World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v20.i47.17932

World J Gastroenterol 2014 December 21; 20(47): 17932-17940
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

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

Ren-Nan Feng, Shan-Shan Du, Cheng Wang, Yan-Chuan Li, Li-Yan Liu, Fu-Chuan Guo, Chang-Hao Sun

Ren-Nan Feng, Shan-Shan Du, Yan-Chuan Li, Li-Yan Liu, Fu-Chuan Guo, Chang-Hao Sun, Department of Nutrition and Food Hygiene, School of Public Health, Harbin Medical University, Harbin 150081, Heilongjiang Province, China
Cheng Wang, Department of Environmental Hygiene, School of Public Health, Harbin Medical University, Harbin 150081, Heilongjiang Province, China
Author contributions: Feng RN, Du SS and Wang C contributed equally to this work; Feng RN and Sun CH designed the research; Wang C, Li YC and Guo FC performed the research; Feng RN, Liu LY and Du SS analyzed the data; Feng RN, Du SS, Liu LY and Wang C wrote the manuscript; Feng RN provided financial support for this work; all the authors were involved in revising the manuscript.
Supported by National Natural Science Fund of China, No. 81130049, No. 81202184; and 12th China Five-Year Scientific and Technical Plan, No. 2012BAI02B02
Correspondence to: Chang-Hao Sun, PhD, Department of Nutrition and Food Hygiene, School of Public Health, Harbin Medical University, No. 157 Baojian Street, Nangang District, Harbin 150081, Heilongjiang Province, China. changhao2002sun@gmail.com
Telephone: +86-451-87502881 Fax: +86-451-87502885
Received: April 5, 2014 Revised: June 12, 2014
Accepted: July 11, 2014
Published online: December 21, 2014

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/m^2], 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 χ^2 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 circumstance, they had significantly higher visceral adiposity index than overweight-obese controls. Lean-NAFLD patients had comparable triglyceride, cholesterin and low-density lipoprotein cholesterin 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-

mographic, biochemical and blood examinations, and adds significant risk for diabetes, hypertension and MetS in lean individuals.

Key words: Lean-non-alcoholic fatty liver disease; Metabolic disorder; Diabetes; Risk; Chinese

Core tip: Obesity is an important risk factor for non-alcoholic fatty liver disease (NAFLD). NAFLD can also occur in lean subjects. Chinese people have lower body mass index than Americans and Europeans, but a similar prevalence of NAFLD. There might be different metabolic characters in Chinese population. We conducted this study to characterize metabolic features of lean-NAFLD and identify its association with metabolic disorders.

Feng RN, Du SS, Wang C, Li YC, Liu LY, Guo FC, Sun CH. Lean-non-alcoholic fatty liver disease increases risk for metabolic disorders in a normal weight Chinese population. *World J Gastroenterol* 2014; 20(47): 17932-17940 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i47/17932.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i47.17932

INTRODUCTION

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)[1]. Patients with NAFLD are more likely to have insulin resistance (IR), abnormal glucose metabolism and higher risk for the development of diabetes[4]. It is an independent risk factor for chronic diseases, such as cardiovascular and renal diseases[5,6], 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[16]. Visceral adiposity index was calculated according to a published formula: male: visceral adiposity index (VAI) = WC/[39.68 + (1.88 × BMI)] × (TG/1.03) × (1.31/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 ultrasonographist, 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[19] 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/m^2, overweight-obese: BMI ⩾ 24 kg/m^2). Statistical analysis was performed using SPSS (version 16.0; Beijing Stats Data Mining Co. Ltd, Beijing, China). The χ^2 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
	Controls	NAFLD	Controls	NAFLD	
Participants, n (%)	597 (81.67)	134 (18.33)	284 (27.10)	764 (72.90)	
Age (yr)	43.19 ± 11.59	48.17 ± 10.5[a]	46.72 ± 11.15[b]	46.92 ± 11.19	< 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/m^2)	21.37 ± 1.71	22.74 ± 1.13[a]	25.98 ± 1.66[b]	27.57 ± 2.63[a,c]	< 0.01
Body weight (kg)	57.64 ± 7.14	64.09 ± 7.31[a]	71.32 ± 9.49[b]	78.81 ± 11.64[a,c]	< 0.01
Body fat (%)	24.83 ± 5.40	26.17 ± 4.96[a]	29.61 ± 4.73[b]	30.05 ± 4.49[c]	< 0.01
Body fat mass (kg)	14.26 ± 3.37	16.59 ± 2.68[a]	20.91 ± 3.34[b]	23.59 ± 4.61[a,c]	< 0.01
WC (cm)	75.50 ± 7.06	82.42 ± 6.29[a]	87.06 ± 7.16[b]	93.45 ± 8.70[c]	< 0.01
VAI	1.52 ± 1.99	2.04 ± 2.21[a]	1.85 ± 2.32[b]	2.08 ± 1.50	< 0.01
SBP (mmHg)	119.48 ± 15.45	126.46 ± 16.24[a]	129.37 ± 19.86[b]	132.20 ± 17.29[c]	< 0.01
DBP (mmHg)	74.04 ± 10.04	80.05 ± 11.74[a]	79.33 ± 12.17[b]	82.84 ± 10.57[a,c]	< 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	< 0.01
Obesity (%)	0.00	0.00	11.97	37.70	< 0.01

[a]P < 0.05 *vs* control in same weight group; [b]P < 0.05 *vs* Lean-control group, [c]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.

ing FBG, fasting insulin, TC, TG, HDL-C, LDL-C, ALT, AST, ALP, GGT, UA, BUN and CREA. 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 TC, AST, GGT, UA and CREA were lower in lean-NAFLD than in overweight-obese NAFLD.

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.

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 wee 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, P = 0.30) when NAFLD patients were compared with controls in lean groups. Moreover, NAFLD cases were more likely to have central obesity than lean-controls. Hyperlipidemia, hypertension and diabetes were not more serious in overweight-obese NAFLD patients than overweight-obese controls. NAFLD patients had

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

	Lean-NAFLD		Overweight-obese-NAFLD		*P* value
	Controls	NAFLD	Controls	NAFLD	
FBG (mmol/L)	5.30 ± 1.36	5.91 ± 1.85[a]	5.52 ± 1.31[b]	5.76 ± 1.42[a]	< 0.01
Fasting insulin (IU/mL)	6.42 ± 3.76	8.27 ± 3.93[a]	7.28 ± 4.33	10.84 ± 5.28[a,c]	< 0.01
HOMA-IR	1.55 ± 0.97	2.16 ± 1.42[a]	1.87 ± 1.35[b]	2.73 ± 1.53[a,c]	< 0.01
TC (mmol/L)	4.86 ± 0.93	5.20 ± 1.01[a]	5.00 ± 0.90[b]	5.10 ± 0.92	< 0.01
TG (mmol/L)	1.18 ± 1.13	1.71 ± 1.23[a]	1.40 ± 1.01[b]	1.83 ± 1.19[a]	< 0.01
HDL-C (mmol/L)	1.58 ± 0.35	1.45 ± 0.30[a]	1.44 ± 0.30[b]	1.35 ± 0.27[a,c]	< 0.01
LDL-C (mmol/L)	2.90 ± 0.79	3.12 ± 0.78[a]	3.09 ± 0.77[b]	3.13 ± 0.78	< 0.01
ALT (U/L)	18.32 ± 13.85	21.61 ± 11.92[a]	21.10 ± 16.13[b]	27.23 ± 18.25[a,c]	< 0.01
AST (U/L)	19.27 ± 6.85	21.07 ± 9.26[a]	20.23 ± 11.10	22.37 ± 9.87[a]	< 0.01
ALP (U/L)	64.34 ± 18.16	71.96 ± 20.49[a]	66.94 ± 21.26	70.00 ± 18.47[a]	< 0.01
GGT (U/L)	26.11 ± 27.99	35.76 ± 34.92[a]	33.42 ± 33.95[b]	47.26 ± 48.44[a,c]	< 0.01
UA (μmol/L)	280.04 ± 82.31	303.30 ± 86.72[a]	307.59 ± 85.54[b]	340.60 ± 92.68[a,c]	< 0.01
BUN (mmol/L)	5.00 ± 1.24	5.15 ± 1.25	5.16 ± 1.19	5.14 ± 1.24	0.15
CRE (μmol/L)	69.26 ± 14.37	70.34 ± 13.84	71.72 ± 14.18[b]	74.53 ± 14.48[c]	< 0.01

[a]$P < 0.05$ *vs* control in same weight group; [b]$P < 0.05$ *vs* Lean-control group; [c]$P < 0.05$ *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	Controls	NAFLD	
WBC (10^9/L)	5.73 ± 1.46	6.40 ± 1.44[a]	6.25 ± 1.58[b]	6.72 ± 1.66[a,c]	< 0.01
NEUT (10^9/L)	3.28 ± 1.12	3.70 ± 1.04[a]	3.62 ± 1.19[b]	3.88 ± 1.25[a,c]	< 0.01
LYMPH (10^9/L)	1.96 ± 0.52	2.14 ± 0.56[a]	2.10 ± 0.57[b]	2.26 ± 0.60[a,c]	< 0.01
MONO (10^9/L)	0.36 ± 0.14	0.39 ± 0.13[a]	0.39 ± 0.16[b]	0.42 ± 0.15[a]	< 0.01
EO (10^9/L)	0.09 ± 0.09	0.13 ± 0.14[a]	0.11 ± 0.10	0.14 ± 0.13[a]	< 0.01
BASO (10^9/L)	0.01 ± 0.04	0.01 ± 0.03	0.01 ± 0.03	0.02 ± 0.03	0.22
RBC (10^{12}/L)	4.50 ± 0.41	4.76 ± 0.42[a]	4.72 ± 0.48[b]	4.96 ± 0.44[a,c]	< 0.01
HGB (g/L)	136.13 ± 15.24	145.87 ± 16.44[a]	143.30 ± 17.05[b]	152.19 ± 14.22[a,c]	< 0.01
HCT (%)	41.36 ± 4.11	44.09 ± 4.41[a]	43.40 ± 4.55[b]	45.68 ± 3.90[a,c]	< 0.01

[a]$P < 0.05$ *vs* control in same weight group; [b]$P < 0.05$ *vs* Lean-control group; [c]$P < 0.05$ *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.

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/m^2) 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[12]. 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 4 Odds ratios of non-alcoholic fatty liver disease compared with controls

	[1]OR (95%CI)	[2]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	6.29 (4.78-8.28)	2.34 (1.65-3.31)
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)	1.33 (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.

er in overweight-obese NAFLD than in lean-NAFLD. WBC is a marker of inflammation, and we observed higher levels of WBC and its subtypes in the metabolic disorders[26]. Its count was independently associated with the presence of NAFLD regardless of classical cardiovascular risk factors and other components of metabolic syndrome. Hepatic steatosis is not only a focal fat deposition in the liver, but also a systemic inflammation[27]. RBC, HGB and HCT have a similar rising trend for WBC in NAFLD. These hematological parameters were strongly associated with the prevalence of IR, cerebrovascular damage and metabolic syndrome[28,29]. High HGB, HCT and RBC significantly added to the risk of NAFLD[30]. Serum hemoglobin, which may have a significant predictive value for NAFLD, is an antioxidant, binding to free hemoglobin and inhibiting oxidative injury. Inflammation and oxidative injury both contribute to NAFLD. Thus, NAFLD patients have higher levels of hemoglobin than normal controls[30,31]. The increase of HCT, a decisive factor of blood viscosity, is always followed by a decrease in blood flow rate, leading to an insufficient glucose supply to the muscles, and subsequently IR[32]. Meanwhile, insulin may stimulate erythropoiesis through its growth-promoting effect and increase HCT[33]. Insulin-like growth factor-1 (IGF-1) can stimulate erythropoiesis, and enhance the synthesis of plasma protein in endocrine manner[26]. The above mechanism may be involved in the association between abnormality in blood examination results and NAFLD; however, we could not find any evidence for this phenomenon, and no full-scale blood examination including all parameters has been reported. More research is required to clarify this point.

We also found that NAFLD patients had higher risks for hyperlipidemia, hypertension, diabetes and MetS than the controls. A large number of studies have shown that NAFLD often progresses to dyslipidemia, hypertension, diabetes, cardiovascular disease and CKD, and increases all-cause mortality in many countries[34-39]. Central obesity and IR play important roles in the development of NAFLD[40]. 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[41]. ALT is also associated with endothelial dysfunction and predicts coronary heart disease[42]. GGT is an enzyme responsible for extracellular catabolism and may be linked to greater oxidative stress, which is implicated in IR[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[44]. Visceral adiposity produces inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor (TNF), leading to more serious IR[45]. Liver histology and most cardiometabolic abnormalities can be predicted by the adipose IR index[46].

Gene mutation may also contribute to NAFLD development[47] because of its obvious familial inheritance[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[47]. Microbiota perturbation in the gastrointestinal tract may be important in the progression of NAFLD, particularly its role in obesity, insulin resistance and inflammation[49]. In animal models, supplement of lactobacillus fermentum can improve IR, blood lipid metabolism and ameliorate NAFLD[50,51]. Its interaction with he diet is another critical point for this disease[49]. NAFLD is a multifactorial disease, with complex clinical characteristics[31]. 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[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[53], it is essential to distinguish lean from overweight-obese

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.

COMMENTS

Background

Non-alcoholic fatty liver disease (NAFLD) has become an important public health issue and obesity is an established risk factor for its development. However, it can also be observed in normal weight individuals, which is called lean-NAFLD. Chinese people have lower body mass index, but a similar prevalence of NAFLD with Western people. We suspected that lean-NAFLD was more serious and has different clinical characteristics in Chinese population.

Research frontiers

Lean-NAFLD has become more and more common, as shown in epidemical studies. It has its own metabolic characteristics and is a major cause of cryptogenic liver disease in normal weight population, when compared with obesity patients. In this study, the authors demonstrated that lean-NAFLD may have different disease status from obese-NAFLD and may be a risk factor for metabolic disorder in lean individuals.

Innovations and breakthroughs

Recent reports have highlighted the importance of obese-NAFLD in the development of metabolic disorders, including diabetes, hypertension and hyperlipidemia. This is the first study to report that NAFLD in lean individuals is a more serious condition than in obese ones, because it adds risk for metabolic diseases. Furthermore, the authors suggested that lean-NAFLD may have different biochemical indexes and blood cell examination results.

Terminology

This study suggests that lean-NAFLD is a dangerous condition, and significantly adds risk for diabetes, hypertension and metabolic syndrome.

Peer review

The authors provided a detailed survey to study the prevalence and disorders of metabolism and blood cell examination in lean-non-alcoholic fatty liver disease (lean-NAFLD). The results of their comparative analysis are clearly presented. It is noticeable that NAFLD subjects with normal weight are more likely to have diabetes, hypertension and metabolic syndrome. Lean-NAFLD has its own metabolic characteristics, such as lower blood glucose, blood pressure, hyperlipidemia, insulin resistance, blood cell count and hemoglobin, which are different from overweight-obese patients. Overall, this paper presents a timely and useful survey of lean-NAFLD features based on the available clinical parameters.

REFERENCES

1 **Hashimoto E**, Taniai M, Tokushige K. Characteristics and diagnosis of NAFLD/NASH. *J Gastroenterol Hepatol* 2013; **28** Suppl 4: 64-70 [PMID: 24251707 DOI: 10.1111/jgh.12271]

2 **Preiss D**, Sattar N. Non-alcoholic fatty liver disease: an overview of prevalence, diagnosis, pathogenesis and treatment considerations. *Clin Sci* (Lond) 2008; **115**: 141-150 [PMID: 18662168 DOI: 10.1042/CS20070402]

3 **Loomba R**, Sanyal AJ. The global NAFLD epidemic. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 686-690 [PMID: 24042449 DOI: 10.1038/nrgastro.2013.171]

4 **Choi JH**, Rhee EJ, Bae JC, Park SE, Park CY, Cho YK, Oh KW, Park SW, Lee WY. Increased risk of type 2 diabetes in subjects with both elevated liver enzymes and ultrasonographically diagnosed nonalcoholic fatty liver disease: a 4-year longitudinal study. *Arch Med Res* 2013; **44**: 115-120 [PMID: 23398788 DOI: 10.1016/j.arcmed.2013.01.007]

5 **Ortiz-Lopez C**, Lomonaco R, Orsak B, Finch J, Chang Z, Kochunov VG, Hardies J, Cusi K. Prevalence of prediabetes and diabetes and metabolic profile of patients with nonalcoholic fatty liver disease (NAFLD). *Diabetes Care* 2012; **35**: 873-878 [PMID: 22374640 DOI: 10.2337/dc11-1849]

6 **El Azeem HA**, Khalek el-SA, El-Akabawy H, Naeim H, Khalik HA, Alfifi AA. Association between nonalcoholic fatty liver disease and the incidence of cardiovascular and renal events. *J Saudi Heart Assoc* 2013; **25**: 239-246 [PMID: 24198448 DOI: 10.1016/j.jsha.2013.07.004]

7 **Wong VW**, Wong GL, Tsang SW, Fan T, Chu WC, Woo J, Chan AW, Choi PC, Chim AM, Lau JY, Chan FK, Sung JJ, Chan HL. High prevalence of colorectal neoplasm in patients with non-alcoholic steatohepatitis. *Gut* 2011; **60**: 829-836 [PMID: 21339204 DOI: 10.1136/gut.2011.237974]

8 **Targher G**, Mantovani A, Pichiri I, Rigolon R, Dauriz M, Zoppini G, Morani G, Vassanelli C, Bonora E. Non-alcoholic fatty liver disease is associated with an increased prevalence of atrial fibrillation in hospitalized patients with type 2 diabetes. *Clin Sci* (Lond) 2013; **125**: 301-309 [PMID: 23596966 DOI: 10.1042/CS20130036]

9 **Pagadala MR**, Zein CO, Dasarathy S, Yerian LM, Lopez R, McCullough AJ. Prevalence of hypothyroidism in nonalcoholic fatty liver disease. *Dig Dis Sci* 2012; **57**: 528-534 [PMID: 22183820 DOI: 10.1007/s10620-011-2006-2]

10 **Feng RN**, Zhao C, Wang C, Niu YC, Li K, Guo FC, Li ST, Sun CH, Li Y. BMI is strongly associated with hypertension, and waist circumference is strongly associated with type 2 diabetes and dyslipidemia, in northern Chinese adults. *J Epidemiol* 2012; **22**: 317-323 [PMID: 22672914 DOI: 10.2188/jea.JE20110120]

11 **Adams TD**, Davidson LE, Litwin SE, Kolotkin RL, LaMonte MJ, Pendleton RC, Strong MB, Vinik R, Wanner NA, Hopkins PN, Gress RE, Walker JM, Cloward TV, Nuttall RT, Hammoud A, Greenwood JL, Crosby RD, McKinlay R, Simper SC, Smith SC, Hunt SC. Health benefits of gastric bypass surgery after 6 years. *JAMA* 2012; **308**: 1122-1131 [PMID: 22990271 DOI: 10.1001/2012.jama.11164]

12 **Vos B**, Moreno C, Nagy N, Féry F, Cnop M, Vereerstraeten P, Devière J, Adler M. Lean non-alcoholic fatty liver disease (Lean-NAFLD): a major cause of cryptogenic liver disease. *Acta Gastroenterol Belg* 2011; **74**: 389-394 [PMID: 22103042]

13 **Kim HJ**, Kim HJ, Lee KE, Kim DJ, Kim SK, Ahn CW, Lim SK, Kim KR, Lee HC, Huh KB, Cha BS. Metabolic significance of nonalcoholic fatty liver disease in nonobese, nondiabetic adults. *Arch Intern Med* 2004; **164**: 2169-2175 [PMID: 15505132 DOI: 10.1001/archinte.164.19.2169]

14 **Liu CJ**. Prevalence and risk factors for non-alcoholic fatty liver disease in Asian people who are not obese. *J Gastroenterol Hepatol* 2012; **27**: 1555-1560 [PMID: 22741595 DOI: 10.1111/j.1440-1746.2012.07222.x]

15 **Das UN**. Metabolic syndrome X is common in South Asians, but why and how? *Nutrition* 2002; **18**: 774-776 [PMID: 12297221 DOI: 10.1016/S0899-9007(02)00826-2]

16 **Matthews DR**, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; **28**: 412-419 [PMID: 3899825]

17 **Amato MC**, Giordano C, Galia M, Criscimanna A, Vitabile S, Midiri M, Galluzzo A. Visceral Adiposity Index: a reliable indicator of visceral fat function associated with cardiometabolic risk. *Diabetes Care* 2010; **33**: 920-922 [PMID: 20067971 DOI: 10.2337/dc09-1825]

18 **Jian-gao F**. Guidelines for management of nonalcoholic fatty liver disease: an updated and revised edition. *Zhonghua Ganzangbing Zazhi* 2010; **18**: 163-166 [PMID: 20698076]

19 **Alberti KG**, Zimmet P, Shaw J. The metabolic syndrome--a new worldwide definition. *Lancet* 2005; **366**: 1059-1062 [PMID: 16182882 DOI: 10.1016/S0140-6736(05)67402-8]
20 **Cusi K**. Role of insulin resistance and lipotoxicity in non-alcoholic steatohepatitis. *Clin Liver Dis* 2009; **13**: 545-563 [PMID: 19818304 DOI: 10.1016/j.cld.2009.07.009]
21 **Puri P**, Baillie RA, Wiest MM, Mirshahi F, Choudhury J, Cheung O, Sargeant C, Contos MJ, Sanyal AJ. A lipidomic analysis of nonalcoholic fatty liver disease. *Hepatology* 2007; **46**: 1081-1090 [PMID: 17654743 DOI: 10.1002/hep.21763]
22 **Bonora E**, Targher G. Increased risk of cardiovascular disease and chronic kidney disease in NAFLD. *Nat Rev Gastroenterol Hepatol* 2012; **9**: 372-381 [PMID: 22565095 DOI: 10.1038/nrgastro.2012.79]
23 **Ryu S**, Chang Y, Kim DI, Kim WS, Suh BS. gamma-Glutamyltransferase as a predictor of chronic kidney disease in nonhypertensive and nondiabetic Korean men. *Clin Chem* 2007; **53**: 71-77 [PMID: 17110470]
24 **Xu C**, Yu C, Ma H, Xu L, Miao M, Li Y. Prevalence and risk factors for the development of nonalcoholic fatty liver disease in a nonobese Chinese population: the Zhejiang Zhenhai Study. *Am J Gastroenterol* 2013; **108**: 1299-1304 [PMID: 23567356 DOI: 10.1038/ajg.2013.104]
25 **Das K**, Chowdhury A. Lean NASH: distinctiveness and clinical implication. *Hepatol Int* 2013; **7**: S806-S813
26 **Eheim A**, Medrikova D, Herzig S. Immune cells and metabolic dysfunction. *Semin Immunopathol* 2014; **36**: 13-25 [PMID: 24212254 DOI: 10.1007/s00281-013-0403-7]
27 **Lee YJ**, Lee HR, Shim JY, Moon BS, Lee JH, Kim JK. Relationship between white blood cell count and nonalcoholic fatty liver disease. *Dig Liver Dis* 2010; **42**: 888-894 [PMID: 20472517 DOI: 10.1016/j.dld.2010.04.005]
28 **Kawamoto R**, Tabara Y, Kohara K, Miki T, Kusunoki T, Abe M, Katoh T. Hematological parameters are associated with metabolic syndrome in Japanese community-dwelling persons. *Endocrine* 2013; **43**: 334-341 [PMID: 23307027 DOI: 10.1007/s12020-012-9662-7]
29 **Tabara Y**, Igase M, Saito I, Nishida W, Kohara K, Sakurai S, Kawamura R, Okada Y, Hitsumoto S, Onuma H, Nagai T, Takata Y, Uetani E, Takita R, Kido T, Ochi N, Osawa H, Tanigawa T, Miki T. Association of hematological parameters with insulin resistance, insulin sensitivity, and asymptomatic cerebrovascular damage: the J-SHIP and Toon Health Study. *Clin Hemorheol Microcirc* 2013; **55**: 297-311 [PMID: 23109550 DOI: 10.3233/CH-2012-1634]
30 **Jiang Y**, Zeng J, Chen B. Hemoglobin combined with triglyceride and ferritin in predicting non-alcoholic fatty liver. *J Gastroenterol Hepatol* 2014; **29**: 1508-1514 [PMID: 24628002 DOI: 10.1111/jgh.12580]
31 **Yu C**, Xu C, Xu L, Yu J, Miao M, Li Y. Serum proteomic analysis revealed diagnostic value of hemoglobin for nonalcoholic fatty liver disease. *J Hepatol* 2012; **56**: 241-247 [PMID: 21756851 DOI: 10.1016/j.jhep.2011.05.027]
32 **Moan A**, Nordby G, Os I, Birkeland KI, Kjeldsen SE. Relationship between hemorrheologic factors and insulin sensitivity in healthy young men. *Metabolism* 1994; **43**: 423-427 [PMID: 8159097 DOI: 10.1016/0026-0495(94)90070-1]
33 **Bersch N**, Groopman JE, Golde DW. Natural and biosynthetic insulin stimulates the growth of human erythroid progenitors in vitro. *J Clin Endocrinol Metab* 1982; **55**: 1209-1211 [PMID: 6752170 DOI: 10.1210/jcem-55-6-1209]
34 **Anstee QM**, Targher G, Day CP. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 330-344 [PMID: 23507799 DOI: 10.1038/nrgastro.2013.41]
35 **Gaggini M**, Morelli M, Buzzigoli E, DeFronzo RA, Bugianesi E, Gastaldelli A. Non-alcoholic fatty liver disease (NAFLD) and its connection with insulin resistance, dyslipidemia, atherosclerosis and coronary heart disease. *Nutrients* 2013; **5**: 1544-1560 [PMID: 23666091 DOI: 10.3390/nu5051544]
36 **Stepanova M**, Rafiq N, Makhlouf H, Agrawal R, Kaur I, Younoszai Z, McCullough A, Goodman Z, Younossi ZM. Predictors of all-cause mortality and liver-related mortality in patients with non-alcoholic fatty liver disease (NAFLD). *Dig Dis Sci* 2013; **58**: 3017-3023 [PMID: 23775317 DOI: 10.1007/s10620-013-2743-5]
37 **Ryoo JH**, Suh YJ, Shin HC, Cho YK, Choi JM, Park SK. Clinical association between non-alcoholic fatty liver disease and the development of hypertension. *J Gastroenterol Hepatol* 2014; **29**: 1926-1931 [PMID: 24910023 DOI: 10.1111/jgh.12643]
38 **Gianotti G**, Cenni A, Bianchi G, Masetti M, Zappoli P, Muscari A, Zoli M. Diastolic dysfunction and cardiovascular risk in old subjects: possible association with NAFLD? *Arch Gerontol Geriatr* 2014; **58**: 188-195 [PMID: 24268461 DOI: 10.1016/j.archger.2013.10.012]
39 **Sesti G**, Fiorentino TV, Arturi F, Perticone M, Sciacqua A, Perticone F. Association between noninvasive fibrosis markers and chronic kidney disease among adults with nonalcoholic fatty liver disease. *PLoS One* 2014; **9**: e88569 [PMID: 24520400 DOI: 10.1371/journal.pone.0088569]
40 **Adams LA**, Waters OR, Knuiman MW, Elliott RR, Olynyk JK. NAFLD as a risk factor for the development of diabetes and the metabolic syndrome: an eleven-year follow-up study. *Am J Gastroenterol* 2009; **104**: 861-867 [PMID: 19293782 DOI: 10.1038/ajg.2009.67]
41 **Vozarova B**, Stefan N, Lindsay RS, Saremi A, Pratley RE, Bogardus C, Tataranni PA. High alanine aminotransferase is associated with decreased hepatic insulin sensitivity and predicts the development of type 2 diabetes. *Diabetes* 2002; **51**: 1889-1895 [PMID: 12031978 DOI: 10.2337/diabetes.51.6.1889]
42 **Schindhelm RK**, Dekker JM, Nijpels G, Bouter LM, Stehouwer CD, Heine RJ, Diamant M. Alanine aminotransferase predicts coronary heart disease events: a 10-year follow-up of the Hoorn Study. *Atherosclerosis* 2007; **191**: 391-396 [PMID: 16682043 DOI: 10.1016/j.atherosclerosis.2006.04.006]
43 **Fraser A**, Harris R, Sattar N, Ebrahim S, Davey Smith G, Lawlor DA. Alanine aminotransferase, gamma-glutamyltransferase, and incident diabetes: the British Women's Heart and Health Study and meta-analysis. *Diabetes Care* 2009; **32**: 741-750 [PMID: 19131466 DOI: 10.2337/dc08-1870]
44 **Hwang JH**, Stein DT, Barzilai N, Cui MH, Tonelli J, Kishore P, Hawkins M. Increased intrahepatic triglyceride is associated with peripheral insulin resistance: in vivo MR imaging and spectroscopy studies. *Am J Physiol Endocrinol Metab* 2007; **293**: E1663-E1669 [PMID: 17911339 DOI: 10.1152/ajpendo.00590.2006]
45 **Després JP**, Lemieux I, Bergeron J, Pibarot P, Mathieu P, Larose E, Rodés-Cabau J, Bertrand OF, Poirier P. Abdominal obesity and the metabolic syndrome: contribution to global cardiometabolic risk. *Arterioscler Thromb Vasc Biol* 2008; **28**: 1039-1049 [PMID: 18356555 DOI: 10.1161/ATVBAHA.107.159228]
46 **Musso G**, Cassader M, De Michieli F, Rosina F, Orlandi F, Gambino R. Nonalcoholic steatohepatitis versus steatosis: adipose tissue insulin resistance and dysfunctional response to fat ingestion predict liver injury and altered glucose and lipoprotein metabolism. *Hepatology* 2012; **56**: 933-942 [PMID: 22684858 DOI: 10.1002/hep.25739]
47 **Cohen JC**, Horton JD, Hobbs HH. Human fatty liver disease: old questions and new insights. *Science* 2011; **332**: 1519-1523 [PMID: 21700865 DOI: 10.1126/science.1204265]
48 **Schwimmer JB**, Celedon MA, Lavine JE, Salem R, Campbell N, Schork NJ, Shiehmorteza M, Yokoo T, Chavez A, Middleton MS, Sirlin CB. Heritability of nonalcoholic fatty liver disease. *Gastroenterology* 2009; **136**: 1585-1592 [PMID: 19208353 DOI: 10.1053/j.gastro.2009.01.050]
49 **Goel A**, Gupta M, Aggarwal R. Gut microbiota and liver disease. *J Gastroenterol Hepatol* 2014; **29**: 1139-1148 [PMID: 24547986 DOI: 10.1111/jgh.12556]
50 **Bhathena J**, Martoni C, Kulamarva A, Tomaro-Duchesneau

C, Malhotra M, Paul A, Urbanska AM, Prakash S. Oral probiotic microcapsule formulation ameliorates non-alcoholic fatty liver disease in Bio F1B Golden Syrian hamsters. *PLoS One* 2013; **8**: e58394 [PMID: 23554890 DOI: 10.1371/journal.pone.0058394]

51 **Tomaro-Duchesneau C**, Saha S, Malhotra M, Jones ML, Labbé A, Rodes L, Kahouli I, Prakash S. Effect of orally administered L. fermentum NCIMB 5221 on markers of metabolic syndrome: an in vivo analysis using ZDF rats. *Appl Microbiol Biotechnol* 2014; **98**: 115-126 [PMID: 24121931 DOI: 10.1007/s00253-013-5252-8]

52 **Lear SA**, Humphries KH, Kohli S, Chockalingam A, Frohlich JJ, Birmingham CL. Visceral adipose tissue accumulation differs according to ethnic background: results of the Multicultural Community Health Assessment Trial (M-CHAT). *Am J Clin Nutr* 2007; **86**: 353-359 [PMID: 17684205]

53 **Wood NJ**. Liver: Nonobese individuals in the developing world are at risk of nonalcoholic fatty liver and liver disease. *Nat Rev Gastroenterol Hepatol* 2010; **7**: 357 [PMID: 20626072 DOI: 10.1038/nrgastro.2010.95]

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

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327