Association between serum α-L-fucosidase and non-alcoholic fatty liver disease: Cross-sectional study

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AIM: To explore the association between serum α-L-fucosidase (AFU) and non-alcoholic fatty liver disease (NAFLD).

METHODS: A total of 16473 individuals (9456 men and 7017 women) were included in the current study, who presented for a health examination at the First Affiliated Hospital of Zhejiang University School of Medicine in 2014. The baseline characteristics of the cohort were compared by NAFLD status. Linear regression analysis and stepwise multiple regression analysis were applied to assess the risk factors for NAFLD. Receiver operating characteristic curve was used to determine the optimal cut-off value to identify the risk of NAFLD. The patients were divided into three groups: (1) NAFLD group; (2) non-NAFLD group; and (3) healthy control group.

RESULTS: The prevalence of NAFLD was 36.0% in men and 21.2% in women. The serum α-L-fucosidase levels were significantly higher in the NAFLD group compared to the non-NAFLD group and the healthy control group. The adjusted odds ratio (OR) for NAFLD was 1.77 (95% CI: 1.55-2.02) for men and 1.62 (95% CI: 1.37-1.91) for women. The optimal cut-off value was 200 U/L for men and 150 U/L for women with an area under the curve (AUC) of 0.76 for men and 0.66 for women.

CONCLUSIONS: Serum α-L-fucosidase levels were significantly higher in patients with NAFLD compared to healthy controls. α-L-Fucosidase may be a useful biomarker for the diagnosis of NAFLD.

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used to determine the sensitivity and specificity of AFU in the diagnosis of NAFLD.

**RESULTS:** The prevalence rates of NAFLD and metabolic syndrome (MetS) were 38.0% and 25.4%, respectively. The NAFLD group had significantly higher AFU levels than the non-NAFLD group (27.7 ± 7.9 U/L vs 26.0 ± 7.3 U/L, \( P < 0.001 \)) and the prevalence rate of NAFLD increased with progressively higher serum AFU levels. AFU was positively correlated with MetS and its five components: central obesity, hypertriglyceridemia, low-density lipoprotein cholesterol, and elevated blood pressure and fasting glucose. Stepwise multiple logistic regression analysis showed that AFU was associated with an increased risk of NAFLD (OR = 1.009, 95%CI: 1.003-1.014, \( P < 0.001 \)). The best cut-off value of AFU for the diagnosis of NAFLD was 27.5 U/L. The area under the curve (diagnostic efficacy index) was 0.606. The sensitivity and specificity were 54.6% and 61.8%, respectively.

**CONCLUSION:** AFU level is significantly associated with NAFLD, and elevated AFU level is an independent risk factor for NAFLD.

**Key words:** α-L-fucosidase; Biomarker; Non-alcoholic fatty liver disease; Metabolic syndrome; Cross-sectional study

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**Core tip:** Alpha-L-fucosidase (AFU) is a well-established marker for hepatocellular carcinoma. This study was the first attempt to investigate the relationship between AFU level and non-alcoholic fatty liver disease (NAFLD) in a large cross-sectional cohort from a southern urban Han Chinese population. It provided evidence that AFU level was significantly associated with NAFLD, and elevated AFU level was an independent risk factor for NAFLD. AFU may be a potential biomarker for the diagnosis of NAFLD.

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**INTRODUCTION**

Non-alcoholic fatty liver disease (NAFLD) has attracted attention for its high prevalence (20%-30%) in developed countries[12]. The development of NAFLD is closely associated with central obesity, type 2 diabetes, hypertension, and dyslipidemia, which form a cluster of metabolic disorders that is now recognized as metabolic syndrome (MetS)[3,4]. For this reason, NAFLD is often considered a hepatic manifestation of MetS[5].

Alpha-L-fucosidase (AFU) is a sort of lysosomal enzyme present in all mammalian cells and hydrolyzes sugars containing L-fucose[5]. Deugnier et al[6] first found that AFU is overexpressed in patients with hepatocellular carcinoma (HCC) in 1984. The sensitivity and specificity for the diagnosis of HCC were about 80% and 70%, respectively, in contrast with 40% and almost 100% for α-fetoprotein (AFP)[7]. A simultaneous determination of both markers can improve the sensitivity to 82%[7]. AFU has been clinically used widely as a supplement to AFP in early detection of HCC.

NAFLD is a clinicopathological syndrome that ranges from simple steatosis to steatohepatitis, fibrosis or cirrhosis of the liver[8], and cirrhosis is the most important risk factor for HCC, regardless of etiology[9]. Thus, NAFLD is often considered a precursor for HCC[10]. Due to the high sensitivity of AFU in early detection of HCC, we hypothesized that AFU could be a biomarker for diagnosis of NAFLD, which is a precursor of HCC.

In this study, we performed a large cross-sectional survey to analyze the association between AFU and NAFLD in a Chinese population.

**MATERIALS AND METHODS**

**Study population**

We conducted a cross-sectional study among adults who presented for their annual health examinations at the First Affiliated Hospital of Zhejiang University School of Medicine in 2014. The analyses were limited to participants who had full records of anthropometric and biochemical data, as well as results of hepatic ultrasonography examination. Exclusion criteria included: (1) those taking antihypertensive or antidiabetic agents, lipid-lowering agents, or uric-acid-lowering agents; (2) those with alcohol consumption > 140 g/wk for men and 70 g/wk for women; (3) those with a history of other known causes of chronic liver disease such as viral hepatitis or autoimmune hepatitis; and (4) those using hepatotoxic medications (e.g., sulfonamides and azithromycin). A total of 16473 participants (9456 men and 7017 women) were included in the final analysis. All participants were informed verbally about the purpose and design of the study. The personal information of each participant was anonymized both at collection and prior to analysis. The study was approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang University School of Medicine.

**Study data**

Study data included four parts: medical history, questionnaire, and anthropometric and biochemical measurements. All medical histories including previous
diseases and drug prescription were assessed by examining physicians. Questions about alcohol intake included the frequency of alcohol consumption per week and the usual amount per day. Persons smoking at that time were considered to be current smokers.

The anthropometric measurements involved height, weight, blood pressure and waist circumference (WC). Height and weight were measured while wearing light clothing without shoes. Body mass index (BMI) was calculated as weight (kg) divided by the square of the height (m). Blood pressure, including systolic blood pressure (SBP) and diastolic blood pressure (DBP), was measured on the right arm with participants in a sitting position after a 5-min rest. WC was measured with the measuring tape positioned midway between the lowest rib and the superior border of the iliac crest as the patient exhaled normally.

Biochemical measurements were performed after participants were instructed to complete an overnight fast. Fasting blood samples were obtained from an antecubital vein, and the samples were used for the analysis of biochemical values. The values included triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), γ-glutamyltransferase (GGT), AFU, uric acid (UA), and fasting plasma glucose (FPG). All biochemical values were measured using a Hitachi 7600 clinical analyzer (Hitachi, Tokyo, Japan) and Sysmex XE-2100 auto-analyzer (Sysmex, Kobe, Japan) using standard methods.

Diagnosis of NAFLD and definitions of MetS
Abdominal ultrasonographic examinations were carried out by experienced radiologists who were unaware of the aims of the study and were blinded to the laboratory values, using a Toshiba Nemio 20 sonography machine (Toshiba, Tokyo, Japan) with a 3.5-MHz probe. Images were captured in a standard fashion, with the patient in the supine position, with the right arm raised above the head. Fatty liver disease was diagnosed and its degree was assessed according to the criteria described by the Chinese Liver Disease Association[11].

The diagnosis of MetS was based on the definition recommended by the Asia-Pacific Working Party on NAFLD 2006[12]. MetS was diagnosed if any three or more of the following were present: (1) central obesity: WC > 90 cm for men and > 80 cm for women and/or BMI > 25 kg/m² in both genders; (2) hypertriglyceridemia: TGs ≥ 1.7 mmol/L; (3) low HDL-C: HDL-C < 1.03 mmol/L for men and < 1.29 mmol/L for women; (4) elevated blood pressure: blood pressure ≥ 130/85 mmHg; and (5) elevated fasting glucose: FPG ≥ 5.6 mmol/L or previously diagnosed type 2 diabetes.

Statistical analysis
Statistical analyses were performed using SPSS for Windows version 13.0 (SPSS, Chicago, IL, United States). Continuous variables are presented as the mean ± SD or the median and interquartile range (IQR), as appropriate. The Student’s t test or Mann-Whitney U test was used for comparisons of continuous data, while the χ² test was used for comparisons of categorical variables. Linear regression analysis was used to determine the relationship between AFU level and prevalence of NAFLD and MetS. Stepwise multiple regression analysis (Backward: Wald; Entry: 0.05, Removal: 0.10) was applied to assess the risk factors for NAFLD. P < 0.05 (two-tailed test) was considered statistically significant. The receiver operating characteristic (ROC) curve was used to determine the sensitivity and specificity of AFU in the diagnosis of NAFLD.

RESULTS

Patient characteristics
Of the 16473 subjects enrolled in this study, 6263 (38.0%) and 4177 (25.4%) fulfilled the diagnostic criteria for NAFLD and MetS, respectively. The prevalence rates of MetS components, including central obesity, hypertriglyceridemia, low HDL-C, elevated blood pressure and elevated FPG, were 46.48%, 29.11%, 36.73%, 33.98% and 12.19%, respectively. Demographic and biochemical characteristics were compared by NAFLD status (Table 1). Patients with NAFLD exhibited higher AFU. Meanwhile, BMI, WC, SBP, DBP, white blood cell count, UA, FPG, TG, TC, LDL, very-low density lipoprotein, alanine aminotransferase (ALT), aspartate aminotransferase (AST), GGT, cholinesterase, alkaline phosphatase, carcinoembryonic antigen and HDL were higher in the NAFLD group.

Association of AFU level with NAFLD
In order to have a further understanding of the association between AFU and NAFLD, all 16473 subjects were classified into quartiles by their AFU levels (quartile 1 was defined as AFU ≤ 22 U/L, quartile 2 was 22-27 U/L, quartile 3 was UA 27-31 U/L, and quartile 4 was ≥ 31 U/L). As seen in Table 2, the prevalence rate of NAFLD was significantly and positively correlated with AFU levels. The prevalence rate for NAFLD substantially increased with increasing AFU levels. Compared with individuals in the lowest AFU quartile, those in the highest quartile had a prevalence ratio of 1.85.

Association of AFU level with MetS and its components
NAFLD is often considered a hepatic manifestation of MetS. To understand better the role of AFU in increasing incidence of NAFLD, we performed another investigation on the association between AFU and MetS. The results showed a significantly higher prevalence rate of MetS with higher AFU levels. In
addition, all the five components (central obesity, hypertriglyceridemia, low HDL-C, elevated blood pressure, and elevated FPG) were also seen to be significantly and positively correlated with AFU (Figure 1). It can be inferred that AFU level may be not only an important factor for NAFLD, but also a significant factor for MetS.

**Risk factors for NAFLD**

To explore the independent risk factors associated with the presence of NAFLD, we performed stepwise multiple regression analysis with a logistic regression model. AFU was found to be a significant independent risk factor for NAFLD (OR = 1.009, 95% CI: 1.003–1.014, P < 0.001). The other risk factors are listed in Table 3, including age, gender, height, weight, BMI, WC, DBP, platelet count, white blood cell count, neutrophil, albumin, UA, FPG, TG, HDL, AFU, ALT, AST, cholinesterase, and AFP.

**Sensitivity and specificity of AFU for diagnosis of NAFLD**

The ROC curve of AFU plotted for the diagnosis of NAFLD is shown in Figure 2. The best cut-off value for AFU was 27.5 U/L, at which the sensitivity was 54.6% and the specificity was 61.8%. The area under the curve (diagnostic efficacy index) was 0.606.

**DISCUSSION**

This study may be the first to investigate the relationship between AFU level and NAFLD. The prevalence rates of NAFLD and MetS were 38.0% and 25.4%, respectively, which were comparable with recent studies that investigated the association between NAFLD and MetS in the Chinese population[13–15]. In this study, we provided evidence that AFU level was independently associated with NAFLD. The NAFLD group tended to have elevated AFU levels compared with the non-NAFLD group. In addition, the prevalence rate of NAFLD increased with elevated AFU levels, which means that the subjects with elevated AFU levels had a higher risk of NAFLD. We further analyzed the association between AFU and MetS to confirm indirectly the relationship between AFU and MetS. Similarly, the results showed that AFU was positively correlated with MetS and its five components. Logistic regression analysis was performed to screen the risk factors for NAFLD and AFU was found to be an independent risk factor for NAFLD. Finally, the sensitivity was 54.6% and specificity was 61.8% for the diagnosis of NAFLD at the best cut-off value of 27.5 U/L.

However, the physiological mechanism for this association remains unclear. There exist several possible explanations for the relationship. One of the most convincing explanations is that the AFU in the serum comes from lysosomal leakage. The subjects with NAFLD tend to have hypertriglyceridemia and low HDL-C, and lipid peroxidation has been demonstrated to be involved in the formation of NAFLD[16,17]. Lipid peroxidation modifies the functional characteristics not only of the cell membranes, but also membranes of intracellular organelles such as mitochondria and lysosomes[18,19]. The ensuing changes following lysosomal membrane oxidation induce perturbation in this membrane permeability and may result in leakage of lysosomal AFU[20]. According to this explanation, AFU is deemed to be an indicator to monitor the change in membrane permeability.

Another reasonable explanation was related to inflammatory response in NAFLD. It has been demonstrated that development and progression of hepatic inflammation play a key role in the formation and progress of NAFLD[21,22]. As seen in this and previous studies, higher white blood cell counts are known to be associated with the presence of NAFLD[23]. AFU can modulate inflammation by reducing the interaction between fucosylated adhesion molecules, which normally support white blood cell extravasation[24]. Thus, AFU could be seen as a mediator in the NAFLD-associated chronic hepatic inflammation[25].

AFU seems not to be a satisfactory biomarker for the diagnosis of NAFLD with respect to the sensitivity and specificity compared with other biomarkers, such as cholinesterase.

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**Table 1 Comparison of clinical characteristics between subjects with and without non-alcoholic fatty liver disease**

| Variable | With NAFLD | Without NAFLD | t value | P value |
|----------|------------|---------------|---------|---------|
| Age (yr) | 47.9 (10.3) | 44.3 (11.2) | 20.844 | < 0.001 |
| Gender | 4616/1647 | 4840/5337 | 1097.928 | < 0.0011 |
| (male/female, n) | | | | |
| BMI (kg/m²) | 26.1 (2.9) | 22.5 (2.7) | 80.032 | < 0.001 |
| WC (cm) | 90.7 (8.2) | 79.7 (8.5) | 80.773 | < 0.001 |
| SBP (mmHg) | 134.2 (17.5) | 123.1 (17.3) | 39.908 | < 0.001 |
| DBP (mmHg) | 82.3 (11.1) | 74.6 (11.2) | 42.506 | < 0.001 |
| WBC (10³/L) | 6.41 (1.6) | 5.83 (1.5) | 23.672 | < 0.001 |
| UA (mmol/L) | 369.8 (87.8) | 303.3 (81.2) | 49.434 | < 0.001 |
| FPG (mmol/L) | 8315 (1585) | 74.6 (11.2) | 4.72 (4.46-5.01) | 0.210 |
| TG (mmol/L) | 4.62 (0.9) | 4.72 (0.6) | 2.6 (2.0-3.5) | 0.029 |
| TC (mmol/L) | 1.70 (2.0-2.45) | 1.00 (0.73-1.43) | 44.960 | < 0.001 |
| LDL-C (mmol/L) | 4.9 (0.9) | 4.62 (0.9) | 22.188 | < 0.001 |
| HDL-C (mmol/L) | 2.7 (0.7) | 2.6 (0.6) | 13.685 | < 0.001 |
| AFU (U/L) | 28.7 (7.9) | 26.0 (7.3) | 22.591 | < 0.001 |
| ALT (U/L) | 25 (18-37) | 16 (11-22) | 30.396 | < 0.001 |
| AST (U/L) | 5.83 (1.5) | 5.83 (1.5) | 49.434 | < 0.001 |
| GGT (U/L) | 4.9 (0.9) | 4.62 (0.9) | 22.188 | < 0.001 |
| Cholinesterase (U/L) | 9537 (1579) | 8315 (1585) | 48.125 | < 0.001 |
| ALP (U/L) | 68 (20.1) | 61 (19.9) | 19.818 | < 0.001 |
| AFP (μg/L) | 2.6 (2.0-3.5) | 2.4 (1.8-3.4) | 0.210 | < 0.001 |

Note: Data are expressed as mean ± SD or median (IQR).
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Table 2  Prevalence rate of non-alcoholic fatty liver disease according to quartile of α-L-fucosidase

| AFU level quartile | Total  | NAFLD | χ²  | P value | PR%   | PR   |
|--------------------|--------|-------|------|---------|-------|------|
| Quartile 1         | 4119   | 1137  | -    | -       | 27.60 | 1.00 |
| Quartile 2         | 4118   | 1375  | 32.527 | < 0.001 | 33.39 | 1.21 |
| Quartile 3         | 4118   | 1652  | 143.969 | < 0.001 | 40.11 | 1.45 |
| Quartile 4         | 4118   | 2099  | 471.421 | < 0.001 | 50.97 | 1.85 |

AFU: α-L-fucosidase; PR%: Prevalence rate; PR: Prevalence ratio; NAFLD: Non-alcoholic fatty liver disease.

Figure 1  Prevalence rates of metabolic syndrome and its five components in patients with different quartile levels of α-L-fucosidase.

Table 3  Risk factors for non-alcoholic fatty liver disease

| Variable     | β     | SE    | Wald χ² | P value | OR   | 95%CI         |
|--------------|-------|-------|---------|---------|------|---------------|
| Age          | 0.023 | 0.002 | 90.042  | < 0.001 | 1.023| 1.018-1.028   |
| Male gender  | 0.510 | 0.072 | 49.919  | < 0.001 | 1.665| 1.445-1.918   |
| Height       | -0.040| 0.011 | 13.337  | < 0.001 | 0.961| 0.941-0.982   |
| Weight       | 0.055 | 0.013 | 18.069  | < 0.001 | 1.057| 1.030-1.084   |
| BMI          | 0.067 | 0.034 | 6.456   | < 0.001 | 1.090| 1.020-1.166   |
| WC           | 0.048 | 0.019 | 88.152  | < 0.001 | 1.049| 1.039-1.060   |
| DBP          | 0.010 | 0.002 | 21.935  | < 0.001 | 1.010| 1.005-1.014   |
| Plt          | 0.001 | 0.000 | 3.157   | < 0.001 | 1.001| 1.000-1.002   |
| WBC          | 0.192 | 0.034 | 30.938  | < 0.001 | 1.211| 1.132-1.296   |
| NEU          | -0.202| 0.043 | 21.986  | < 0.001 | 0.817| 0.751-0.889   |
| ALB          | 0.039 | 0.008 | 26.043  | < 0.001 | 1.039| 1.024-1.055   |
| UA           | 0.003 | 0.000 | 97.787  | < 0.001 | 1.003| 1.003-1.004   |
| FIB          | 0.005 | 0.000 | 74.473  | < 0.001 | 1.022| 1.177-1.279   |
| TG           | 0.126 | 0.022 | 107.298 | < 0.001 | 1.253| 1.201-1.308   |
| HDL          | -0.493| 0.082 | 36.514  | < 0.002 | 0.611| 0.520-0.717   |
| AFU          | -0.015| 0.006 | 3.923   | < 0.001 | 0.985| 0.970-0.999   |

β: Partial regression coefficient; SE: Standard error of partial regression coefficient; NAFLD: Non-alcoholic fatty liver disease; BMI: Body mass index; WC: Waist circumference; DBP: Diastolic blood pressure; Plt: Platelet; WBC: White blood cell; NEU: Neutrophil; ALB: Albumin; UA: Uric acid; FIB: Fasting blood glucose; TG: Triglyceride; HDL: High-density lipoprotein; AFU: α-L-fucosidase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ChE: Cholinesterase; AFP: α-fetoprotein.

Figure 2  Receiver operating characteristic curve of α-L-fucosidase plotted for diagnosis of non-alcoholic fatty liver disease. The area under the curve (diagnostic efficacy index) is 0.606.

as cytokeratin 18 (AUROC = 0.8)\textsuperscript{26,27}, HAIR score (hypertension, ALT, insulin resistance, AUROC = 0.9)\textsuperscript{28}. But AFU has the advantages of widespread application and convenience of use as a simple biomarker. This is a preliminary study in the investigation of NAFLD biomarkers and further studies are needed to improve the sensitivity and specificity (i.e., setting up a new scoring system including other available biochemical...
AFU was established as a tumor marker in a series of studies reporting that its activity increases significantly in the serum of HCC patients. In the current study, AFU was demonstrated as an independent risk factor for NAFLD. In addition, the link between AFU and NAFLD may provide a potential explanation for why AFU is often elevated in HCC patients. Tumor cell injury, tissue necrosis and mononuclear macrophage accumulation are often present in HCC, thus, elevated AFU level could be an indicator of changes in membrane permeability following cell injury or inflammation response.

There were several limitations to this study. First, the diagnosis of NAFLD was based on ultrasonographic examination. Although liver biopsy is recognized as the gold standard for the diagnosis of NAFLD, invasiveness and complications make it impractical for screening of NAFLD. Ultrasonographic examination has been widely used because of its non-invasiveness and reasonable accuracy, although it is still not sensitive enough to detect mild steatosis. Second, the subjects enrolled in this study were mostly office staff, which is a middle-income group. The prevalence rate of NAFLD and MetS may have been overestimated. Third, it is single-center experience and there was no validation study for AFU. It is hard to confirm the generation of our findings. We are planning to conduct a multi-center large cohort study to investigate the applicability of our findings to the rest of the Chinese population. Moreover, it is still an unresolved question whether elevated AFU is a bystander effect, a cause, or a consequence of NAFLD.

In summary, our large cross-sectional study shows that AFU levels are positively associated with NAFLD and may act as an independent risk factor. AFU may be a potential biomarker for the diagnosis of NAFLD. Further studies are needed to reveal the detailed relationship and the possible mechanisms between serum AFU and NAFLD.

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