biochemical Analyzer (Roche Diagnostics, Mannheim, Germany). A ROCHE Elecsys 2010 Chemiluminescence Immune Analyzer (Roche Diagnostics) measured the serum fasting insulin concentration. The homeostasis model assessment of insulin resistance (HOMA-IR) index was calculated as previously described[10]. Visceral adiposity index was calculated according to a published formula: male: visceral adiposity index (VAI) = WC/[39.68 + (1.88 × BMI)] × (TG/1.03) × (1.52/HDL); female: VAI = WC/[36.58 + (1.89 × BMI)] × (TG/0.81) × (1.52/HDL) (WC in cm, both TG and HDL in mmol/L)[17].

**Diagnostic criteria**

An abdominal ultrasonographic examination was performed to determine liver fatty infiltration using a 3.5-MHz probe (SSI-8000, Philips, Netherlands) by an experienced ultrasonographer, who was blind to the subjects’ disease history or blood laboratory analysis. The liver of each participant was assessed for size, contour, echogenicity, structure and posterior beam attenuation.

According to the guidelines for NAFLD management formulated by the Chinese National Workshop on Fatty Liver Disease in 2010[18], NAFLD can be diagnosed according to the following criteria: (1) alcohol consumption < 140 g/wk for male adults and < 70 g/wk for female adults; (2) absence of viral hepatitis [hepatitis B virus (HBV)/hepatitis C virus (HCV)], hepatolenticular degeneration, autoimmune diseases, a history of total parenteral nutrition, or intake of any hepatotoxic drugs (e.g., tamoxifen, amiodarone, sodium valproate, methotrexate, and glucocorticoid); and (3) ultrasonographic examination suggesting fatty infiltration in liver.

MetS was defined according to the International Diabetes Federation criteria[16] as waist circumference (WC) ≥ 90 cm for men and WC ≥ 80 cm for women plus at least two of the following components: (1) hypertriglyceridemia: TG ≥ 1.7 mmol/L (150 mg/dL), or under specific treatment for this lipid abnormality; (2) low HDL-C: HDL-C < 1.03 mmol/L (40 mg/dL) for men and < 1.29 mmol/L (50 mg/dL) for women or under specific treatment for this lipid abnormality; (3) raised blood pressure: systolic blood pressure (SBP) ≥ 130 mmHg, or diastolic blood pressure (DBP) ≥ 85 mmHg, or having previously diagnosed hypertension; and (4) hyperglycemia: fasting glucose ≥ 5.6 mmol/L (110 mg/dL).

A patient was defined as having hypertension if his blood pressure was higher than 140/90 mmHg or with disease history, and diabetes mellitus was defined when fasting blood glucose was higher than 7.0 mmol/L or with disease history. If serum triglycerides was ≥ 1.70 mmol/L or serum cholesterol ≥ 5.18 mmol/L or with disease history, hyperlipidemia would be diagnosed.

**Statistical analysis**

The subjects were divided into four groups according to their weight and NAFLD status: Lean control and NAFLD, overweight-obese control and NAFLD (lean: BMI < 24 kg/m², overweight-obese: BMI ≥ 24 kg/m²). Statistical analysis was performed using SPSS (version 16.0; Beijing Stats Data Mining Co. Ltd, Beijing, China). The χ² test was used to test variation in frequency, and analysis of variance (ANOVA) was used to assess differences in the means of continuous variables. Data are presented as means ± SD. Multiple variable logistic regression was used to calculate the odds ratios (ORs) of diabetes, hypertension, hyperlipidemia and MetS after adjusted for potentially confounding variables, including age, sex, BMI, smoking, alcohol consumption and physical activities. All P values were two-tailed, and P value < 0.05 was considered statistically significant.

**RESULTS**

**Demographic characteristics**

The basic demographic characteristics (age, gender composition, education, physical activity, smoking, alcohol consumption and chronic diseases) of the 1779 participants are summarized in Table 1. NAFLD had a male predominance, and BMI and blood pressure were higher in NAFLD patients than in controls in the same group. Overweight-obese-NAFLD patients had higher body fat, VAI and blood pressure than the lean-NAFLD group. Diabetes, hypertension, hyperlipidemia and MetS were more common in lean and overweight-obese NAFLD patients than in healthy controls.

**Comparison of biochemical indicators**

All biochemical indicators are shown in Table 2, includ-
Table 1  Baseline demographic characteristics of non-alcoholic fatty liver disease patients and controls

|                      | Lean-NAFLD (n = 731) | overweight-obese-NAFLD (n = 1048) | P value |
|----------------------|-----------------------|-----------------------------------|---------|
| Participants, n (%)  | Controls              | NAFLD                             |         |
|                      | 597 (81.67)           | 134 (18.33)                       |         |
| Age (yr)             | 43.19 ± 11.59         | 48.17 ± 10.5*                     | < 0.01  |
| Male (%)             | 28.48                 | 54.48                             | 51.41   | 72.25   | < 0.01 |
| Education (%)        |                       |                                   |         |
| Never                | 0.66                  | 1.92                              | 0.90    | 0.87    | 0.30   |
| Primary              | 0.66                  | 0.00                              | 2.26    | 1.56    |        |
| Junior               | 4.20                  | 2.88                              | 6.33    | 3.65    |        |
| Senior               | 15.27                 | 11.54                             | 19.46   | 18.92   |        |
| College              | 63.50                 | 66.35                             | 58.37   | 61.98   |        |
| Postgraduate         | 15.71                 | 17.31                             | 12.67   | 13.02   |        |
| BMI (kg/m²)          | 21.37 ± 1.71          | 22.74 ± 1.13*                     | 25.98 ± 1.66b | 27.57 ± 2.63c | < 0.01 |
| Body weight (kg)     | 57.64 ± 7.14          | 64.09 ± 7.31*                     | 71.32 ± 9.49b | 78.81 ± 11.64c | < 0.01 |
| Body fat (%)         | 24.83 ± 5.40          | 26.17 ± 4.96*                     | 29.61 ± 4.73b | 30.51 ± 4.49c | < 0.01 |
| Body fat mass (kg)   | 14.26 ± 3.37          | 16.59 ± 2.68*                     | 20.91 ± 3.34b | 23.59 ± 4.61c | < 0.01 |
| WC (cm)              | 75.50 ± 7.06          | 82.42 ± 6.29*                     | 87.06 ± 7.16b | 93.45 ± 8.70c | < 0.01 |
| VAI                  | 1.52 ± 1.99           | 2.04 ± 2.21*                      | 1.85 ± 2.32b | 2.08 ± 1.50c | < 0.01 |
| SBP (mmHg)           | 119.48 ± 15.45        | 126.46 ± 16.24*                   | 129.37 ± 19.84b | 132.20 ± 17.29c | < 0.01 |
| DBP (mmHg)           | 74.04 ± 10.04         | 80.05 ± 11.74*                    | 79.33 ± 12.17b | 82.84 ± 10.57c | < 0.01 |
| Physical activity (%)|                       |                                   |         |
| None                 | 83.92                 | 89.52                             | 80.27   | 85.10   | 0.45   |
| Moderate             | 14.98                 | 10.48                             | 18.39   | 13.86   |        |
| Vigorous             | 1.10                  | 0.00                              | 1.35    | 1.04    |        |
| Drinking (%)         | 23.82                 | 36.89                             | 39.25   | 49.02   | < 0.01 |
| Smoking (%)          |                       |                                   |         |
| Never                | 86.09                 | 82.52                             | 81.45   | 68.34   | < 0.01 |
| % 1 cigarettes/d     | 1.10                  | 0.97                              | 1.36    | 2.25    |        |
| % 10 cigarettes/d    | 5.08                  | 3.88                              | 5.43    | 7.96    |        |
| < 20 cigarettes/d    | 5.74                  | 8.74                              | 7.24    | 14.01   |        |
| > 20 cigarettes/d    | 1.99                  | 3.88                              | 4.52    | 7.44    |        |
| Diabetes (%)         | 4.58                  | 15.67                             | 9.54    | 16.49   | < 0.01 |
| Hypertension (%)     | 12.23                 | 34.71                             | 32.08   | 43.67   | < 0.01 |
| Hyperlipidemia (%)   | 34.20                 | 49.25                             | 47.69   | 59.47   | < 0.01 |
| MS (%)               | 3.06                  | 14.53                             | 26.47   | 46.64   | < 0.01 |
| Central obesity (%)  | 14.96                 | 29.41                             | 69.55   | 84.64   |       |
| Obesity (%)          | 0.00                  | 0.00                              | 11.97   | 37.70   | < 0.01 |

*P < 0.05 vs control in same weight group; †P < 0.05 vs Lean-control group; ‡P < 0.05 vs Lean-NAFLD group. NAFLD: Non-alcoholic fatty liver disease; BMI: Body mass index; WC: Waist circumstance; VAI: Visceral adiposity index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MS: Metabolic syndrome.

Association with diseases

Table 4 provides the odd ratios (ORs) from multivariate-adjusted logistic regression analysis for diabetes, hypertension, hyperlipidemia and MetS. We calculated crude ORs and adjusted ORs, which were adjusted by confounding factors, including age, sex, BMI, smoking, alcohol consumption and physical activity status.

NAFLD significantly added to the risks of almost all chronic diseases: central obesity (OR = 1.97, 95%CI: 1.38-2.80), hyperlipidemia (OR = 1.37, 95%CI: 1.04-1.80), hypertension (OR = 1.37, 95%CI: 1.04-1.80), diabetes (OR = 1.68, 95%CI: 1.08-2.62) and MetS (OR = 2.34, 95%CI: 1.65-3.31). Lean-NAFLD was an independent risk factor for these diseases, except for hyperlipidemia (OR = 1.29, 95%CI: 0.55-3.29). NAFLD patients tended to have higher FBG, fasting insulin, HOMA-IR, TG, LDL-C, ALT, AST, ALP, GGT and UA, and lower HDL-C compared with healthy controls. Fasting insulin, HOMA-IR, TG, and HDL-C were more likely to have central obesity than lean-NAFLD patients.

Results of blood examination

The differences in blood examination results among the four groups are shown in Table 3. Both WBC and RBC of NAFLD patients were higher than their controls, and overweight-obese NAFLD had the highest levels among the four groups. This phenomenon was also observed in subtypes of WBC: overweight-obese and lean-NAFLD ranked first and second, respectively in counts of NAUT, LYMPH, MONO and EO. However, the same amount of BASO (P = 0.217) was observed in the four groups. Meanwhile, RBC, HGB and HCT increased with the development of NAFLD.
higher risk for MetS (OR = 1.89, 95%CI: 1.29-2.77; OR = 2.17, 95%CI: 1.17-4.05) than overweight-obese and lean-controls.

**DISCUSSION**

In the current study, we classified the patients with NAFLD as lean- and overweight-obese NAFLD. The prevalence of NAFLD was 18.33% in the lean group and 72.90% in the overweight-obese group. There was a male predominance of NAFLD in lean and overweight-obese individuals (28.48% vs 54.48%, and 51.41% vs 72.55%, respectively). Compared with controls in the same weight group, both overweight-obese and lean-NAFLD patients had higher levels of BMI, WC, VAI, blood pressure, glucose, dyslipidemia, liver enzymes (ALT, AST, ALP and GGT) and renal function parameters (UA, BUN and GREA). NAFLD was clearly associated with dysfunctional fat and adipose tissue IR, which worsened glucose and fat metabolic status, resulting in pathoglycemia and dyslipidemia.[20,21]. NAFLD also added to the risk of chronic kidney disease (CKD)[22] by increasing micro-albuminuria and decreasing glomerular filtration rate.[23] Xu et al.[24] also found that age, gender, WC, blood pressure, dyslipidemia were significantly associated with NAFLD in a prospective 5-year follow-up of non-obese (BMI < 25 kg/m²) Chinese subjects. The prevalence of NAFLD almost doubled in the 5-year period. Lean-NAFLD is often asymptomatic and has lower clinical biochemical indicators. A summary of studies on NAFLD stated that the features of lean-NAFLD were different from country to country.[25] Thus, it is difficult to detect and treat in its early stages. It has been proven to be an unrecognized clinicopathological entity and a frequent cause of cryptogenic liver disease[13]. More efforts should be made to halt or reverse the progress of NAFLD in non-obese individuals.[14].

The WBC and its subtype cells (NEUT, LYMPH, MONO, EO and BASO) were higher in NAFLD than in controls in both weight groups, and they were even high-

### Table 2  Clinical biochemical characteristics of non-alcoholic fatty liver disease and controls

|                  | Lean-NAFLD | Overweight-obese-NAFLD |  P value |
|------------------|------------|------------------------|---------|
|                  | Controls   | NAFLD                  |         |
| FBG (mmol/L)     | 5.30 ± 1.36| 5.91 ± 1.85a           | <0.05   |
| Fasting insulin (IU/mL) | 6.42 ± 3.76 | 8.27 ± 3.93b         | <0.01   |
| HOMA-IR          | 1.55 ± 0.97| 2.16 ± 1.42a           | <0.01   |
| TC (mmol/L)      | 4.86 ± 0.93| 5.20 ± 1.01b           | <0.01   |
| TG (mmol/L)      | 1.18 ± 1.13| 1.71 ± 1.23c           | <0.01   |
| HDL-C (mmol/L)   | 1.58 ± 0.35| 1.45 ± 0.30d           | <0.01   |
| LDL-C (mmol/L)   | 2.90 ± 0.79| 3.12 ± 0.76e           | <0.01   |
| ALT (U/L)        | 18.32 ± 13.85| 21.61 ± 11.92f       | <0.01   |
| AST (U/L)        | 19.27 ± 6.85| 21.07 ± 9.26g         | <0.01   |
| ALP (U/L)        | 64.34 ± 18.16| 71.96 ± 20.49h       | <0.01   |
| GGT (U/L)        | 26.11 ± 27.99| 35.76 ± 34.92i       | <0.01   |
| UA (μmol/L)      | 280.04 ± 82.31| 303.30 ± 86.72j     | <0.01   |
| BUN (mmol/L)     | 5.00 ± 1.24| 5.15 ± 1.25          | 0.15    |
| CRE (μmol/L)     | 69.26 ± 14.37| 70.34 ± 13.84       |         |

*P < 0.05 vs control in same weight group; **P < 0.05 vs Lean-control group; ***P < 0.05 vs Lean-NAFLD group. NAFLD: Non-alcoholic fatty liver disease; FBG: Fasting blood glucose; TC: Total cholesterol; TG: Triglycerides; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: γ-glutamyl transferase; UA: Serum uric acid; BUN: Blood urea nitrogen; CRE: Serum creatinine.

### Table 3  Hematological comparison between non-alcoholic fatty liver disease and controls among four groups

|                  | Lean-NAFLD | Overweight-obese-NAFLD |  P value |
|------------------|------------|------------------------|---------|
|                  | Controls   | NAFLD                  |         |
| WBC (10^3/L)     | 5.73 ± 1.46| 6.40 ± 1.44a           | <0.01   |
| NEUT (10^9/L)    | 3.28 ± 1.12| 3.70 ± 1.04a           | <0.01   |
| LYMPH (10^9/L)   | 1.96 ± 0.52| 2.14 ± 0.56b           | <0.01   |
| MONO (10^9/L)    | 0.36 ± 0.14| 0.39 ± 0.13c           | <0.01   |
| EO (10^9/L)      | 0.09 ± 0.09| 0.15 ± 0.14d           | <0.01   |
| BASO (10^9/L)    | 0.01 ± 0.04| 0.01 ± 0.03            | <0.01   |
| RBC (10^6/L)     | 4.50 ± 0.41| 4.76 ± 0.42e           | <0.01   |
| HGB (g/L)        | 136.13 ± 15.24| 145.87 ± 16.44f   | <0.01   |
| HCT (%)          | 41.36 ± 4.11| 40.09 ± 4.41g         | <0.01   |

*P < 0.05 vs control in same weight group; **P < 0.05 vs Lean-control group; ***P < 0.05 vs Lean-NAFLD group. NAFLD: Non-alcoholic fatty liver disease; WBC: White blood cell count; NEUT: Neutrophils count; LYMPH: Lymphocytes count; MONO: Monocytes count; EO: Eosinophils count; BASO: Basophils count; RBC: Red blood cell count; HGB: Hemoglobin; HCT: Hematocrit value.
NAFLD often progresses to dyslipidemia, hypertension, diabetes, cardiovascular disease and CKD, and increases all-cause mortality in many countries\cite{46,49}. Central obesity and IR play important roles in the development of NAFLD\cite{49}. Hepatic enzymes (ALT, AST and GGT) may also contribute to the development of diabetes, and ALT and GGT can predict type 2 diabetes, independent of the degree of adiposity. ALT appears to be positively associated with IR and gluconeogenesis, and reflects inflammation, which impairs insulin signaling in the liver and systemically\cite{41}. ALT is also associated with endothelial dysfunction and predicts coronary heart disease\cite{42}. GGT is an enzyme responsible for extracellular catabolism and may be linked to greater oxidative stress, which is implicated in IR\cite{43}. In summary, NAFLD patients, especially those with elevated liver enzymes, have a higher risk of diabetes and other metabolic disorders.

Lean-NAFLD patients tended to have more visceral adiposity than lean-controls in our study, which can be used to measure the hepatic lipid content. The accumulation of lipid exposes the liver to high concentrations of free fatty acids and triglycerides, resulting in impairment of hepatic metabolic processes. Intrahepatic triglycerides are positively associated with the amount of visceral fat, and a strong negative correlation was observed between triglycerides and systemic insulin sensitivity\cite{33}. Visceral adiposity produces inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor (TNF), leading to more serious IR\cite{44}. Liver histology and most cardiometabolic abnormalities can be predicted by the adipose IR index\cite{45}.

Gene mutation may also contribute to NAFLD development\cite{46} because of its obvious familial inheritance\cite{48}. A missense mutation in the patatin-like phospholipase domain-containing 3 (PNPLA3) gene (also called adiponutrin), resulted in an approximately 2-fold higher hepatic TG content and an OR of 3.26 for the development of NAFLD. Its relation with hepatic TG content and NAFLD has been identified in many studies\cite{49}. Microbiota perturbation in the gastrointestinal tract may be important in the progression of NAFLD, particularly its role in obesity, insulin resistance and inflammation\cite{46}. In animal models, supplement of lactobacillus fermentum can improve IR, blood lipid metabolism and ameliorate NAFLD\cite{50,51}. Its interaction with he diet is another critical point for this disease\cite{49}. NAFLD is a multifactorial disease, with complex clinical characteristics\cite{52}. More research should be carried out to explore the pathogenesis of NAFLD and associated metabolic disorders.

Chinese people have their own lifestyle and genetic characteristics, which are different from Westerners\cite{52}, and are therefore more likely to have lean-NAFLD. Although many studies focused on lean-NAFLD, none of them has demonstrated the harm of NAFLD in lean and overweight-obese individuals. In addition, there is no population-based study in north China. With the increasing prevalence of NAFLD in lean individuals\cite{53}, it is essential to distinguish lean from overweight-obese

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**Table 4** Odds ratios of non-alcoholic fatty liver disease compared with controls

| Parameter                        | OR (95%CI)          | OR (95%CI)          |
|----------------------------------|---------------------|---------------------|
| All NAFLD vs all controls        |                     |                     |
| Hyperlipidemia                   | 2.19 (1.81-2.65)    | 1.37 (1.04-1.80)    |
| Hypertension                     | 2.98 (2.37-3.74)    | 1.49 (1.10-2.03)    |
| Diabetes                         | 2.97 (2.14-4.11)    | 1.68 (1.08-2.62)    |
| MS                               | 2.59 (1.78-3.82)    | 2.34 (1.65-3.51)    |
| Central obesity                  | 6.56 (5.16-8.33)    | 1.97 (1.38-2.80)    |
| Lean-NAFLD vs lean controls      |                     |                     |
| Hyperlipidemia                   | 1.87 (1.28-2.73)    | 1.29 (0.80-2.09)    |
| Hypertension                     | 3.26 (2.08-5.10)    | 1.72 (1.00-2.96)    |
| Diabetes                         | 3.87 (2.11-7.08)    | 2.47 (1.14-5.35)    |
| MS                               | 5.38 (2.66-10.89)   | 3.19 (1.38-7.35)    |
| Central obesity                  | 2.37 (1.44-3.90)    | 2.17 (1.17-4.05)    |
| Overweight-obese NAFLD vs overweight-obese controls | | |
| Hyperlipidemia                   | 1.61 (1.22-2.12)    | 1.36 (0.96-1.91)    |
| Hypertension                     | 1.64 (1.20-2.24)    | 1.35 (0.92-1.93)    |
| Diabetes                         | 1.87 (1.21-2.91)    | 1.34 (0.80-2.27)    |
| MS                               | 2.43 (1.75-3.38)    | 1.89 (1.29-2.77)    |

1. OR: Crude OR; 2. OR: Adjusted by age, sex, body mass index, smoking, alcohol consumption and physical activities. NAFLD: Non-alcoholic fatty liver disease; OR: Odds ratio; CI: Confidence interval; MS: Metabolic syndrome.
NAFLD, so that specific treatment can be provided to halt or prevent the development of NAFLD.

In summary, our data provided the estimated prevalence rate of lean-NAFLD in a Chinese population, and its metabolic characteristics compared with overweight-obese patients. The lean-NAFLD group had lower levels of blood glucose, blood pressure, hyperlipidemia, IR, blood cell count and HGB than the overweight-obese NAFLD group. Normal weight individuals are more likely to have diabetes, hypertension and MetS if they have NAFLD. Thus, it is a more dangerous condition than overweight-obese NAFLD.

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P- Reviewer: Marotta F, Nayak NC, Yang Y  S- Editor: Ding Y  L- Editor: Stewart G  E- Editor: Wang CH
