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Serum Fetuin-A Associated With Fatty Liver Index, Early Indicator of Nonalcoholic Fatty Liver Disease

A Strobe-Compliant Article

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Abstract: Increased fetuin-A has been reported in association with type 2 diabetes and other metabolic diseases. However, the large population data concerning fetuin-A and nonalcoholic fatty liver disease (NAFLD) were limited. In this study, we aimed to investigate the association of serum fetuin-A with fatty liver index (FLI), the indicator of NAFLD.

A population-based cross-sectional analysis was performed in 5219 middle-aged and elderly participants who were recruited from 2 nearby urban communities in Shanghai, China. Serum fetuin-A concentrations were measured by enzyme-linked immunosorbent assay (ELISA). The fourth quartiles of FLI, alanine aminotransferance (ALT), aspartate aminotransferance (AST), and γ-glutamyl transpeptadase (GGT) were defined as elevated FLI, ALT, AST, and GGT, respectively.

Fetuin-A was positively associated with log-transformed-FLI, -ALT, -AST, and -GGT after adjustment for the confounding factors (all $P < 0.05$). Multivariate logistic regression analysis showed that each one-standard deviation increase in serum fetuin-A (120.1 mg/L) was associated with 12% (95% confidence interval [CI] 1.01–1.25, $P = 0.04$), 13% (95% CI 1.06–1.21, $P < 0.001$), and 10% (95% CI 1.03–1.17, $P = 0.005$) increased risk of elevated FLI, ALT, and AST, respectively. Categorical analysis showed that as compared to the lowest quartile, the highest quartile of serum fetuin-A associated with a 35% (95% CI 0.98–1.86), 50% (95% CI 1.24–1.83), and 33% (95% CI 1.10–1.60) increased risk of elevated FLI, ALT, and AST, respectively. No significant association was found with GGT.

In Chinese adults, serum fetuin-A concentrations were significantly associated with elevated FLI, ALT, and AST, the early indicators of NAFLD.

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Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, CRP = C reactive protein, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, FBG = fasting plasma glucose, FLI = Fatty liver index, FSI = fasting serum insulin, GGT = γ-glutamyl transpeptidase, HDL-c = high density lipoprotein cholesterol, HOMA-IR = homeostasis model assessment of insulin resistance, LDL-c = low density lipoprotein cholesterol, SBP = systolic blood pressure, TC = total cholesterol, TG = triglycerides, WHR = waist-to-hip ratio.

INTRODUCTION

Human fetuin-A (alpha-2-Heremans Schmid glycoprotein), a glycoprotein, was produced by the liver and secreted into blood in high concentrations.[1] Epidemiology studies showed that higher serum fetuin-A concentrations were independently associated with type 2 diabetes (T2D),[2] insulin resistance,[3] metabolism syndrome,[4] and cardiovascular diseases (CVDs).[5]

Nonalcoholic fatty liver disease (NAFLD) is a chronic disease characterized by accumulation of fat in the liver. The definition of NAFLD refers to a spectrum of disorders ranging from simple fatty deposition (simple steatosis) to more severe manifestations, such as nonalcoholic steatotic hepatitis (NASH), which can progress to fibrosis, cirrhosis, and liver failure, in the absence of substantial alcohol consumption or other causes of liver disease such as viral hepatitis.[6] It has been reported that NAFLD was a major public health threat and related to high risk for T2D and CVDs.[7]

The fatty liver index (FLI) was an algorithm developed to act as a simple surrogate indicator of hepatic steatosis.[8] The calculation of FLI is based on waist circumference, body mass index (BMI), and levels of serum triglycerides (TG) and γ-glutamyl transpeptidase (GGT). Previous studies suggested that FLI is valuable in identifying participants with NAFLD[9] and those who were at high risk for T2D[10] and CVDs.[11] To date, large-scale population-based studies investigating the relationship between fetuin-A and NAFLD were limited.

In the present study, we hypothesized that serum fetuin-A levels would associate with this early indicator of NAFLD, FLI, as well as serum liver enzymes levels in middle-aged and elderly Chinese.

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METHODS

Study Population

The study participants were from an ongoing community-based population study investigating cardiometabolic risk factors of T2D and related metabolic diseases, which was conducted in Baoshan district, Shanghai, during 2005 and 2009. The study population, design, and protocol have been previously described in detail.[4,12] Briefly, a standard questionnaire was used to collect information about lifestyle factors, disease, and medical history. Anthropometric measurements and 75-g oral glucose tolerances test (OGTT) were preformed; blood and urine samples were collected. Participants meeting the following criteria were sequentially excluded: (1) with severe hepatic dysfunction such as hepatitis, cirrhosis, or malignancy (n = 36), (2) the estimated glomerular filtration rate <60 mL/min/1.73 m^2 (n = 97), (3) with missing fetuin-A concentrations (n = 125) and liver enzymes concentrations (n = 122), (4) with serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), or GGT levels >3 standard deviations (SDs) above the average values of the study population (n = 76), and alcohol consumption exceeding 140 g/week for men and 70 g/week for women (n = 132). Thus, 5848 participants aged 40 years or above were recruited and 5219 participants were included in the final analysis.

Anthropometric and Laboratory Measurements

All participants received a detailed interview in the morning on an appointed day. During the interview, experienced physicians asked each participant the questions about the history of chronic diseases and the use of medications, habits of tobacco smoking, and alcoholic drinking, and so on. Body height and weight, and waist and hip circumference of each participant were measured by the trained investigators. Body mass index (BMI) was calculated as body weight in kilograms divided by height squared in meters (kg/m^2). The waist-to-hip ratio (WHR) was calculated as waist (cm)/hip (cm). Blood pressure was measured in triplicate on the same day after at least 10-min rest by using an automated electronic device (OMRON Model HEM-752 FUZZY, Omron Company, Dalian, China), and the average value of the 3 measurements was used for analysis.

All participants underwent OGTT and fasting and 2-h blood samples were obtained. Fasting and 2-h postloading plasma glucose (FPG and 2 h postloading PG) were measured by using the hexokinase method on a clinical chemistry diagnostic system (C16000, Abbott Laboratories, Otawara-shi, Japan). Fasting serum triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), creatinine, C reactive protein (CRP) and serum ALT, AST and GGT were measured by using an autoanalyser (ADVIA-1650 Chemistry System, Bayer Corporation, Germany). The concentrations of fasting serum insulin (FSI) were measured by using an electrochemiluminescence assay (Roche-Diagnostics, Switzerland).

Serum concentrations of fetuin-A were measured by using a human fetuin-A sandwich enzyme-linked immunosorbent assay (ELISA) kit (MAB1184 R&D Company, CA). The inter assay coefficient of variation is 5.2%, and the intra assay coefficient of variant is 7.8%.

The insulin resistance index (homeostasis model assessment of insulin resistance, HOMA-IR) was calculated as fasting insulin (μIU/mL) × fasting glucose (mmol/L)/22.5.[13] The abbreviated modification of diet in renal disease (MDRD) formula recalibrated for Chinese[14] was used to estimate the eGFR. The formula for calculating eGFR was: $eGFR = 186 \times (\text{creatinine} \times 0.011)^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times 1.233$, where 1.233 was the adjusting coefficient for Chinese and eGFR was expressed in mL/min per 1.73 m^2.

The fatty liver index (FLI)[15] was calculated as:

$$FLI = (e^{0.953 * \log_e(\text{triglycerides}) + 0.139 * \text{BMI} + 0.718 * \log_e(\text{GGT}) + 0.053 * \text{waist circumference} - 15.745} / (1 + e^{0.953 * \log_e(\text{triglycerides}) + 0.139 * \text{BMI} + 0.718 * \log_e(\text{GGT}) + 0.053 * \text{waist circumference} - 15.745}) * 100.$$

DEFINITIONS

Elevated FLI, ALT, AST, and GGT were defined as the fourth quartile of FLI (> 58), ALT (>23 U/L), AST (>26 U/L), and GGT (>36 U/L) level, respectively.

Statistical Analysis

SAS version 9.3 (SAS Institute, Cary, NC) was used for database management and statistical analysis. Continuous variables with normal distribution were given as means ± standard deviation (SD) and those with skewed distribution were given as medians (interquartile ranges [IQR]). Serum fetuin-A, FLI, ALT, AST, GGT, TG, FSI, HOMA-IR, CRP, and eGFR were normalized by logarithmic transformation before statistical analyses because of skewed distributions. All the participants were divided into 4 groups based on fetuin-A concentration quartiles. Across the 4 groups, comparisons of continuous variables were performed with 1-way analysis of variance and Dunnett–Bonferroni tests; comparisons of proportions were performed with Cochran–Armitage trend tests. Multivariate linear regression models were fitted to evaluate the association of serum fetuin-A concentrations with FLI and serum levels of liver enzymes. Univariate and multivariate logistic regression analyses were used to evaluate the odds ratios (ORs) of increase of serum fetuin-A concentrations for elevated FLI and ALT, AST, and GGT. Statistical significance was set to a 2-sided P value of <0.05.

ETHICS

This study was approved by the Institutional Review Board of Rui-Jin Hospital, Shanghai Jiao Tong University School of Medicine. Each participant gave the written informed consent.

RESULTS

Characteristics of Participants

The average age and BMI of our study, including 2045 (39.2%) men and 3174 (60.8%) women, were 61.5 ± 9.9 years and 25.35 ± 3.36 kg/m^2, respectively. The distribution of serum fetuin-A concentrations was positively skewed with a median of 295.1 (IQR, 234.5–366.4) mg/L. FLI, ALT, AST, and GGT had skewed distributions with median (IQR) of 33.64 (16.00–57.57), 22 (18–26) U/L, 15 (11–23) U/L, 24 (17–36) U/L, respectively. The prevalence of impaired glucose tolerance, type 2 diabetes mellitus, and hypertension were 31.0%, 30.6%, and 55.6%, respectively. Sociodemographic and clinical characteristics of the participants according to fetuin-A quartiles were displayed in Table 1. As expected, BMI, WHR, systolic blood pressure (SBP), diastolic blood pressure (DBP), TC, TG, LDL-c, FPG, 2 h postloading PG, FSI, and HOMA-IR were increased with fetuin-A quartiles and HDL-c was decreased with fetuin-A quartiles (all $P < 0.05$). There were no significant differences in age, sex distribution, the percentage of current smoking and alcohol drinking, eGFR, and CRP across the fetuin-A quartiles (Table 1).

TABLE 1. Characteristics of Study Population According to Quartiles of Fetuin-A Levels

	Fetuin-A (mg/L)				
	Quartile 1 (≤234.4)	**Quartile 2 (234.5–295.0)**	**Quartile 3 (295.1–366.3)**	**Quartile 4 (≥366.4)**	***P* value**
Number	1,304	1,305	1,305	1,305	
Fetuin-A (mg/L)	198.3 (170.4–219.4)	265.0 (249.8–279.2)	325.0 (309.5–344.8)	431.4 (391.8–494.5)	/
Age (year)	61.7 ± 9.8	61.2 ± 10.0	61.6 ± 10.0	61.6 ± 9.7	0.56
Male, (*n*, %)	511 (39.2)	492 (37.7)	504 (38.6)	538 (41.2)	0.24
BMI (kg/m^2)	25.0 ± 3 .2	25.2 ± 3.4	25.6 ± 3.4‡	25.6 ± 3.4‡	<0.001
WHR	0.89 ± 0.07	0.90 ± 0.06	0.90 ± 0.06‡	0.90 ± 0.06‡	<0.001
SBP (mmHg)	138 ± 23	139 ± 23	140 ± 22	141 ± 22†	0.02
DBP (mmHg)	78 ± 11	79 ± 11*	79 ± 10	80 ± 10‡	<0.001
Current smoking, (*n*, %)	246 (18.9)	248 (19.0)	233 (17.9)	269 (20.6)	0.40
Current drinking, (*n*, %)	195 (15.0)	186 (14.3)	192 (14.7)	189 (14.5)	0.83
TG (mmol/L)	1.29 (0.88–1.85)	1.41 (0.97–2.10)‡	1.49 (1.03–2.14)‡	1.52 (1.06–2.23)‡	<0.001
TC (mmol/L)	4.97 ± 0.91	5.09 ± 0.96†	5.09 ± 1.00†	5.15 ± 1.05‡	<0.001
LDL-c (mmol/L)	2.47 ± 0.71	2.51 ± 0.71	2.53 ± 0.76	2.57 ± 0.74†	0.006
HDL-c (mmol/L)	1.40 ± 0.36	1.37 ± 0.33	1.37 ± 0.33*	1.37 ± 0.32*	0.02
FPG (mmol/L)	5.8 ± 1.5	5.8 ± 1.6	6.1 ± 2.1‡	6.1 ± 1.9‡	<0.001
2 h post-loading PG (mmol/L)	9.3 ± 5.0	9.3 ± 4.8	10.1 ± 5.6‡	10.1 ± 5.4‡	<0.001
FSI (uIU/mL)	5.97 (3.70–9.59)	6.60 (4.00–10.00)	7.18 (4.40–11.41)‡	7.34 (4.35–11.51)‡	<0.001
HOMA-IR	1.44 (0.85–2.46)	1.59 (0.92–2.60)	1.80 (1.04–3.09)‡	1.85 (1.04–3.15)‡	<0.001
eGFR (ml/min/1.73 m^2)	116.4 (99.4–132.7)	113.5 (97.6–131.1)	114.2 (98.6–130.5)	112.8 (98.2–129.9)	0.20
CRP (mg/L)	0.50 (0.10–2.27)	0.50 (0.10–2.24)	0.58 (0.12–2.43)	0.60 (0.13–2.40)	0.09
ALT (U/L)	14.0 (11.0–21.0)	15.0 (11.0–23.0)†	16.0 (11.0–24.0)‡	16.0 (11.0–26.0)‡	<0.001
AST (U/L)	21.0 (18.0–26.0)	21.0 (18.0–25.0)	22.0 (18.0–27.0)‡	22.0 (19.0–28.0)‡	<0.001
GGT (U/L)	23.0 (16.9–33.0)	22.9 (17.0–34.0)	24.4 (18.0–39.7)‡	25.0 (18.0–38.0)‡	<0.001
FLI	27.81 (12.56–49.91)	32.23 (15.53–54.49)‡	37.03 (18.63–60.74)‡	38.76 (18.93–62.20)‡	<0.001

Data are presented as means ± standard deviation (SD), medians (interquartile ranges), or number (proportions). ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, CRP = C-reactive protein, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, FLI = fatty liver index, FPG = fasting plasma glucose; FSI = fasting serum insulin, 2 h post-loading PG = 2 h post-loading plasma glucose, FSI = fasting serum insulin, GGT = γ-glutamyl transpeptidase, HDL-c = low density lipoprotein cholesterol, HOMA-IR = homeostasis model assessment of insulin resistance, LDL-c = low density lipoprotein cholesterol, SBP = systolic blood pressure, TC = total cholesterol, TG = triglycerides, WHR = waist-to-hip ratio. *P* values were calculated by the 1-way analysis variance for continuous variables and Cochran–Armitage trend χ^2 tests for categorical variables.

$^*P < 0.05$.

$^†P < 0.01$.

$^‡P < 0.001$ compared with the group of the first quartile of fetuin-A and were calculated by Dunnett–Bonferroni tests.

Levels of FLI and Liver Enzymes Across Fetuin-A Quartiles

FLI and liver enzymes levels increased with increment of fetuin-A quartile groups (all *P* for trend < 0.001). Compared with the participants in the lowest quartile of fetuin-A, those in the third and the highest quartiles had significantly higher levels of FLI, ALT, AST, and GGT (all $P < 0.001$, Table 1).

The prevalence of elevated FLI, ALT, and AST was gradually increased across fetuin-A quartiles (all *P* for trend < 0.001, Figure 1). From fetuin-A quartile 1 to quartile 4, the prevalence of elevated FLI was increased from 18.9% to 29.9%, the corresponding number for ALT was from 19.6% to 29.7% and 20.9% to 28.2% for AST, respectively.

The Associations of Fetuin-A with Risk of Elevated FLI and Liver Enzymes

After adjusted for age, sex, BMI, WHR, current smoking, current drinking, blood pressure, serum lipids, plasma glucose, CRP and eGFR, fetuin-A was positively and significantly correlated with ALT and AST (both $P < 0.001$), marginally associated with FLI and GGT ($P = 0.02$ and $P = 0.04$, respectively) (Table 2).

Logistic regression analyses were performed to estimate the ORs for elevated FLI and liver enzymes levels across fetuin-A quartiles, with the first fetuin-A quartile as reference (Table 3). After further adjustment for age, sex, BMI, WHR, current smoking, current drinking, blood pressure, serum lipid profiles, plasma glucose levels, and CRP in model 3, the highest quartile of serum fetuin-A associated a 35% (95% CI 0.98–1.86), 50% (95% CI 1.24–1.83), and 33% (95% CI 1.10–1.60) increased risk of elevated FLI, ALT, and AST, respectively (all *P* for trend < 0.05). The continuous variable analysis showed the similar results. Each one-standard deviation (SD) increase in serum fetuin-A (120.1 mg/L) was associated with 12% (95% confidence interval [CI] 1.01–1.25, $P = 0.04$), 13% (95% CI 1.06–1.21, $P < 0.001$), and 10% (95% CI 1.03–1.17, $P = 0.005$) increased risk of elevated FLI, ALT, and AST, respectively. No significant and independent association was found with GGT.

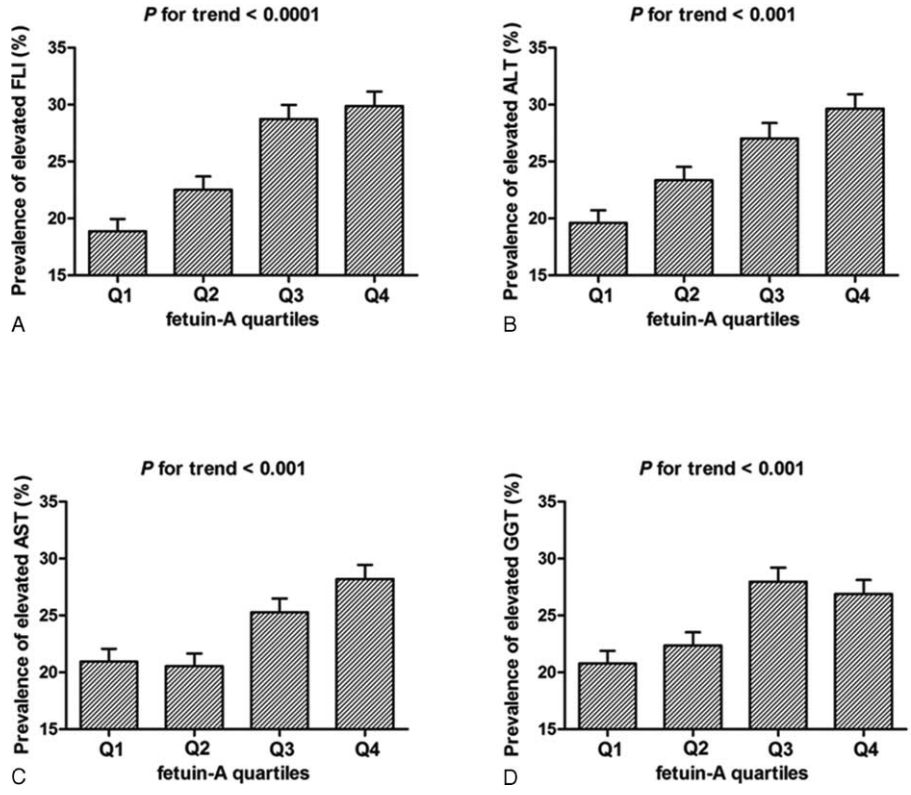

FIGURE 1. Prevalence of elevated FLI and elevated liver enzymes according to quartiles of serum fetuin-A levels. Panels A, B, C, and D showed prevalence of elevated FLI, AST, ALT, and GGT across quartiles of serum fetuin-A concentrations, respectively. ALT = alanine aminotransferase, AST = aspartate aminotransferase, FLI = fatty liver index, GGT = γ-glutamyl transpeptidase.

DISCUSSION

In a middle-aged and elderly Chinese population, we found that higher serum fetuin-A concentrations were associated with increased FLI, ALT, and AST, which were the early indicators of NAFLD. The associations were independent of conventional metabolic risk factors.

The association between fetuin-A and NAFLD was studied in a different context. A prospective study demonstrated high fetuin-A levels to be independently associated with NAFLD,[16] and a decrease in liver fat was accompanied by a decrease in plsama fetuin-A levels.[17] In adult patients with biopsy-proven NAFLD, serum fetuin-A levels were moderately increased, as compared with those without NAFLD.[18] In addition, a significant and positive association between liver fetuin-A mRNA expression and NASH in humans was reported.[19] Our data showed that fetuin-A was significantly associated with elevated FLI and liver enzymes, the early indicators of NAFLD, which was consistent with the above-mentioned results.

TABLE 2. Linear Regression Analysis of Log-Transformed Fetuin-A (mg/L) With Liver Fatty Index and Liver Enzymes

	Model 1		Model 2		Model 3	
	β ± SE	*P* Value	β ± SE	*P* Value	β ± SE	*P* Value
Log-FLI	0.32 ± 0.03	<0.001	0.14 ± 0.02	<0.001	0.03 ± 0.01	0.02
Log-ALT	0.18 ± 0.02	<0.001	0.13 ± 0.02	<0.001	0.10 ± 0.02	<0.001
Log-AST	0.07 ± 0.01	<0.001	0.06 ± 0.01	<0.001	0.05 ± 0.01	<0.001
Log-GGT	0.13 ± 0.02	<0.001	0.08 ± 0.02	<0.001	0.04 ± 0.02	0.04

β = regression coefficient, Log-ALT = log-transformed alanine aminotransferase, Log-AST = log-transformed aspartate aminotransferase, Log-FLI = log-transformed fatty liver index, Log-GGT = log-transformed γ-glutamyl transpeptidase, SE = standard error.

Model 1 is unadjusted.

Model 2 is adjusted for age, sex, BMI, waist-to-hip ratio, current smoking, and current drinking.

Model 3 is additionally adjusted for systolic blood pressure, diastolic blood pressure, triglycerides, total cholesterol, LDL-cholesterol, HDL-cholesterol, fasting plasma glucose, 2 h post-loading plasma glucose, fasting serum insulin, CRP and eGFR-based on model 2.

TABLE 3. The Risk of Elevated Liver Fatty Index and Liver Enzymes Level According to Serum Fetuin-A Concentrations

	Model 1	Model 2	Model 3
Elevated of FLI (>58)			
Quartile 1	1.00	1.00	1.00
Quartile 2	1.24 (1.03–1.51)	1.25 (0.97–1.62)	1.03 (0.74–1.44)
Quartile 3	1.73 (1.44–2.08)	1.69 (1.32–2.16)	1.37 (1.00–1.89)
Quartile 4	1.83 (1.53–2.20)	1.80 (1.41–2.30)	1.35 (0.98–1.86)
P for trend 1	<0.001	<0.001	0.02
1-SD increase (120.1 mg/L)	1.25 (1.18–1.33)	1.26 (1.15–1.36)	1.12 (1.01–1.25)
P for trend 2	<0.001	<0.001	0.04
Elevated of serum ALT (>23 U/L)			
Quartile 1	1.00	1.00	1.00
Quartile 2	1.25 (1.04–1.51)	1.19 (0.98–1.44)	1.16 (0.95–1.41)
Quartile 3	1.52 (1.26–1.82)	1.37 (1.14–1.66)	1.34 (1.10–1.63)
Quartile 4	1.73 (1.44–2.07)	1.56 (1.29–1.88)	1.50 (1.24–1.83)
P for trend 1	<0.001	<0.001	<0.001
1-SD increase (120.1 mg/L)	1.21 (1.14–1.29)	1.17 (1.10–1.24)	1.13 (1.06–1.21)
P for trend 2	<0.001	<0.001	<0.001
Elevated of serum AST (>26 U/L)			
Quartile 1	1.00	1.00	1.00
Quartile 2	0.98 (0.81–1.18)	0.96 (0.79–1.16)	0.97 (0.79–1.17)
Quartile 3	1.28 (1.07–1.53)	1.21 (1.01–1.46)	1.19 (0.98–1.43)
Quartile 4	1.48 (1.24–1.78)	1.41 (1.18 –1.70)	1.33 (1.10–1.60)
P for trend 1	<0.001	<0.001	< 0.001
1-SD increase (120.1 mg/L)	1.15 (1.08–1.22)	1.13 (1.06–1.20)	1.10 (1.03–1.17)
P for trend 2	<0.001	<0.001	0.005
Elevated of serum GGT (>36 U/L)			
Quartile 1	1.00	1.00	1.00
Quartile 2	1.10 (0.91–1.32)	1.07 (0.88–1.30)	1.03 (0.84–1.25)
Quartile 3	1.48 (1.24–1.77)	1.39 (1.16–1.68)	1.27 (1.05–1.54)
Quartile 4	1.40 (1.17–1.68)	1.29 (1.07–1.56)	1.10 (0.90–1.33)
P for trend 1	<0.001	<0.001	0.13
1-SD increase (120.1 mg/L)	1.13 (1.06–1.20)	1.09 (1.02–1.16)	1.02 (0.96–1.09)
P for trend 2	<0.001	0.01	0.54

Data are presented as odds ratios, 95% confidence interval. *P* for trend 1 was tested for linear trend of the fetuin-A categories (quartile 1, quartile 2, quartile 3, and quartile 4); *P* for trend 2 was tested for the linear trend of each SD (120.1 mg/L) increase of fetuin-A. ALT = alanine aminotransferase, AST = aspartate aminotransferase, FLI = fatty liver index, GGT = γ-glutamyl transpeptidase, SD = standard deviation.

Model 1 is unadjusted.

Model 2 is adjusted for age, sex, BMI, waist-to-hip ratio, current smoking, and current drinking.

Model 3 is additionally adjusted for systolic blood pressure, diastolic blood pressure, triglycerides, total cholesterol, LDL-cholesterol, HDL-cholesterol, fasting plasma glucose, 2 h post-loading plasma glucose, fasting serum insulin, CRP, and eGFR-based on model 2.

Epidemiology studies showed that FLI was a simple and accurate predictor for NAFLD[15] and had striking agreement with regular abdominal ultrasound diagnosis of NAFLD.[20] In a European population, FLI identified patients with NAFLD was with an area under the receiver operating characteristic curve of 0.813. The sensitivity and specificity of FLI > 60 for predicting the presence of NAFLD were 60.4% and 82.3%, respectively.[21] Liver enzymes were widely used as serum markers for liver function. The abnormal level of serum liver enzymes was very common in patients with NAFLD.[6] Serum GGT is usually above the normal range in many patients of NAFLD, whereas its degree of elevation is larger and more common in the patients of alcoholic hepatitis.[22] These literature findings supported our hypotheses that serum fetuin-A concentrations associated with early NAFLD indicated by FLI, ALT, and AST.

Fetuin-A was demonstrated as a natural inhibitor of insulin receptors and at last lead to insulin resistance.[23] Additionally, previous study demonstrated that fetuin-A works as an endogenous ligand for toll-like receptor 4 (TLR4), which has a key role in activating an inflammatory signaling pathway of adipocyte and inducing insulin resistance.[24] It was reported that in middle-aged and nondiabetic subjects, the values of FLI > 60 was associated with increased risk for insulin resistance and type 2 diabetes in the Insulin Sensitivity and Cardiovascular disease (RISC) study.[25] It has also showed that in healthy individuals, increased GGT and ALT were biomarkers of both systemic and hepatic insulin resistance.[26] Thus, insulin resistance may mediate the association between fetuin-A and indicators of NAFLD, including FLI and liver enzymes.

Increased fetuin-A was shown to induce adiposity dysfunction by inhibiting the expression of adiponectin while increasing those of fatty acids and inflammatory cytokines,[27] which can induce fat accumulation in the liver and at last progress to NAFLD. On the other hand, fetuin-A was a known extracellular inhibitor of transforming growth factor β,[28] which signaling in hypatocytes contributes to hepatocyte death and fat

accumulation[29] and results in FLI and liver enzymes increasing. Accordingly, elevated serum fetuin-A levels may represent a counteracting mechanism in against development of NAFLD.

The strengths of our study were its well-defined community setting, a relative large sample size, and an inclusion of various covariates into adjustment models to control for confounding factors. Nevertheless, several limitations should be acknowledged. First, our study was a cross-sectional and observational study, so it was not appropriate to infer casualty. Second, we used FLI and liver enzymes as surrogate markers of NAFLD. NAFLD is usually diagnosed in clinical settings by using ultrasound or liver biopsy, which was not easily applicable in large epidemiological studies. Finally, although we controlled for a wide array of possible confounders, including lifestyle, blood pressure, plasma glucose, serum lipids, and CRP levels, we cannot excluded the possibility that at least some of association still can be explained by unmeasured or residual confounding.

In conclusion, we showed that elevated serum fetuin-A concentrations were associated with elevated FLI and serum ALT and AST levels, which are early indicators of NAFLD. Our findings indicated that fetuin-A might be involved in the pathogenesis and development of NAFLD. Well-designed prospective population studies and animal studies aiming to elucidate the roles of fetuin-A in the pathogenesis and development of NAFLD are warranted in the future.

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