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Original Article

Prevalence and risk factors of fatty liver disease in urban adult residents of Qingdao: an epidemiological survey

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Abstract: Objective: This study was an epidemiological survey aiming to investigate the prevalence and risk factors of fatty liver disease (FLD) in urban adult residents of Qingdao, Shandong, China. Methods: Multistage stratified and cluster sampling was performed to randomly select residents older than 20 years from Shinan District, Shibei District and Sifang District of Qingdao. Questionnaire investigation, physical examination and detection of blood liver biochemical parameters, fast blood glucose, blood lipid and trioxypurine, and ultrasonography of the liver, gallbladder and spleen were performed. Results: A total of 3998 adult residents were included in this study. There were 1967 men and 2031 women with an average age of 47.11±15.08 years (range: 20-82 years). FLD was found in 1353 residents with the prevalence of 33.84%. In addition, non-alcoholic fatty liver disease (NAFLD) and alcoholic fatty liver disease (AFLD) were found in 1134 (28.36%) and 219 (5.48%) residents, respectively. After adjustment based on the age and gender constituents of Chinese residents in 2000, the overall standardized prevalence of FLD, NAFLD and AFLD was 30.57%, 25.25% and 5.32%, respectively. Binary logistic regression analysis showed the waist-to-hip ratio, triglyceride, low density lipoprotein cholesterol, body mass index, trioxypurine and aspartate aminotransferase were closely related to FLD. Conclusion: The prevalence of FLD (mainly NAFLD) is relatively high in urban adult residents of Qingdao (30.57%). Obesity, hyperuricemia and dyslipidemia are major risk factors for FLD.

Keywords: Fatty liver disease, prevalence, risk factor, obesity, hyperuricemia, dyslipidemia

Introduction

Fatty liver disease (FLD) is one of the most common liver diseases causing liver dysfunction in Western countries. Previously, FLD was regarded as a reversible disease that does not threaten the human health. However, robust evidence indicates that FLD may progress into end-stage liver diseases, such as liver cirrhosis, liver failure, and even hepatocellular carcinoma (HCC) [1]. The incidence of FLD is increasing in developing countries, especially in cities where the diet habits and living lifestyle have changed [2]. As one of chronic diseases, FLD has attracted increasing attention due to its influence on human health in developing countries including China. In the past decade, many epidemiological surveys on FLD have been conducted in China, but most focus on special populations such as healthy subjects receiving routine physical examination. In available studies, two focus on the general population: one reported the incidence of FLD in general population of Shanghai, a coastal city of east China in 2005 [3] and the other in general population of Beijing, an inland city of north China [4]. As is known to all, there are differences in the diet habitants and lifestyle between north and south areas and between inland and coastal cities of China. Findings from above two studies fail to reflect the epidemiology of FLD in Qingdao, a coastal city of north China. In addition, the dietary structure has changed significantly with the improvement of economic status, and animal foods have increased in daily diet in recent years. Moreover, with the increase in the communication with Western countries, the lifestyle and living habits of some Chinese may also be influenced by those of Western countries. These may affect the prevalence of

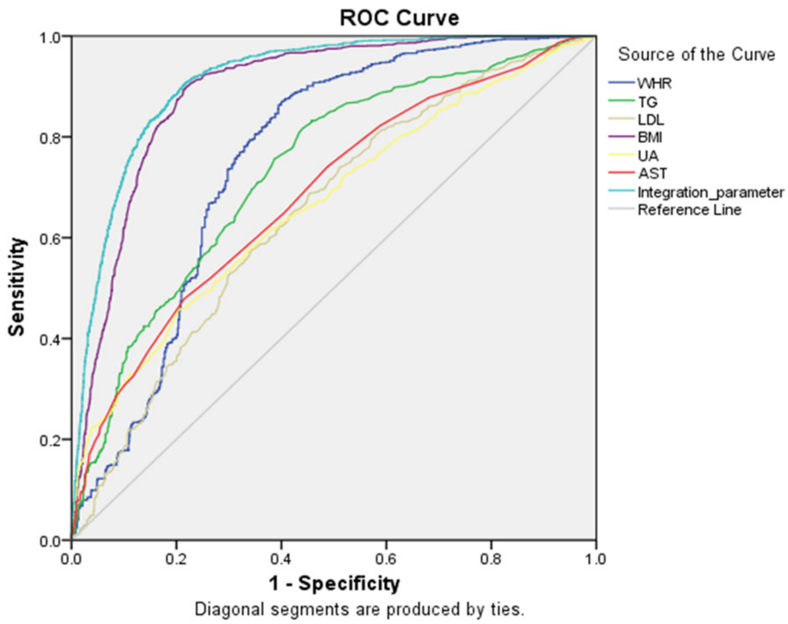

Figure 1. Receiver operating characteristic curve of screening factors in diagnosing FLD. WHR, waist/hip ratio; BMI, body mass index; TG, triglyeride; UA, uric acid; LDL, low-density lipoprotein; AST, aspartate aminotransferase; FLD, fatty liver disease. Integrated parameter derived from optimal logistic regression equation: -25.826 + WHR * 2.322 + BMI * 0.742 + TG (mmol/L) * 0.374 + LDL (mmol/L) * 0.292 + AST (U/L) * 0.043 + UA (mmol/L) * 0.005.

FLD [4]. Therefore, this epidemiological survey was carried out in order to accurately determine the prevalence and risk factors of FLD in urban adult residents of Qingdao by multistage-stratified randomization and cluster sampling, and the prevalence and risk factors of FLD were explored in these subjects.

Materials and methods

Ethics

This study was approved by the Ethics Committee of the Sixth People' Hospital of Qingdao. Informed consent was obtained from each participant before study.

Sampling

Qingdao was composed of seven districts and five county-level cities with the resident population of 8.7151 millions in 2010. The demographic composition is similar among these districts in gender, age, occupation, etc. On the basis of multistage stratified cluster sampling, 3 districts were selected at the center of Qingdao. Then, two neighborhood committees were randomly chosen from each street committee of Qingdao, and 60-80 subjects from each neighborhood committee. Currently, the neighborhood committee is the most primary organization in China. Residents chosen randomly from them can represent the general condition of these districts (**Figure 1**).

In the present epidemiological study, sample size was calculated according to the prevalence and risk factors of FLD in a general adult population of Shanghai [3] and the age and gender constituents were determined on the basis of a population survey of the sixth national population census in Qingdao.

Questionnaire and physical examination

The contents of questionnaire for the epidemiology of FLD included general situation, education level, occupation, income, history of chronic diseases (autoimmune hepatitis, primary biliary cirrhosis, drug-induced liver injury, chronic hepatitis C and chronic hepatitis B), history of drinking and smoking, intensity and duration of daily activity and demographics. The survey was carried out by well-trained physicians of the Sixth People's Hospital of Qingdao from January 2013 to December 2014.

Physical examination was performed by well-trained clinicians from the Sixth People's Hospital of Qingdao after filling in the questionnaire form. The somatological parameters included height, bodyweight, waist circumference, hip circumference, waist-to-hip ratio (WHR), body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) and were recorded by well-trained clinicians.

Collection of blood samples and laboratory tests of biochemical parameters

Fasting blood samples were collected in the morning from each participant. Then, the serum

Table 1. Individuals recruited into present study in different age groups

Age (year)	Male(n)		Female (n)		Total (n)	
	Sum	FLD	Sum	FLD	Sum	FLD
20-29	286	72 (25.17%)	310	30 (9.68%)	596	102 (17.11%)
30-39	413	169 (40.92%)	421	59 (14.01%)	834	228 (27.34%)
40-49	425	200 (47.06%)	437	123 (28.15%)	862	323 (37.47%)
50-59	342	171 (50.00%)	356	125 (35.11%)	698	296 (42.41%)
60-69	314	130 (41.40%)	316	135 (42.72%)	630	265 (42.06%)
≥70	187	65 (34.76%)	191	74 (38.74%)	378	139 (36.77%)
total	1967	807 (41.03%)	2031	546 (26.88%)	3998	1353 (33.84%)

Table 2. Prevalence of fatty liver disease (FLD)

Age (years)	Total (n)		Male (n)		Female (n)		*P*
	FLD	non-FLD	FLD	non-FLD	FLD	non-FLD	
20-29	102	494	72	214	30	280	<0.0001
30-39	228	606	169	244	59	362	<0.0001
40-49	323	539	200	225	123	314	<0.0001
50-59	296	402	171	171	125	231	=0.0001
60-69	265	365	130	184	135	181	=0.7371
70+	139	239	65	122	74	117	=0.4219
Total	1353	2645	807	1160	546	1485	<0.0001

Notes: Significant difference was observed in the prevalence of FLD between men and women younger than 60 years, but not in those older than 60 years.

was separated and processed for the detection of fast blood glucose (FBG), triglyceride (TG), total cholesterol (TCh), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), apolipoprotein-A (APOA), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transpeptidase (GGT), total bilirubin (TB), alkaline phosphatase (AKP), total protein (TP), albumin (ALB) and uric acid (UA) with a biochemical automatic analyzer (Olympus 2700, Japan).

Transabdominal ultrasound examination

The liver was examined by using ultrasound based on the Guideline for the Diagnosis and Treatment of Nonalcoholic Fatty Liver Diseases [5, 6] developed by the Chinese Society of Hepatology. Ultrasound examination was performed by well trained physicians in the Department of Ultrasound of the Sixth People's Hospital with GE Logiq 100 pro Portable Ultrasound System (frequency of probe: 3.5 MHz). At the same time, ultrasound examination of the liver, gallbladder, pancreas, spleen and kidney was also conducted. Fasting participants were detected by ultrasonography, and FLD was diagnosed according to the criteria for alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD) developed by the Fatty Liver Disease and Alcoholic Liver Disease Group, Chinese Society of Hepatology, Chinese Medical Association [5, 6]. Diagnostic criteria for FLD are as follows: dispersion enhancement of near-field echo (echo of the kidney and spleen is lower than that of the liver) and gradually fading far-field echo. The ALD and NAFLD were diagnosed according to the above guidelines: when patients had a history of heavy drinking (drinking for more than 5 years, and amount of alcohol of ≥40 g/d in males and ≥20 g/d in females), ALD was considered; when there was no history of heavy drinking, NAFLD was diagnosed [6].

Liver ultrasound examination was used for population screening because the liver biopsy has a great difficulty in its application in large-scale community epidemiological investigation, although it is a diagnostic golden standard in FLD.

Statistical analysis

The medians, means and standard deviations (SDs), the proportions and ranges were calculated when appropriate. Fisher's exact test was used for categorical variables and the Mann-Whitney U or Kruskal-Wallis H test for continuous variables. Parameters were subjected to binary logistic regression analysis and the odds ratio was calculated. Then, parameters with significant difference were subjected to multivariate analysis. The receiver operating characteristic (ROC) curve was delineated, and the area under curve (AUC) was calculated to evaluate the predictive value of FLD-related risks. Statistical analysis was performed with SPSS

Table 3. Characteristics of participants with and without fatty liver disease (FLD)

Parameters	FLD (n=1353)	Non-FLD (n=2645)	P
Age, years (mean±SD)	50.45±13.89	45.40±15.38	<0.001
Sex (male:female), n	807:546	1160:1485	<0.001
Weight, kg (mean±SD)	76.41±8.15	65.32±8.70	<0.001
BMI, kg/m^2 (mean±SD)	27.03±1.84	23.51±2.36	<0.001
Waist circumference (cm) (mean±SD)	94.84±5.80	84.36±8.96	<0.001
Hip circumference (cm) (mean±SD)	102.54±4.60	96.73±5.52	<0.001
WHR (mean±SD)	0.93±0.05	0.87±0.07	<0.001
SBP (mmHg) (mean±SD)	132.60±15.60	122.91±18.52	<0.001
DBP (mmHg) (mean±SD)	85.40±9.28	80.33±9.80	<0.001
HR (bpm) (mean±SD)	74.13±5.96	71.96±5.00	<0.001
ALT (U/L) (mean±SD)	34.21±28.49	21.65±13.31	<0.001
AST (U/L) (mean±SD)	28.17±14.37	21.85±7.03	<0.001
TG (mmol/L) (mean±SD)	2.27±1.20	1.54±0.85	<0.001
TCh (mmol/L) (mean±SD)	5.74±0.99	5.32±1.08	<0.001
HDL-C (mmol/L) (mean±SD)	1.48±0.30	1.60±0.32	<0.001
LDL-C (mmol/L) (mean±SD)	3.29±0.79	2.89±0.82	<0.001
UA (mmol/L) (mean+SD)	368.57±89.83	325.06±72.21	<0.001
FBG (mmol/L) (mean±SD)	5.79±2.09	5.1 7±1.55	<0.001
APOA (g/L) (mean±SD)	1.21±0.27	1.34±0.27	<0.001
Heavy drinker (%)	219/1353 (16.19%)	324/2645 (12.25%)	0.0006
Diabetes (%)	349/1353 (25.79%)	83/2645 (3.14%)	<0.001
Obesity (%)	187/1353 (13.82%)	145/2645 (5.48%)	<0.001

Notes: SD, standard deviation; BMI, body mass index; WHR, waist/hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; ALT, aminotransferase; AST, aspartate aminotransferase; TG, triglyeride; TCh, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LD-CL, low-density lipoprotein cholesterol; UA, uric acid; FBG, fasting blood glucose; APOA, apolipoprotein-A; Diabetes, FBG >7.0 mmol/L; Obesity, BMI ≥28 kg/m^2.

version 20.0. A value of two tailed P<0.05 was considered statistically significant.

Results

Demographics

The pre-designed sample size was 4000 individuals older than 20 years. Finally, a total of 3998 participants were recruited into present study. There were 1967 males and 2031 females with the male to female ratio of 0.97. The mean age was 47.11±15.08 years (range: 20-82 years) (**Table 1**).

Prevalence of FLD

A total of 1353 residents were diagnosed as having FLD with the prevalence of 33.84%. In addition, NAFLD and AFLD were found in 1134 (28.36%) residents and 219 (5.48%) residents, respectively. After adjustment based on the age and gender constituents of Chinese residents in 2000, the overall standardized prevalence of FLD, NAFLD and AFLD was 30.57%, 25.25% and 5.32%, respectively in Qingdao. Moreover, FLD was found in 807 (41.03%) men and 546 (26.88%) women, showing significant difference between men and women (P<0.001). Significant difference was observed in the prevalence of FLD between men and women younger than 60 years, but not in those older than 60 years (**Table 2**). In addition, the prevalence of FLD increased over age (P<0.001), and reached a peak in participants aged 50-60 years, and there is no significant difference between males and females in this trend (**Table 2**).

Risk factors of FLD

The demographics, somatological and biochemical parameters were compared between FLD subjects and non-FLD subjects. Results

Table 4. Logistic regression analysis of risk factors of FLD

Risk factors	β	SE	P	OR	95% CL for OR
WHR	2.322	0.906	0.010	10.201	1.726-60.282
TG	0.374	0.049	0.000	1.454	1.320-1.600
LDL	0.292	0.058	0.000	1.3391	1.194-1.500
UA	0.005	0.001	0.000	1.005	1.003-1.006
BMI	0.742	0.030	0.000	2.099	1.980-2.225
AST	0.043	0.005	0.000	1.043	1.032-1.055
CONSTANT	-25.826	0.987	0.000	0.000	

Notes: Results showed WHR, BMI, TG, LDL-C, AST and UA were closely related to FLD.

Table 5. AUC of risk factors in the diagnosis of FLD

	AUC	SE	P	95% CI for AUC
WHR	0.756	0.008	<0.001	0.741-0.770
TG	0.734	0.008	<0.001	0.717-0.750
BMI	0.891	0.005	<0.001	0.881-0.901
UA	0.666	0.009	<0.001	0.648-0.684
LDL	0.649	0.009	<0.001	0.632-0.667
AST	0.686	0.009	<0.001	0.668-0.703
Integrated parameter	0.913	0.05	<0.001	0.904-0.922

Notes: Statistical significance implies that the corresponding AUC was significantly different from 0.5. Integrated parameter derived from optimal logistic regression equation: -25.826 + WHR * 2.322 + BMI * 0.742 + TG (mmol/L) * 0.374 + LDL (mmol/L) * 0.292 + AST (U/L) * 0.043 + UA (mmol/L) * 0.005. AUC, area under the curve; CI, confidence interval; WHR, waist/hip ratio; BMI, body mass index; TG, triglyeride; UA, uric acid; LDL, low-density lipoprotein; AST, aspartate aminotransferase; FLD, fatty liver disease; SE, standard error.

showed that the body weight, BMI, waist circumference, hip circumference, WHR, SBP, DBP, serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST), FBG, TG, TCh, HDL-C, LDL-C and UA in FLD subjects were significantly higher than in non-FLD subjects (**Table 3**).

Binary logistic regression model was used to analyze the independent risk factors for FLD. A total of 20 parameters in the univariate analysis were recruited into the stepwise regression analysis model. Results showed WHR, BMI, TG, LDL-C, AST and UA were closely related to FLD (**Table 4**). There was significant relationship between WHR and FLD (OR=10.201). These risk factors (WHR, BMI, TG, LDL-C, AST and UA) and integrated parameter were independent risk factors of FLD based on the optimal logistic regression equation and could be used as screening factors of FLD for delineating the ROC curve (**Figure 1**). In these parameters, the largest AUC was found in the integrated parameter (0.913), followed by BMI (AUC=0.891), WHR (AUC=0.756) and TG (AUC=0.734), showing an acceptable predictive value. The AUC of remaining parameters was lower than 0.7, indicating a poor diagnostic value (**Table 5**).

Discussion

The prevalence of NAFLD varies in different countries because of the differences in the population, sample size and methodology [4]. The prevalence of NAFLD is 20-24% in adults [7, 8] and 15-20% in children [9] in Europe. In two large epidemiological studies on FLD in United States, magnetic resonance mass spectrometry (MRS) showed that the prevalence of FLD was 31% in 1825 participants, and NAFLD morbidity was only 5.5% in subjects with elevated liver enzyme of unknown cause [10, 11]. A recent study on the epidemiology of NAFLD in middle-aged population indicates that the prevalence of NAFLD and NASH is 46% and 12.2%, respectively [12]. In general population, however, the prevalence of NAFLD in Asia is 8-30% [2, 13-16]. Wong and his colleagues used MRS to study the prevalence of NAFLD in general Hong Kong Chinese population, and found that the prevalence of NAFLD was 27.3% (95% confidence interval (CI): 24.5% to 30.2%) [17]. The prevalence of FLD is increasing with the improvement of economic status and the change in living style in China, especially in large cities. In 2005, an epidemiological study showed that the prevalence of NAFLD was 15.35% in Shanghai [3]. A cohort study in 2003 showed that the prevalence of NAFLD was 16.3% in Guangzhou, a city of south China [14], but it was as high as 20.5% in 2008 [18]. A study in 2010 indicated that the prevalence of FLD was 35.1% in Beijing residents, which was higher than previously reported [4]. These findings show that the prevalence of FLD is still on the rise. In addition, there is evidence showing that the change in the prevalence of FLD is parallel to that of obesity in Chinese adults in recent years [19, 20]. The overall prevalence of overweight and obesity (BMI ≥ 24 kg/m^2) was

23.2% (35.6% in large cities) in 2002 [19], and as high as 42.6% (48.1% in large cities) in 2010 [20]. This explained the differences in the prevalence of FLD in 2005 in Shanghai, 2010 in Beijing and 2013-2014 in Qingdao. The rapid rise in the prevalence of overweight, obesity and FLD may be ascribed to the change in the dietary habit in past 3 decades. The traditional diet in Chinese has changed since 1989, the plant food consumption reduces and the animal food consumption increases significantly. A more obvious change is the meat consumption in males and females which increases to 141.54±125.2 g/d and 118.4±111.8 g/d, respectively in 2006 from 97.0±111.5 g/d and 80.2±97.0 g/d, respectively in 1989 [21]. At the same time, people in Qingdao enjoy eating seafood and drinking beer.

In the present study, the ultrasound examination of the liver was employed for population screening as recommended by the Guidelines for the Diagnosis and Treatment of Nonalcoholic Fatty Liver Disease [5, 6] developed by the Chinese Society of Hepatology because liver biopsy is infeasible for large-scale epidemiological survey although it is the golden standard for the diagnosis of FLD. However, ultrasound can only diagnose FLD, and can not evaluate the cause of FLD. Thus, the questionnaire survey was conducted to collect information on the medical history and history of alcohol use. Thus, this might underestimate the prevalence of NAFLD, and the true prevalence of NAFLD might be higher than that in the present study, which was a main limitation of our study. In addition, participants were recruited from the central urban districts, and the prevalence of FLD in the suburban of Qingdao needs to be further studied.

In the present study, univariate analysis and binary logistic regression analysis showed WHR, BMI, UA, TG, LDL-C and AST were closely associated with FLD. This suggests that the main risk factors of FLD include obesity, hyperuricemia and dyslipidemia, which is in line with the previously reported [22-27]. In our study, the relationship between WHR and FLD was the most powerful, and the relative risk was 10.201. When compared with waist circumference, hip circumference and BMI, WHR was better in predicting FLD. These have been reported in previous epidemiological studies in Fujian and Beijing [4, 28]. In our study, results showed WHR, BMI, UA, TG, LDL-C and AST could be used to evaluate the risk for FLD but alcohol intake was not a risk factor of FLD because intemperants in general residents of Qingdao are rare. The long-term heavy drinking was not the main risk factors of FLD by binary logistic regression analysis in our study. The prevalence of hyperuricemia in Qingdao is higher, and hyperlipidemia, overweight and other factors are related to hyperuricemia [29]. A cohort study reports that serum uric acid is an independent predictor for ultrasonographically detected FLD even in normal- weight men [30]. Moreover, UA, TG and LDL-C are predictors of FLD [30-32]. There was significant difference in serum AST between subjects with FLD and without FLD in our study, which may be associated with latent multi-organ injury including the heart, liver, kidney, etc as a result of obesity, hyperuricemia and dyslipidemia because AST mainly exists in the heart, liver, kidney and other organs [33]. A recent study showed that the age, BP, BMI, ALT, AST, SCr, FBG, TC, TG, LDL-C and SUA in subjects with NAFLD were significantly higher than in those without NAFLD, but the HDL-C, drinking and exercise were relatively low in NAFLD subjects [34]. These results suggest that these factors are closely associated with the risk for NAFLD. Notably, hyperuricemia was found to be an important risk factor for NAFLD [34]. In addition, TG, UA and AST were found to increase with the increase in UA, and there was an independent association of increased serum UA with the prevalence and severity of ultrasound-diagnosed NAFLD in a large population of non-diabetic US adults [35]. The AUC of WHR, BMI, UA, TG, LDL-C and AST was 0.756, 0.891, 0.666, 0.734, 0.649 and 0.686, respectively in our study, showing a low accuracy in the diagnosis of FLD, but the AUC of integrated parameter of WHR, BMI, UA, TG, LDL-C and AST was 0.913 suggesting a high accuracy in the diagnosis of FLD. Our results showed WHR and BMI were able to serve as important parameters for the evaluation of obesity in Qingdao, which was not consistent with the findings of the study in Beijing. Whether this is related to the change in dietary habits needs to be confirmed. In addition, whether the integrated parameter of WHR, BMI, UA, TG, LDL-C and AST may act as a more accurate parameter for predicting the diagnosis of FLD needs to be further investigated in studies with large sample size, and the optimal cut-off value should be studied. In particular, some biochemical cause-and-effect relationship between other parameters (such as FBG, lipids, etc) and FLD has not yet been fully elucidated. Thus, this should be resolved in prospective cohort studies with large sample size.

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Disclosure of conflict of interest

None.

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