Observational Study

Medicine®

OPEN

Metabolic characteristics of obese children with fatty liver

A STROBE-compliant article

Kanglu Zhao, MD[a,b], Hongzhen Ju, MD[a], Haili Wang, Bachelor[b,c,*]

Abstract

To investigate metabolic differences between simple obese children and those comorbid with fatty liver disease.

Obese children hospitalized in our center from 2014 to 2016 were included and divided into simple obese group and obese with fatty liver group by ultrasound-based diagnosis of fatty liver. Epidemiology data and serum biochemical studies were recorded. Body Mass Index (BMI) and homeostasis model insulin resistance index (HOMA-IR) were calculated accordingly.

A total of 186 obese children were enrolled in this study, including 93 cases of obese children and 93 obese patients' comorbid with fatty liver. The proportion of male, age, waist circumference (WC), BMI, fasting blood-glucose (FBG), glycosylated hemoglobin A1c (HbA1c), fasting insulin (FINS), and HOMA-IR were significantly higher in obese patients with fatty liver ($P < .05$). Age and BMI were found to be independent risk factors for fatty liver disease (OR >1, $P < .05$).

Among obese children, male and elder patients and individuals with higher uric acid are more susceptible to fatty liver.

Abbreviations: BMI = Body Mass Index, FBG = fasting blood-glucose, FINS = fasting insulin, HbA1c = glycosylated hemoglobin A1c, HDL-C = high density lipoprotein cholesterol, HOMA-IR = homeostasis model insulin resistance index, LDL-C = low density lipoprotein cholesterol, NAFLD = non-alcoholic fatty liver disease, TC = total cholesterol, TG = triglyceride, UA = uric acid, WC = waist circumference.

Keywords: children, fatty liver disease, metabolic disorder, obesity, uric acid

Key Points

- Few studies have compared metabolic characteristics of simple obese children and those comorbid with fatty liver.
- Our study found that serum uric acid levels in children with fatty liver were significantly higher than simple obese group, indicating that uric acid might be a predictor of fatty liver in obesity.
- We further analyzed association between uric acid and body mass index, waist circumference, homeostasis model insulin resistance index, and a linear correlation was discovered.

Editor: Hirayuki Enomoto.

No author has any conflict of interest to claim.

[a] Department of Infectious Disease, The Fourth Affiliated Hospital Zhejiang University, School of Medicine, Yiwu, [b] Department of Infectious Disease, The First Affiliated Hospital Zhejiang University, School of Medicine, Hangzhou, [c] Department of Outpatient Clinic, Xiangshan People's Hospital, Ningbo, Zhejiang, China.

[*] Correspondence: Haili Wang, Department of Outpatient Clinic, Xiangshan People's Hospital, Ningbo, Zhejiang, 315700, China (e-mail: yiiic@163.com).

Medicine (2019) 98:16(e14939)

Received: 13 November 2018 / Received in final form: 22 February 2019 / Accepted: 28 February 2019

http://dx.doi.org/10.1097/MD.0000000000014939

1. Introduction

Recent years have witnessed an increase in incidence of metabolic disorders in children. In China, prevalence of overweight and obese children was elevating rapidly in these years, with an annual increase rate of 0.27% to 0.63% for overweight, and 0.10% to 0.58% for obese.[1] Obesity is a well-established risk factor for metabolic disorders such as fatty liver and diabetes. The population of children with fatty liver is growing rapidly.[2] Especially in obese children, the incidence of fatty liver in non-obese children was 0.1%, while in obese children up to 1.8%.[3]

Obesity is main manifestation of metabolic syndrome. Obese patients are more likely to develop fatty liver, insulin resistance, cardiovascular disease, cerebrovascular disease, and hypertension compared with non-obese people, causing higher casualty.[4]

As now the most common reason for chronic liver disease, fatty liver needs early intervention like exercise and lifestyle modification, and otherwise, late stage may progress to steatohepatitis, liver fibrosis, cirrhosis, and even hepatocellular carcinoma. So, early diagnosis and intervention of fatty liver are of supreme importance.

Herein, we conducted a retrospective case–control study, focusing on metabolic characteristics of fatty liver in obese children in order to obtain its predictive factors.

2. Results

2.1. General information

A total of 186 patients were included, with 93 being simple obese and 93 comorbid with non-alcoholic fatty liver disease (NAFLD). Among simple obese group, 54 were male (age from 1–16 years old, median age of 9 years old), with body mass index (BMI) of

Table 1

General characteristics and metabolic factors in obese children with/without fatty liver.

	Simple obese group ($n=93$)	Obese with fatty liver group ($n=93$)	*P* value
Gender, male	54, 58%	73, 78%	.003
Age, yr	9 (1,16)	12 (7,16)	.000
BMI, Kg/m^2	25.5 ± 3.4	28.1 ± 3.7	.000
WC, cm	83.5 ± 11.5	92.0 ± 9.9	.000
FBG, mmol/L	5.4 ± 0.5	5.7 ± 0.4	.000
HbA1c, %	5.4 (5.0, 8.0)	5.5 (4.9, 6.5)	.000
FINS, mmol/L	18.3 (5.4, 68.1)	26.9 (5.3, 97.6)	.005
HOMA-IR, mmol·mIU/L^2	4.3 (1.3, 13.5)	6.4 (1.3, 23.4)	.001
TG, mmol/L	1.00 (0.43, 4.35)	1.11 (0.40, 2.39)	.122
TC, mmol/L	4.13 ± 0.63	4.05 ± 0.83	.475
HDL-C, mmo/L	1.21 (0.69, 2.67)	1.24 (0.63, 4.88)	.539
LDL-C, mmo/L	2.30 ± 0.53	2.30 ± 0.65	.963
UA, μmol/L	322 (164, 577)	411 (232, 650)	.000

BMI = Body Mass Index, WC = waist circumference, FBG = fasting blood glucose, FINS = fasting insulin, HOMA-IR = homeostasis model insulin resistance index, TG = triglyceride, TC = total cholesterol, HDL-C = high density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol, UA = uric acid.

25.5 ± 3.4 Kg/m^2 and waist circumference (WC) of 83.5 ± 11.5 cm. Among obese with fatty liver group, 73 were male (aged 7–16 years, median age 12 years old), with BMI of 28.1 ± 3.7Kg/m^2 and WC 92.0 ± 9.9 cm. Compared with simple obese group, obese with fatty liver group were elder, male predominant, significantly higher BMI and WC ($P < .05$) (Table 1, Fig. 1).

2.2. Blood glucose, blood lipid, and uric acid (UA)

Fast blood glucose (FBG), glycosylated hemoglobin A1c (HbA1c), fast insulin (FINS), homeostasis model insulin resistance index (HOMA-IR), triglyceride (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), UA in 2 groups referred to Table 1 and Figure 1. The levels of FBG, HbA1c, FINS, HOMA-IR, and UA in fatty liver group were significantly higher than those in simple obese group ($P < .05$). There were no significant differences in TG, TC, HDL-C, and LDL-C between 2 groups.

2.3. Predicting factors of fatty liver

Previous studies have shown obesity, dyslipidemia, IR, WC, BMI, diabetes, hypertension, coronary heart disease, atherosclerosis, high-fat diet are predictors for fatty liver.[5,6] The relationship between sex, age, BMI, WC, HOMA-IR, TG, TC, HDL-C, LDL-C, UA, and fatty liver was analyzed using multivariable logistic regression (Table 2). The results showed that age, UA was positively associated with fatty liver in obese children. Regression equation was as follows: Y (children with fatty liver) = 0.525 × sex (male and female) + 0.201 × age (years) + 0.065 × BMI (Kg/m^2) + 0.105 × HOMA-IR (mmol·mIU/L^2) + 0.165 × TG (mmol/L) −0.468 × TC (mmol/L) + 1.191 × HDL-C (mmol/L) + 0.369 × LDL-C (mmol/L) + 0.004 × UA (μmol/L).

Table 2

Predicting factors of fatty liver in obese children.

Predictors	B	SE	Wald	*P* value	OR value	95% CI
Gender	0.525	0.391	1.803	.179	1.691	0.786∼3.640
Age	0.201	0.091	4.818	.028	1.222	1.022∼1.462
BMI	0.065	0.087	0.568	.451	1.067	0.901∼1.265
WC	0.000	0.031	0.000	.992	1.000	0.940∼1.063
HOMA-IR	0.105	0.054	3.811	.050	1.111	1.000∼1.234
TG	0.165	0.385	0.183	.668	1.179	0.554∼2.510
TC	−0.468	0.546	0.735	.391	0.626	0.215∼1.825
HDL-C	1.191	0.793	2.258	.133	3.290	0.696∼15.554
LDL-C	0.369	0.595	0.385	.535	1.446	0.451∼4.640
UA	0.004	0.002	4.131	.042	1.004	1.000∼1.008

BMI = Body Mass Index, WC = waist circumference, HOMA-IR = homeostasis model insulin resistance index, TG = triglyceride, TC = total cholesterol, HDL-C = high density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol, UA = uric acid.

2.4. The relationship between UA and other indicators

In order to further analyze the relationship between UA and other metabolic factors, study population was categorized into 4 groups according to UA levels (Table 3, Fig. 2). The results showed that as the level of UA increased in children, the significantly higher incidence of fatty liver, the proportion of male, the level of BMI, WC and HOMA-IR ($P < .05$) was elevated, while TC and TG were similar among groups ($P > .05$). Further linear correlation analysis showed that UA was positively related with BMI, WC, and HOMA-IR (r = 0.468, 0.477, and 0.259, P values were less than .05), but not TC (r = −0.06, $P = .42$).

3. Discussions

This study showed that male obese children with older age are more prone to fatty liver. Compared with simple obese children, obese children with fatty liver had higher WC and BMI levels. IR

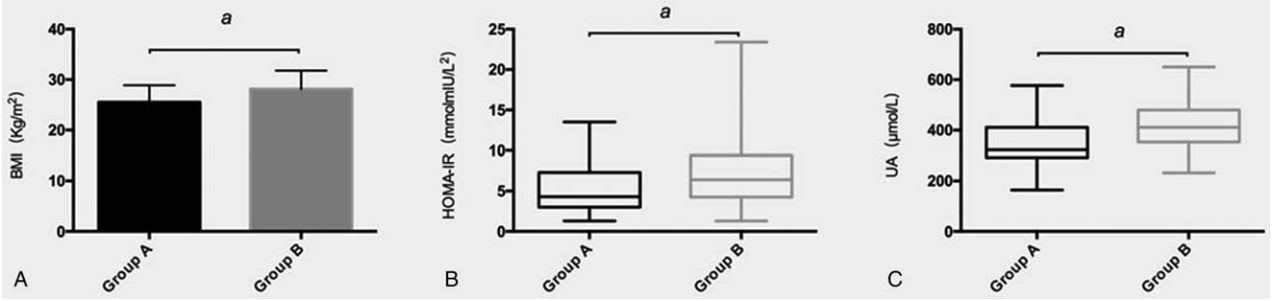

Figure 1. Comparison of BMI (A), HOMA-IR (B), and UA (C) in 2 groups. Group A: simple obesity; Group B: obesity with fatty liver.[a]$P < .05$. BMI = Body Mass Index, HOMA-IR = homeostasis model insulin resistance index, UA = uric acid.

Table 3

Uric acid is associated with other metabolic factors.

UA/100 (μmol/L)	Fatty liver (*n*/*N*, *n*%)	BMI (Kg/m^2)	WC (cm)	HOMA-IR (mmol·mIU/L^2)	TC (mmol/L)
UA <3	14/40, 25.0%	24.7±3.2	81.5±9.2	3.9 [1.4,10.6]	4.13±0.61
3 ≤UA<4	29/69, 42.0%	26.1±3.1	85.1±11.0	5.6 [1.3,23.4]	4.15±0.77
4 ≤UA<5	33/53, 62.3%	27.9±3.6	91.3±10.5	5.6 [1.3,21.0]	3.98±0.81
UA ≥5	17/24, 70.8%	29.9±3.4	97.9±9.6	7.8 [1.5,16.7]	4.10±0.64
F value		14.854	16.424		0.612
x^2 value	12.709			13.764	
P value	.005	.000	.000	.003	.608

BMI = Body Mass Index, WC = waist circumference, HOMA-IR = homeostasis model insulin resistance index, TC = total cholesterol, UA = uric acid.

is more serious in obese with fatty liver children. Multi-variable Logistic regression indicated role of age and UA as independent risk factors for fatty liver.

Childhood fatty liver is now booming and showed different pattern in disease presentation. Complications of children NAFLD are relatively simple, that a meta-analysis showed carotid plaque was more prevalent in adults than in children.[7] In addition, childhood fatty liver and adult fatty liver may respond differently to treatment. Adult NAFLD is more responsive to insulin sensitizers and Vitamin E than children.[8] There are also differences in histology in adults and children.[9] Our study analyzed the metabolic characteristics of fatty liver in children, to provide preliminary data on diagnostic method and therapeutic target in this concern.

Previous studies have shown certain differences in the metabolic characteristics between NAFLD children and simple obese children, especially in western countries. A study in Norway reported NAFLD children had significantly lower insulin-like growth factor 1 standard deviation score (IGF-1 SDS), higher BMI, HOMA-IR, and UA than simple obese children, and IGF-1, BMI, HOMA-IR, and UA were useful markers of NAFLD in obese children and adolescents.[10] As newly established component of metabolic syndrome, UA served as a predictor for NAFLD as well. A meta-analysis showed that higher UA levels led to an increased risk of metabolic syndrome, and showed a linear dose-response relationship.[11] Furthermore, they also showed a causal relationship between UA and childhood NAFLD.[12]

As early diagnosis and intervention is of supreme importance in NAFLD, screening method is in urgent need. In our study, we identified age and serum UA levels as predictors for fatty liver in obese children. More comprehensively, Chernyak et al also screened genomic, proteomic and metabolic predictors of nonalcoholic fatty liver disease and is covered that reducing

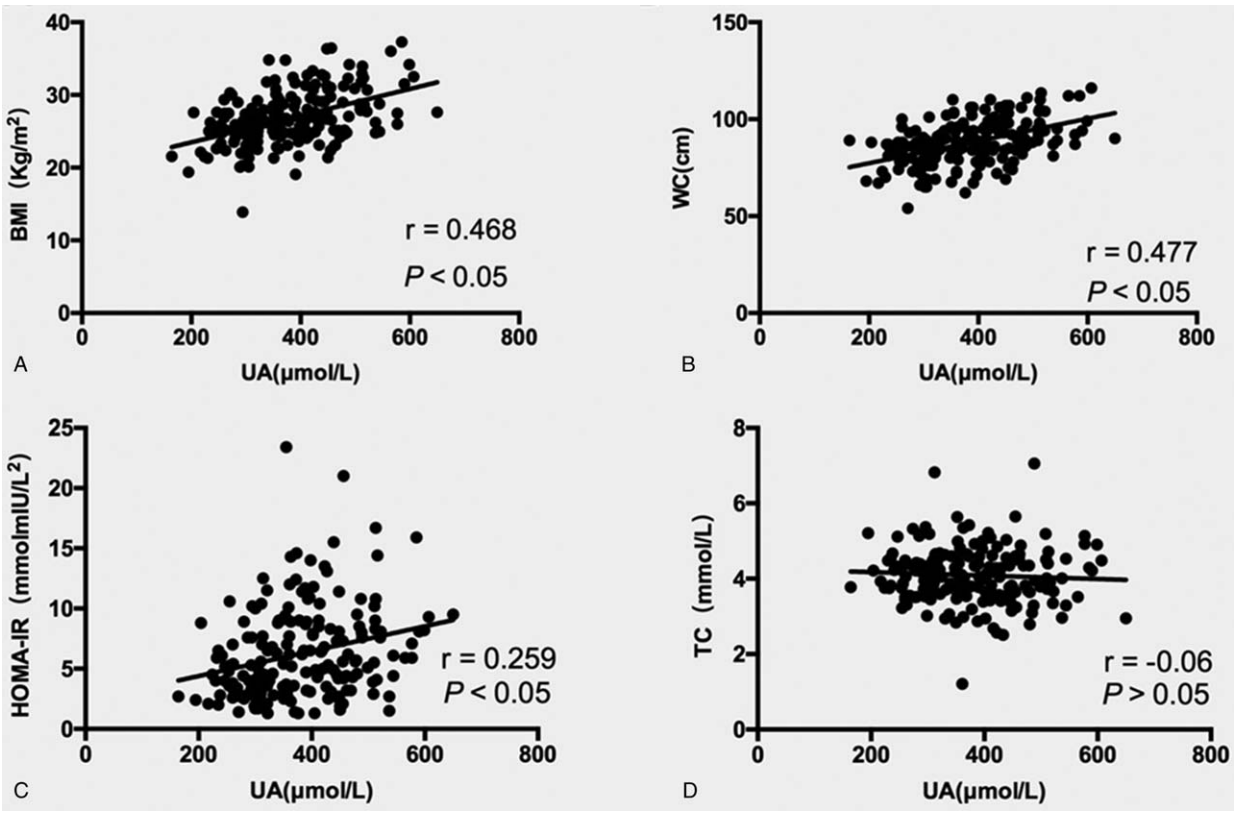

Figure 2. Association between UA and BMI (A), WC (B), HOMA-IR (C), TC (D). BMI = Body Mass Index, HOMA-IR = homeostasis model insulin resistance index, TC = total cholesterol, UA = uric acid, WC = waist circumference.

concentration of adiponectin, increasing level of glucose, TGs, TNF-α and fatty acid transporter L-FABP might be important manifestation of NAFLD.[13] Furthermore, Li et al found female, general and abdominal obesity, and hypertension were independent predictors for IR in NAFLD patients.[14] Dixon's study showed insulin resistance and systemic hypertension, features of the metabolic syndrome, are independently associated with advanced forms of NAFLD.[15]

However, this study has some limitations. First, although ultrasound-based diagnosis of NAFLD is widely accepted under clinical circumstances as a noninvasive cost-effective screening for NAFLD with sensitivity of 89% and specificity of 93%, it cannot replace pathological study as gold standard in disease diagnosis.[16] Second, as the nature of retrospective case-control study, no causal relationship can be drawn from current analysis.

In summary, compared with simple obese children, obese children with fatty liver showed greater insulin resistance and higher levels of UA. Male, elder children are more prone to fatty liver. Serum UA was positively associated with BMI, WC, and HOMA-IR. Age and UA are independent risk factors for fatty liver in obese children, indicating a predictive role in NAFLD screening.

4. Methods

4.1. Study population

A total of 186 obese children under16 years old who were hospitalized in the First Affiliated Hospital of Zhejiang University from January 2014 to December 2016 were enrolled. Obese children were divided into simple obese group and obese with fatty liver group. This study was approved by the Hospital Ethics Committee and performed in accordance with Declaration of Helsinki. In accordance with law, as all participants were under the age of 18 years, informed consent was obtained from a parent and/or legal guardian before their inclusion in the study.

4.2. Inclusion and exclusion criteria

BMI was defined as body weight (kg) divided by square of height (meter). BMI greater than 2 standard deviation of age, sex-matched average was defined as obesity.[17] NAFLD: according to JAMA NAFLD Guidelines[6], liver steatosis with unknown reason (viral hepatitis, drug-induced liver injury, total parenteral nutrition, hepatolenticular degeneration, autoimmune liver disease can lead to fatty liver-specific disease, etc) can be defined as NAFLD. Abdominal ultrasonography was performed for every subject by 2 experienced sonologists using Toshiba Nemio 20 sonography machine with 3.5-MHz probe (Toshiba, Tokyo, Japan). In addition, the severity of NAFLD was classified into 3 grades (mild, moderate, and severe) according to the serum level of alanine aminotransferase. Inclusion criteria were as follows:

(1) Diagnostic as obesity;
(2) Less than 16 years old;
(3) Without secondary obese situations.

Exclusion criteria included:

(1) with incomplete or inaccessible medical records;
(2) with admission of confounding medications (such as metformin, liver protective agents, statins, etc) during hospitalization;
(3) unable to give informed consent.

4.3. Clinical evaluation

Clinical evaluations were performed as follows. Demographic details, medical history, and health status of each participate were obtained and recorded by a trained physician. Individual standing height and body weight with light clothes and without shoes were measured and recorded. BMI was calculated and obtained as body weight (kg) divided by square of height (meters). Fasting blood samples were taken from each participant on 08:00 AM and then processed for biochemical analysis. The biochemical meters, including liver enzymes, serum lipids, fast blood sugar, as well as UA, were measured by a Hitachi 7600 autoanalyzer (Hitachi, Tokyo, Japan) following standard protocols. HOMA-IR was calculated as follows: HOMA-IR = fasting blood-glucose (FBG, mmol/L) × fasting insulin (FINS, mIU/L)/22.5.HOMA-IR greater than 1 mmol·mIU/L^2indicated presence of insulin resistance (IR)[18].

5. Statistical analysis

SPSS 22.0 software (SPSS Inc., Chicago, IL) was adopted in statistical analysis. Data normality was defined using a single sample K–S test. We expressed continuous variables as mean and standard deviation and compared through using Student *t* test or Mann–Whitney *U* test. We compared categorical variables using chi-square test. Binary logistic regression analysis was applied to define NAFLD predictive factors in obesity. $P < .05$ was considered statistically significant.

Author contributions

Kanglu Zhao and Hongzhen Ju proposed with the initial idea and designed the study procedures. Kanglu Zhao collected populational and clinical data and conducted statistical analysis. Guangyu Huang helped made revision to manuscript. Xiawei Huang provided expertise and supervised revision process. Haili Wang supervised and provided consult during the whole study.
Conceptualization: Kanglu Zhao, Hongzhen Ju.
Data curation: Kanglu Zhao.
Supervision: Haili Wang.

References

[1] Wang S, Dong YH, Wang ZH, et al. Trends in overweight and obesity among Chinese children of 7-18 years old during 1985-2014. Zhonghua yu fang yi xue za zhi Chin J Prevent Med 2017;51:300–5.
[2] Fan JG. Epidemiology of alcoholic and nonalcoholic fatty liver disease in China. J Gastroenterol Hepatol 2013;28(suppl 1):11–7.
[3] Meng L, Luo N, Mi J. Impacts of types and degree of obesity on non-alcoholic fatty liver disease and related dyslipidemia in Chinese school-age children. Biomed Environ Sci BES 2011;24:22–30.
[4] EASL, EASD, EASO. Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016;64:1388–402.
[5] Alkassabany YM, Farghaly AG, El-Ghitany EM. Prevalence, risk factors, and predictors of nonalcoholic fatty liver disease among schoolchildren: a hospital-based study in Alexandria, Egypt. Arab J Gastroenterol Off Publ Pan-Arab Assoc Gastroenterol 2014;15:76–81.
[6] Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. Gastroenterology 2012;142:1592–609.
[7] Madan SA, John F, Pyrsopoulos N, et al. Nonalcoholic fatty liver disease and carotid artery atherosclerosis in children and adults: a meta-analysis. Eur J Gastroenterol Hepatol 2015;27:1237–48.
[8] Hsu E, Murray K. Is nonalcoholic fatty liver disease in children the same disease as in adults. Clin Liver Dis 2012;16:587–98.

[9] Kleiner DE, Makhlouf HR. Histology of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis in adults and children. Clin Liver Dis 2016;20:293–312.
[10] Liang S, Cheng X, Hu Y, et al. Insulin-like growth factor 1 and metabolic parameters are associated with nonalcoholic fatty liver disease in obese children and adolescents. Acta Paediatr Oslo, Norway: 1992 2017; 106:298–303.
[11] Yuan H, Yu C, Li X, et al. Serum uric acid levels and risk of metabolic syndrome: a dose-response meta-analysis of prospective studies. J Clin Endocrinol Metabol 2015;100:4198–207.
[12] Sullivan JS, Le MT, Pan Z, et al. Oral fructose absorption in obese children with non-alcoholic fatty liver disease. Pediatr Obes 2015;10:188–95.
[13] Chernyak OO, Sentsova TB, Vorozhko IV, et al. Genomic, proteomic and metabolomic predictors of nonalcoholic fatty liver disease development in obese patients. Part I. Vopr Pitan 2015;84:18–24.
[14] Li M, Zhang S, Wu Y, et al. Prevalence of insulin resistance in subjects with nonalcoholic fatty liver disease and its predictors in a Chinese population. Dig Dis Sci 2015;60:2170–6.
[15] Dixon JB, Bhathal PS, O'Brien PE. Nonalcoholic fatty liver disease: predictors of nonalcoholic steatohepatitis and liver fibrosis in the severely obese. Gastroenterology 2001;121:91–100.
[16] Joseph AE, Saverymuttu SH, al-Sam S, et al. Comparison of liver histology with ultrasonography in assessing diffuse parenchymal liver disease. Clin Radiol 1991;43:26–31.
[17] Cole TJ, Lobstein T. Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. Pediatr Obes 2012; 7:284–94.
[18] Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–9.