Association Between Higher Serum Fetuin-A Concentrations and Abnormal Albuminuria in Middle-Aged and Elderly Chinese With Normal Glucose Tolerance

Mian Li, md[1]
Min Xu, phd[1]
Yufang Bi, md[1]
Aiyun Song, md[1]
Yu Liu, md[1]
Xiaoying Li, md, phd[1,2]
Guang Ning, md, phd[1,2]

OBJECTIVE — To study the association of serum fetuin-A as a potential risk factor with abnormal albuminuria in Chinese individuals with normal glucose tolerance (NGT).

RESEARCH DESIGN AND METHODS — The cross-sectional analysis included 607 men and 1,042 women aged 40 or older with NGT.

RESULTS — Women with combined microalbuminuria and macroalbuminuria ($n = 68$) had significantly higher serum fetuin-A concentrations than those with normal albumin excretion ($n = 974$) (314.3 vs. 280.4 mg/l, $P = 0.007$). Compared with the lowest quartile, the highest quartile of serum fetuin-A had 40% increased risk of abnormal albuminuria after the multiple adjustments in women ($P_{\text{for trend}} = 0.02$). However, the associations were not detected in men.

CONCLUSIONS — Higher serum fetuin-A was associated with abnormal albuminuria independent of BMI, waist circumference, homeostasis model assessment of insulin resistance, blood pressure, and other determinants of albuminuria in middle-aged and elderly Chinese women with NGT.

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Fetuin-A, which is predominantly secreted by the liver, is found to be related to the accumulation of fat in the liver, insulin resistance (1), type 2 diabetes (2), and cardiovascular diseases (CVDs) (3,4). Microalbuminuria is associated with insulin resistance (5,6) and represents a risk factor for CVDs regardless of diabetes status (7). We aimed to study the association of higher serum fetuin-A as a potential risk factor with abnormal albuminuria in Chinese individuals with normal glucose tolerance (NGT).

RESEARCH DESIGN AND METHODS

— This cross-sectional investigation was conducted among 1,649 participants (607 men and 1,042 women) aged 40 years or older with NGT who were recruited from a community-based glucose survey (8). The Institutional Review Board of Ruijin Hospital, Shanghai Jiao-Tong University School of Medicine, approved the study protocol, and all the participants gave written informed consent.

Fasting and 2-h postprandial plasma glucose were measured using an automated biochemical instrument (Beckman CX-7 Biochemical Autoanalyzer; Brea, CA). Serum insulin was measured by a radioimmunoassay (Sangon Company, Shanghai, China).Urinary albumin and creatinine concentrations were determined using the first void sterile urine sample in the early morning by rate nephelometry (Beckman Coulter, Fullerton, CA) and alkaline nitroxanthic acid method, respectively. Serum fetuin-A concentrations were measured by enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN), and the intraassay and interassay coefficient of variation was 5.2 and 7.8%, respectively.

Fasting plasma glucose <6.1 mmol/l and postprandial plasma glucose <7.8 mmol/l and without taking any antidiabetic treatment were defined as NGT according to the 1999 World Health Organization (WHO) criteria (9). BMI was categorized as normal weight (<23 kg/m^2, $n = 375$) and overweight or obese (≥23 kg/m^2, $n = 667$) (10). The albumin-to-creatinine ratio (ACR) was used for the diagnosis of abnormal albuminuria, and was defined as an ACR ≥30 mg/g. The abbreviated Modification of Diet in Renal Disease (MDRD) Study Group formula was used to calculate the estimated glomerular filtration rate (eGFR) (11). Chronic kidney disease was defined as eGFR <60 ml/min per 1.73 m^2 ($n = 166$).

Analysis was performed on SAS version 8.1 (SAS Institute, Cary, NC). Comparisons of means and proportions were performed with the standard normal Z test and χ^2 test. The unadjusted and multivariate adjusted logistic regression analysis was used to investigate the associations between abnormal abuminuria and serum fetuin-A concentrations. A P value <0.05 was considered statistically significant.

RESULTS

— The prevalence of abnormal albuminuria was 4.5% in men and 6.5% in women. Women with abnormal albuminuria had higher serum fetuin-A concentrations than those with normal

From the [1]Shanghai Clinical Center for Endocrine and Metabolic Diseases, Shanghai Institute of Endocrine and Metabolic Diseases, Department of Endocrine and Metabolic Diseases, Rui-Jin Hospital, Shanghai Jiao-Tong University School of Medicine, Shanghai, China; and the [2]State Key Laboratory of Medical Genomics, E-Institute of Shanghai Universities, Shanghai, China.
Corresponding author: Guang Ning, guangning@medmail.com.cn.
M.L. and M.X. contributed equally to this article.
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Table 1—*Association between fetuin-A and abnormal albuminuria*

	Unadjusted	Model 1	Model 2	Model 3	Model 4
Men (n = 607)					
Quartile 1 (<235.6 mg/l)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quartile 2 (235.6–292.5 mg/l)	1.18 (0.39–3.61)	1.62 (0.44–6.02)	2.25 (0.51–9.56)	2.21 (0.52–9.45)	2.18 (0.48–9.86)
Quartile 3 (292.5–368.6 mg/l)	1.08 (0.62–1.89)	0.98 (0.52–1.87)	0.68 (0.32–1.43)	0.69 (0.33–1.46)	0.59 (0.25–1.37)
Quartile 4 (≥ 368.6 mg/l)	1.06 (0.73–1.53)	1.03 (0.67–1.57)	0.97 (0.59–1.57)	0.93 (0.57–1.53)	0.90 (0.54–1.52)
$P_{\text{for trend}}$	0.79	0.88	0.63	0.60	0.45
1 SD increase of fetuin-A	0.89 (0.54–1.28)	0.80 (0.47–1.21)	0.75 (0.42–1.12)	0.74 (0.41–1.19)	0.70 (0.38–1.16)
Women (n = 1,042)					
Quartile 1 (<233.9 mg/l)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Quartile 2 (233.9–283.0 mg/l)	1.28 (0.57–2.88)	1.12 (0.48–2.60)	1.10 (0.47–2.58)	1.08 (0.46–2.53)	1.09 (0.46–2.58)
Quartile 3 (283.0–355.6 mg/l)	1.26 (0.85–1.85)	1.27 (0.85–1.91)	1.28 (0.85–1.91)	1.27 (0.85–1.91)	1.27 (0.85–1.91)
Quartile 4 (≥355.6 mg/l)	1.36 (1.07–1.73)	1.37 (1.07–1.76)	1.39 (1.08–1.80)	1.40 (1.08–1.81)	1.40 (1.08–1.81)
$P_{\text{for trend}}$	0.008	0.01	0.01	0.02	0.02
1 SD increase of fetuin-A	1.30 (1.05–1.58)	1.28 (1.02–1.56)	1.26 (1.01–1.55)	1.26 (1.01–1.55)	1.26 (1.01–1.55)

Data are OR (95% CI). We defined participants with the normal UAE as 0 and abnormal albuminuria (microalbuminuria and macroalbuminuria) as 1. Model 1: adjusted for age, family history of diabetes, smoking habits, and alcohol intake, systolic blood pressure, diastolic blood pressure, serum high-sensitivity-C-reactive protein, and eGFR; Model 2: further adjusted for serum triglyceride, total cholesterol, HDL cholesterol, and LDL cholesterol based on Model 1; Model 3: further adjusted for homeostasis model assessment of insulin resistance based on Model 2; Model 4: further adjusted for BMI and waist circumference based on Model 3.

albumin excretion (314.3 vs. 280.4 mg/l, P = 0.007). Among women, the prevalence of abnormal albuminuria gradually increased across the fetuin-A quartiles. Compared with the lowest quartile, the highest quartile of serum fetuin-A had 40% increased risk of abnormal albuminuria ($P_{\text{for trend}}$ = 0.02) after the multiple adjustments (Table 1). After excluding subjects with chronic kidney disease, the result was not radically changed. However, these associations did not appear in men (online appendix Table 1 and online appendix Fig. 1, available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc10-0595/DC1 and in Table 1). The prevalence of the abnormal albuminuria was 7.2% in women who were overweight and obese and 5.3% in women with normal weight. Each 1 SD increase of fetuin-A was associated with abnormal albuminuria among women who were overweight and obese (odds ratio [OR] 1.38 [95% CI 1.05–1.7], P = 0.02), whereas the association did not appear in women with normal weight (0.95 [0.56–1.45], P = 0.84).

CONCLUSIONS — To our knowledge, this is the first study to explore the association between serum fetuin-A and abnormal albuminuria in NGT subjects. Higher serum fetuin-A was associated with abnormal albuminuria independent of the traditional determinants of albuminuria in middle-aged and elderly Chinese women with NGT.

Fetuin-A was associated with insulin resistance (1,12). It is possible that the role of fetuin-A in mediating insulin resistance may underlie the association between fetuin-A and abnormal albuminuria. However, the association was independent of homeostasis model assessment of insulin resistance index in the present study, suggesting that insulin resistance might partially determine the relation between fetuin-A and abnormal albuminuria. Other potential mechanisms, such as low-grade inflammation (13), could link fetuin-A with elevated urinary albumin excretion (UAE). Additionally, further adjustment for waist circumference did not change the association between fetuin-A and abnormal albuminuria. Liver fat and its secreted products, such as fetuin-A, might be more promising in the determination of the metabolic risk than measurement of waist circumference, adiponectin, or visceral fat (14). Thus, the association between fetuin-A and abnormal albuminuria might be mediated by increased liver fat instead of or independent of waist circumference. However, without precise measurements of body fat distribution, the underlying mechanism cannot be drawn from our study.

Higher fetuin-A was reported to be more strongly associated with a higher CVD risk in women than in men (5). We found a significant interaction between sex and serum fetuin-A for the association with abnormal albuminuria. A more likely explanation is that more metabolic factors were associated with urinary ACR in men with NGT than those in women (online appendix Table 1), which might overcome and veil the effect of fetuin-A on the UAE in men. However, the power is 23% in men to find an OR of 1.40 in women given that the prevalence of abnormal albuminuria in men is 4.5%. Thus, we cannot exclude a significant association of serum fetuin-A and abnormal albuminuria in men due to a relative small sample size. Potential sex-specific associations between fetuin-A and abnormal albuminuria need to be elucidated.

However, the principal limitation of our study was its cross-sectional design, and no causal inference can be drawn. Also, when evaluating UAE, we did not collect 24-h urine. Although ACR in the first morning urine sample is less precise, it was reported to well agree with 24-h UAE and could be a reliable alternative in epidemiological studies (15).

In summary, higher serum fetuin-A was independently associated with abnormal albuminuria in middle-aged and elderly Chinese women with NGT. Prospective studies are required to determine the role of fetuin-A in the development of abnormal albuminuria and CVDs.

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Y.B., A.S., and Y.L. took part in the field work. A.S. and Y.L. performed the measurement of serum fetuin-A concentrations. X.L. provided the suggestions on the study design and draft revision. G.N. contributed to the study conception and design.

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