

Research Paper

Non-alcoholic fatty liver disease is associated with low-grade albuminuria in men without diabetes mellitus

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) is associated with the dysregulation of multiple metabolic and inflammatory pathways. These can lead to extrahepatic disorders involving the kidney, a vulnerable organ responsible for extra-renal complications. Evaluating the association between NAFLD and low-grade albuminuria as a renal complication would be helpful to better understand the pathophysiology and extra-hepatic complications of NAFLD.

Patients and Methods: Our study extracted data from database obtained a representative population sample. Overall, 3867 men were included in this survey. Our study included only men without diabetes mellitus, with a urinary albumin/creatinine ratio < 30 mg/g (n = 1390). Low-grade albuminuria was defined by a urinary albumin/creatinine ratio within the highest quartile. The fatty liver index was calculated in accordance with Bedogni's equation. We defined the NAFLD group as patients with a fatty liver index of ≥ 60.

Results: In the multivariate analysis, the urinary albumin/creatinine ratio in the non-NAFLD and NAFLD groups was 3.05 ± 0.14 and 5.19 ± 0.42 , respectively ($P < 0.001$). The correlation coefficients between the fatty liver index and urinary albumin/creatinine ratio were 0.124 in the Pearson's correlation test and 0.084 in the partial correlation test ($P < 0.001$ and $P = 0.002$, respectively). Linear regression analysis showed a positive association between the fatty liver index and the urinary albumin/creatinine ratio on multivariate analysis. Logistic regression analysis showed that the odds ratio for low-grade albuminuria with NAFLD was 2.31 (95% confidence interval, 1.47–3.61; $P < 0.001$) on the multivariate analysis. Subgroup analyses according to the presence of metabolic syndrome or age (< 50 or ≥ 50 years) showed that the association between NAFLD and the urinary albumin/creatinine ratio was stronger for participants without metabolic syndrome and in those aged < 50 years.

Conclusion: NAFLD was associated with low-grade albuminuria in men without diabetes mellitus in this study. Therefore, men with a relatively high fatty liver index or NAFLD should be closely monitored for low-grade albuminuria, especially in absence of metabolic syndrome.

Key words: Non-alcoholic fatty liver disease, albuminuria, metabolic syndrome

Introduction

Non-alcoholic fatty liver disease (NAFLD) is chronic liver disease; encompassing conditions ranging from fatty liver disease to liver cirrhosis. NAFLD is characterized by fat accumulation without competing etiologies for steatosis such as viral hepatitis or heavy alcohol intake [1,2]. Primary NAFLD is typically associated with metabolic disturbances, such as metabolic syndrome (MetS) and/or insulin resistance, in particular [3,4]. Previous epidemiologic studies have shown that the prevalence of NAFLD is approximately 30% in the USA, 24% in

Europe, and 27% in Asia [5-7]. The prevalence of NAFLD is rapidly increasing [8]. Previous studies have shown a positive association between NAFLD and systemic chronic diseases, such as diabetes mellitus (DM), cardiovascular disease, sarcopenia, and osteoporosis, through various metabolic disturbances [9-13]. New relationships between other chronic diseases and NAFLD have also been demonstrated. These findings suggest that NAFLD is indeed a systemic disorder and is associated with incident cardio-metabolic diseases and mortality

[14,15].

Albuminuria is a well-known risk factor of cardiovascular disease and chronic kidney disease progression [16]. Microalbuminuria is classically defined by an albumin level of 30–300 mg/day in the urine or a urinary albumin/creatinine ratio (UACR) of 30–300 mg/g. However, considering the limitation of single cut-off values, researchers have focused on the importance of high levels of albuminuria of < 30 mg/day (or 30 mg/g); this condition has been called “low-grade albuminuria” (LGA). Previous studies have shown an association between LGA and various cardiometabolic diseases [17–20]. Tanaka et al. demonstrated that LGA leads to high mortality rates [20].

NAFLD is associated with the dysregulation of multiple metabolic and inflammatory pathways (e.g., peripheral/hepatic insulin resistance, chronic inflammation, oxidative stress, or the renin-angiotensin system) [4]. These can lead to extrahepatic disorders such as DM, hypertension, MetS, or cardiovascular disease. Epidemiologic or experimental studies have shown an association between NAFLD and extrahepatic disorders as a consequence of these pathophysiological disorders [4]. The kidney is an organ influenced by extra-renal complications and is vulnerable to different cardio-metabolic disturbances induced by NAFLD. Therefore, NAFLD is a systemic and inflammatory disease and can lead to the development of renal complications. Lin et al. enrolled Chinese adults and provided evidence for the association of LGA and NAFLD using ultrasonography [21]. Although a previous study has investigated the association between these two variables, regional and national disparities should also be considered. An additional study on a Korean population would be helpful to identify the association between the two variables. Thus, an evaluation of the association between NAFLD and LGA would be helpful to better understand the underlying pathophysiology and extra-hepatic complications of NAFLD. If the link between these two variables is identified, LGA may be considered an additive risk factor for mortality or morbidity in patients with NAFLD. Therefore, the aim of the present study was to evaluate the relationship between the two variables.

Patients & Methods

Study population

Our study used the database from the Korean National Health and Nutrition Examination Survey (2011). DM was defined as the self-reported diagnosis of DM as confirmed by a medical doctor, fasting blood

glucose ≥ 126 mg/dL, or HbA1c levels ≥ 6.5%. Micro- or macro-albuminuria was defined as UACR ≥ 30 mg/g. The flow chart of participants included in the study is shown in Figure 1. Overall, 1390 men were included in our analysis. Our study was approved by the institutional review board of the Yeungnam University Hospital. The board waived the need for informed consent, as the subjects' records and information were anonymized and de-identified prior to analysis.

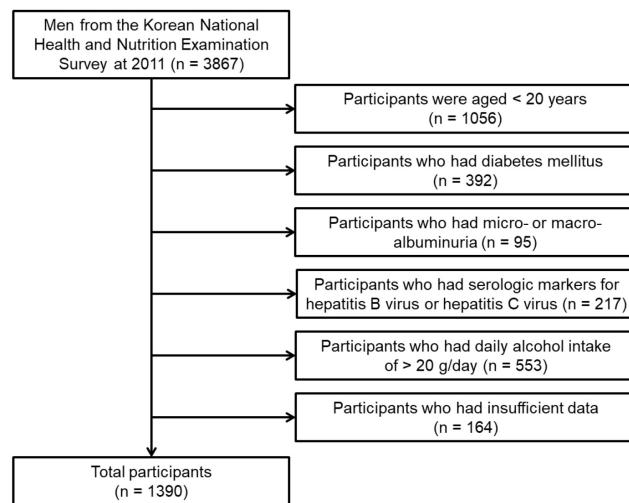


Figure 1. Flow chart of participants

Study variables

Data collected during examination included the following: age, body mass index (BMI, kg/m²), waist circumference (cm), triglyceride level (mg/dL), high-density lipoprotein cholesterol level (HDL-C, mg/dL), fasting blood glucose level (mg/dL), gamma-glutamyltransferase level (GGT, U/L), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), smoking status, education level, exercise, presence of cerebrovascular accidents or coronary artery disease, estimated glomerular filtration rate (eGFR, mL/min/1.73 m²), household income (1000 won/month), UACR (mg/g), and the fatty liver index (FLI).

Smoking status was classified as non-smoker, ex-smoker, and non-smoker. Education level was classified as less than high school, high school level, and college or higher degree. The exercise status was defined as a moderate-intensity activity of > 30 min/day for ≥ 5 days/week or high-intensity activity of > 20 min/day for ≥ 3 days/week [22]. The presence of cerebrovascular accidents was defined as a self-reported diagnosis of stroke from a medical doctor. The presence of coronary artery disease was defined as the self-reported diagnosis of myocardial infarction or angina from a medical doctor. The eGFR

was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation as in a previous study [23]. Urinary albumin levels were measured from random samples using a turbidimetric immunoassay (Hitachi Automatic Analyzer 7600, Hitachi). Urinary creatinine levels were measured using a colorimetric method (Hitachi Automatic Analyzer 7600, Hitachi). Urine albumin and creatinine levels were measured at the same laboratory for all surveys. The inter-assay coefficient of variation for all

laboratory work was consistently low (< 3.1%). The UACR was calculated as mg per g of creatinine (mg/g). The cut-off points of the UACR quartiles were 0.04–0.52 mg/g for the first quartile, 0.53–1.65 mg/g for the second quartile, 1.66–3.87 mg/g for the third quartile, and 3.88–29.9 mg/g for the fourth quartile. LGA was defined as an UACR within the highest quartile, as previously defined [24]. The FLI was calculated in accordance with Bedogni's equation as follows [25]:

$$\text{FLI} = 100 \times \frac{e^{0.953 \times \ln(\text{triglycerides}) + 0.139 \times \text{BMI} + 0.718 \times \ln(\text{GGT}) + 0.053 \times \text{waist circumference} - 15.745}}{1 + e^{0.953 \times \ln(\text{triglycerides}) + 0.139 \times \text{BMI} + 0.7189 \times \ln(\text{GGT}) + 0.053 \times \text{waist circumference} - 15.745}}$$

The FLI ranges between 0 and 100. Previous studies have shown that the FLI score has a high concordance or accuracy for the diagnosis of NAFLD using gold standard methods [25,26]. We defined the NAFLD group as patients with an FLI of ≥ 60 , as previously defined [26].

MetS was defined in accordance with the Adult Treatment Panel III criteria using the modified cutoff values for Asian populations as suggested by the Asia-Pacific guidelines [27].

Statistical analyses

All data were analyzed using the statistical software SAS (Version 9.4, SAS Campus Drive, Cary, NC, USA). Categorical variables were expressed as both counts and percentages. Continuous variables were expressed as means \pm standard deviation (SD) or standard error (SE). Pearson's χ^2 or Fisher's exact test was used to analyze categorical variables. For continuous variables, means were compared using the Student's t-test. Linear regression analysis was performed to assess independent predictors of UACR. Logistic regression analyses were used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs), which were then applied to determining the relationship between NAFLD and LGA. Multivariate analyses were adjusted for age, household income, smoking status, education level, exercise, eGFR, BMI, waist circumference, triglyceride level, HDL-C level, fasting blood glucose level, systolic blood pressure, diastolic blood pressure, and presence of cerebrovascular accident or coronary artery disease. A P-value of < 0.05 was considered statistically significant.

Results

Clinical characteristics of the study participants

The number of participants in the non-NAFLD and NAFLD groups were 1180 and 210, respectively. The clinical characteristics of the participants are

shown in Table 1. The participants in the NAFLD group were older than those in the non-NAFLD group. BMI, waist circumference, triglyceride level, fasting blood glucose level, systolic blood pressure, and diastolic blood pressure were higher in the NAFLD group than in the non-NAFLD group. The HDL-C level was lower in the NAFLD group than in the non-NAFLD group. The proportion of current smokers was greater in the NAFLD group than in the non-NAFLD group. There were no significant differences with regard to education level, exercise status, presence of cerebrovascular accident or coronary artery disease, eGFR level, and household income between the two groups.

Table 1. Clinical characteristics of study participants according to the presence of NAFLD

Variables	Non-NAFLD (n = 1180)	NAFLD (n = 210)	P-value*
Age (years)	50.5 \pm 17.1	48.0 \pm 14.1	0.027
Body mass index (kg/m ²)	23.0 \pm 2.6	27.4 \pm 2.6	<0.001
Waist circumference (cm)	81.7 \pm 7.8	94.7 \pm 6.7	<0.001
Triglycerides (mg/dL)	117.2 \pm 69.0	256.5 \pm 154.4	<0.001
HDL-C (mg/dL)	50.5 \pm 11.5	44.5 \pm 9.4	<0.001
Fasting blood glucose (mg/dL)	92.2 \pm 9.0	97.7 \pm 9.4	<0.001
Systolic blood pressure (mmHg)	118.7 \pm 15.1	122.9 \pm 13.9	<0.001
Diastolic blood pressure (mmHg)	76.8 \pm 9.6	81.4 \pm 9.3	<0.001
Smoking habits			<0.001
Non-smoker	310 (26.3%)	34 (16.2%)	
Ex-smoker	477 (40.4%)	79 (37.6%)	
Current smoker	393 (33.3%)	97 (46.2%)	
Education level			0.585
Less than high school	310 (26.3%)	49 (23.3%)	
High school	419 (35.5%)	74 (35.2%)	
College or more	451 (38.2%)	87 (41.4%)	
Exercise (%)	597 (50.6%)	92 (43.8%)	0.070
Cerebrovascular accident (%)	22 (1.9%)	2 (1.0%)	0.350
Coronary artery disease (%)	31 (2.6%)	7 (3.3%)	0.563
eGFR (mL/min/1.73m ²)	90.7 \pm 15.5	90.8 \pm 15.5	0.942
Household income (1000won/month)	503.8 \pm 1652.6	432 \pm 731.4	0.538
Fatty liver index	23.6 \pm 16.3	73.8 \pm 9.6	<0.001

Data are expressed as numbers (percentages) for categorical variables and as mean \pm standard deviation for continuous variables.

*P-values were determined using the Student's t-test for continuous variables and Pearson χ^2 or Fisher's exact test for categorical variables. Abbreviations: NAFLD, non-alcoholic fatty liver disease; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate.

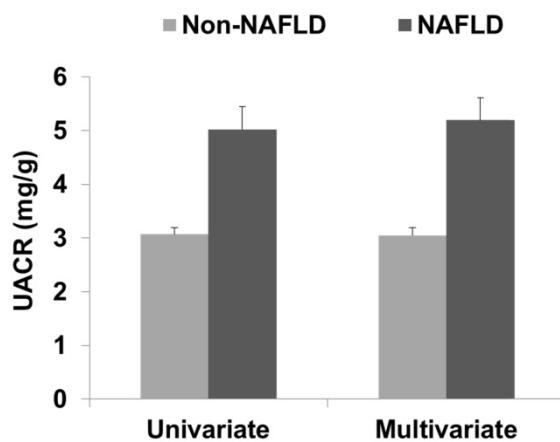


Figure 2. UACR according to the presence of NAFLD. The data are expressed as means and standard errors. The multivariate analysis was adjusted for age, household income, smoking status, education level, exercise, estimated glomerular filtration rate, body mass index, waist circumference, triglyceride level, high-density lipoprotein cholesterol level, fasting blood glucose level, systolic blood pressure, diastolic blood pressure, cerebrovascular accident, and coronary artery disease. Abbreviations: UACR, urine albumin/creatinine ratio; Non-NAFLD, participants without non-alcoholic fatty liver disease; NAFLD, participants with non-alcoholic fatty liver disease.

Table 2. Linear regression analyses of the UACR

Independent variables	Univariate		Multivariate	
	Non-standardized $\beta \pm SE$	P-value*	Non-standardized $\beta \pm SE$	P-value*
Fatty liver index	0.025 ± 0.005	<0.001	0.042 ± 0.013	0.002
Age	0.050 ± 0.008	<0.001	0.043 ± 0.013	0.001
Household income	0.000 ± 0.000	0.177	0.000 ± 0.000	0.349
Smoking habits	0.550 ± 0.167	0.001	0.439 ± 0.169	0.010
Education level	-0.840 ± 0.161	<0.001	-0.459 ± 0.183	0.012
Exercise	0.022 ± 0.258	0.931	0.242 ± 0.255	0.344
eGFR	-0.030 ± 0.008	<0.001	0.015 ± 0.011	0.180
Body mass index	0.106 ± 0.042	0.012	-0.045 ± 0.091	0.622
Waist circumference	0.055 ± 0.014	<0.001	-0.023 ± 0.032	0.479
Triglycerides	0.002 ± 0.001	0.064	-0.004 ± 0.002	0.061
HDL-C	-0.006 ± 0.011	0.585	0.004 ± 0.013	0.743
Fasting blood glucose	0.045 ± 0.014	0.001	0.007 ± 0.015	0.628
Systolic blood pressure	0.046 ± 0.009	<0.001	0.006 ± 0.012	0.601
Diastolic blood pressure	0.046 ± 0.013	0.001	0.037 ± 0.018	0.043
Cerebrovascular accident	2.733 ± 0.988	0.006	1.971 ± 0.982	0.045
Coronary artery disease	1.687 ± 0.790	0.033	1.021 ± 0.793	0.198

*The dependent variable was the UACR, and the multivariate analysis was adjusted for age, household income, smoking status, education level, exercise, eGFR, body mass index, waist circumference, triglyceride level, HDL-C level, fasting blood glucose level, systolic blood pressure, diastolic blood pressure, cerebrovascular accident, and coronary artery disease.

Abbreviations: UACR, urine albumin/creatinine ratio; SE, standard error; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol.

Association between albuminuria and NAFLD

In the univariate analysis, the UACR in the non-NAFLD and NAFLD groups was 3.07 ± 0.13 and 5.02 ± 0.42 , respectively (data are shown as mean \pm SE, $P < 0.001$; Figure 2). In the multivariate analysis, the UACR in the non-NAFLD and NAFLD groups was

3.05 ± 0.14 and 5.19 ± 0.42 , respectively ($P < 0.001$). The correlation coefficients between the FLI and UACR were 0.124 in the Pearson's correlation test and 0.084 in the partial correlation test ($P < 0.001$ and $P = 0.002$, respectively). Linear regression analysis showed a positive association between the FLI and UACR in both the univariate and multivariate analyses (Table 2).

The number of participants with LGA was 226 (22.5%) in the non-NAFLD group and 81 (38.6%) in the NAFLD group ($P < 0.001$). Logistic regression analysis showed that the OR for LGA with NAFLD was 2.16 (95% CI, 1.58–2.94; $P < 0.001$) in the univariate analysis and 2.31 (95% CI, 1.47–3.61; $P < 0.001$) in the multivariate analysis. The OR for LGA with a 1 unit increase in the FLI was 1.01 (95% CI, 1.01–1.02; $P < 0.001$) in the univariate analysis and 1.02 (95% CI, 1.01–1.04; $P = 0.002$) in the multivariate analysis.

Subgroup analyses according to age and the presence of MetS

The number of participants with MetS was 140 in the non-NAFLD group and 131 in the NAFLD group. Participants aged < 50 years were 571 in the non-NAFLD and 118 in the NAFLD group. Among the participants without MetS, the UACR in the non-NAFLD and NAFLD groups was 2.86 ± 0.13 and 4.18 ± 0.58 , respectively (data shown as mean \pm SE; $P = 0.029$). Among the participants with MetS, the UACR in the non-NAFLD and NAFLD groups was 4.60 ± 0.48 and 5.54 ± 0.57 , respectively ($P = 0.209$). Among the participants aged < 50 years, the UACR in the non-NAFLD and NAFLD groups was 2.16 ± 0.13 and 5.07 ± 0.57 , respectively ($P < 0.001$). For participants aged ≥ 50 years, the UACR in the non-NAFLD and NAFLD groups was 3.92 ± 0.22 and 4.96 ± 0.62 , respectively ($P = 0.114$). The participants with LGA showed similar trends in UACR (Figure 3).

Discussion

Our study included only men without DM and with a UACR < 30 mg/g. The UACR in the NAFLD group was higher than that in the non-NAFLD group. The FLI as a continuous variable was correlated with the UACR in both correlation and linear regression analyses. NAFLD as a categorical variable was associated with the presence of LGA. Subgroup analyses according to the presence of MetS or age (< 50 or ≥ 50 years) showed that the association between NAFLD and UACR was stronger in participants without MetS and in those aged < 50 years.

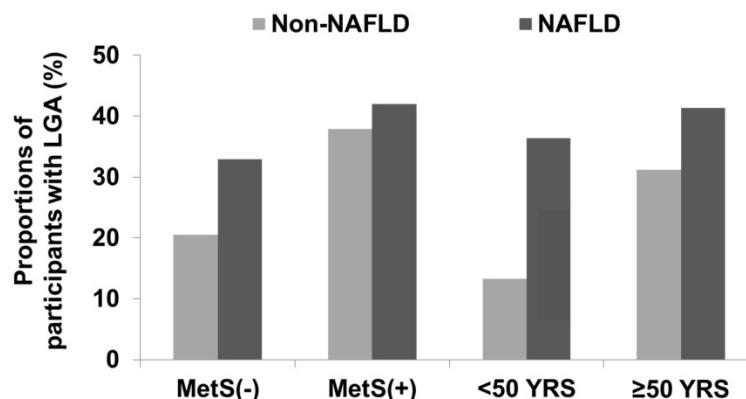


Figure 3. Proportions of participants with LGA according to age or presence of MetS. Among the study population without MetS, the number of participants with LGA was 213 (20.5%) in the non-NAFLD group and 26 (32.9%) in the NAFLD group ($P = 0.009$). Among participants with MetS, those with LGA were 53 (37.9%) in the non-NAFLD group and 55 (42.0%) in the NAFLD group ($P = 0.488$). Among participants aged < 50 years, those with LGA were 76 (13.3%) in the non-NAFLD group and 43 (36.4%) in the NAFLD group ($P < 0.001$). Among participants aged ≥ 50 years, those with LGA were 190 (31.2%) in the non-NAFLD group and 37 (41.3%) in the NAFLD group ($P = 0.054$). Abbreviations: LGA, low-grade albuminuria; MetS, metabolic syndrome.

Our study did not include women. NAFLD is a sexual dimorphic disease, in which premenopausal women have a lower prevalence of NAFLD compared to men or postmenopausal women [28]. Carulli et al. evaluated difference in patients with NAFLD according to sex and showed that men with NAFLD were on an average 10 years younger than women with NAFLD [29]. They suggested that physiological levels of estrogen might be protective for the development of NAFLD due to the improvement in insulin sensitivity, dyslipidemia, and visceral fat accumulation [29]. Postmenopausal women have a higher risk of NAFLD compared to premenopausal women, and the risk of NAFLD in these women was comparable to that of men [30]. In addition, hormone replacement therapy was associated with a decreased risk of NAFLD after menopause [31]. In our study, the prevalence of NAFLD was approximately 15.1%. Although our study reported data exclusively for men, we also performed similar analyses for female patients and our results did not show any significant differences between the two variables (data not shown). The prevalence of NAFLD in women was below 15.1%. A very low prevalence in women may lead to negative results, but instead may be an informative result for postmenopausal women.

The potential association between NAFLD and kidney disease is an interesting concept; however, cause-effect relationship is inconclusive and complex. NAFLD and kidney disease share risk factors, such as metabolic disturbances and inflammation. Previous studies have suggested that NAFLD can lead to chronic kidney disease through dyslipidemia, hypertension, insulin resistance, chronic inflammation, or oxidative stress; however, these studies have defined chronic kidney disease based on the eGFR alone and/or urine dipstick test results for overt proteinuria [32-37]. Overt proteinuria and

decrease in the eGFR are markers for an advanced stage of chronic kidney disease.

Some studies have focused on the association between NAFLD and microalbuminuria [38-41]. Casoinic et al. enrolled patients with type 2 DM and showed there was a positive association between NAFLD and microalbuminuria [39]. However, DM per se is a strong risk factor for albuminuria and DM-specific renal pathologies, such as glomerular vasculopathy or hyperfiltration, which may lead to confusion regarding the independent association between NAFLD and albuminuria in patients with DM. Therefore, the exclusion of patients with DM may help identify an independent association between the two variables.

A UACR of < 30 mg/g has classically been defined as normal. However, the amount of albuminuria is positively correlated with poor outcomes. It is difficult to definitely distinguish participants with ratios below a cut-off value using a single cut-off point from those above. Therefore, the threshold of $\text{UACR} \geq 30 \text{ mg/g}$ associated with adverse outcomes is not absolute [42]. Recent studies have demonstrated adverse outcomes in participants with LGA [17-20]. The prevalence of LGA in the general population with or without comorbidities is greater than that of micro-albuminuria or overt proteinuria. In addition, LGA presents at an earlier stage of renal damage than micro-albuminuria or overt proteinuria. Therefore, early detection and intervention of LGA would be more effective in the prevention of the progression of chronic kidney disease or other pathologies.

Lin et al. investigated the association between LGA and NAFLD in a Chinese population [21]. Their study showed that NAFLD was positively associated with LGA, and the relationship was greater in men and/or the younger population than in women

and/or the elderly population. In addition, there were no significant differences between the two variables in patients with DM. However, their data could not completely exclude patients with hepatitis B and did not include chronic diseases, such as cerebrovascular accidents or coronary artery disease, which would be confounding factors for the UACR. Our data completely excluded patients with hepatitis B and C using laboratory findings, such as hepatitis B surface antigen or anti-HCV antibody, and included patients with cerebrovascular accidents or coronary artery disease. The results of our study and the study by Lin et al. were similar. Significant differences were observed in young adults or participants without MetS, which indicated that the association between NAFLD and LGA was greater in participants without concurrent MetS.

This study has several limitations. First, it was a retrospective cross-sectional study. We could not evaluate the causality between NAFLD and LGA. Second, we used a single urine spot sample to calculate the UACR. Third, NAFLD was not defined using gold standard methods, such as liver biopsy. As liver biopsies are invasive and potentially risky, it would be difficult to perform to identify NAFLD in an epidemiologic study [3]. Clinical practice guidelines recommend that validated steatosis score systems, such as the FLI, NAFLD liver fat score, NAFLD fibrosis score, or fibrosis-4 score, would be valuable to predict the presence of NAFLD for a large-scale screening study [43]. Among these, FLI is one of the best-validated methods for predicting NAFLD. The FLI defined according to Bedogni et al. is one of the most popular equations for predicting fatty liver disease and a previous study using a dichromatic category (i.e., presence or absence of steatosis) showed a high sensitivity and specificity [25]. However, the FLI is limited by its weak association with histological levels of steatosis [44]. A recent study evaluated the diagnostic validity, level of histologic steatosis, and metabolic parameters of a new semi-quantitative index using ultrasonographic findings [45]. This index accurately identified histological severity and was associated with various metabolic indicators.

In conclusion, NAFLD was associated with LGA in men without DM in this study. Therefore, participants with a relatively high FLI or NAFLD should be closely monitored for LGA, especially if they are men without evidence of MetS. A prospective, multi-ethnic study, including accurate parameters such as UACR, a 24-hour urine sample, and a semi-quantitative ultrasonographic index assessing both the presence and grade of NAFLD, is warranted to overcome these limitations.

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Competing Interests

The authors have declared that no competing interest exists.

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