Association between Higher Serum Fetuin-A Concentrations and Abnormal Albuminuria in Middle-aged and Elderly Chinese with Normal Glucose Tolerance

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Additional information for this article can be found in an online appendix at http://care.diabetesjournals.org

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

Research design and methods - 607 men and 1,042 women aged 40 or older with NGT were included in this cross-sectional analysis.

Results - Women with combined micro- 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 for trend = 0.02). However, the associations were not detected in men.

Conclusion - Higher serum fetuin-A were associated with abnormal albuminuria independent of BMI, waist circumference, HOMA-IR, blood pressure and other determinants of albuminuria in middle-aged and elderly Chinese women with NGT.
Fetuin-A Associates with abnormal albuminuria

Analysis was performed on SAS version 8.1 (SAS Institute, Cary, NC, USA). Comparisons of means and proportions were performed with the standard normal z-test and χ² test. The unadjusted and multivariate adjusted logistic regression analysis was used to investigate the associations between abnormal albuminuria 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 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 for trend = 0.02) after the multiple adjustments (Table 1). After excluding subjects with CKD, the result was not radically changed. However, these associations did not appear in men (Appendix Table 1 and Figure 1, and 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 (OR 1.38, 95% CI 1.05-1.7, p = 0.02), whereas the association did not appear in women with normal weight (OR 0.95, 95% CI 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 were 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 roles of fetuin-A in mediating insulin resistance may underlying the association between fetuin-A and abnormal albuminuria. However, the association was independent of HOMA-IR 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 linking fetuin-A with elevated urinary albumin excretion. 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 CVDs 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 in men with NGT, more metabolic factors were associated with urinary ACR than those in women (Online Appendix Table 1 available at http://care.diabetesjournals.org), which might overcome and veil the effect of fetuin-A on the urinary albumin excretion in men. However, the power is 23% in men to find an odds ratio 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. Second, for the evaluation of urinary albumin excretion, we did not collect 24-h urine. Although ACR in first morning urine sample is less precise, it was reported to well agree with 24-hour urinary albumin excretion 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 roles of fetuin-A in the development of abnormal albuminuria and CVDs.

Author contributions - M. Li and M. Xu contributed to data analysis and draft writing; M. Xu, Y.F. Bi and G. Ning contributed to critical revision of the article for important intellectual content; M. Xu, Y.F. Bi, A.Y. Song and Y. Liu took part in the field work; A.Y. Song and Y. Liu performed the measurement of serum fetuin-A concentrations; X.Y. Li provided the suggestions on study design and draft revision; G. Ning contributed to study conception and design.

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REFERENCES
Table 1 — Association between fetuin-A and abnormal albuminuria

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

Data are odds ratios (95% confidence interval). We defined participants with the normal urinary albumin excretion as 0 and abnormal albuminuria (micro- and macroalbuminuria) as 1.

Model 1: adjusted for age, family history of diabetes, smoking habits and alcohol intake, SBP, DBP, serum hs-CRP and eGFR;
Model 2: further adjusted for serum TG, TC, HDL-C and LDL-C based on model 1;
Model 3: further adjusted for HOMA-IR based on model 2;
Model 4: further adjusted for BMI and waist circumference based on model 3.