Research Article

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Association between uric acid and metabolic syndrome in elderly women

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Abstract: Objective. To investigate the relationship between uric acid and metabolic syndrome (MetS) in elderly women.

Methods. A total of 468 women aged ≥60 years participating in a health examination were enrolled. The association between uric acid and MetS and its individual variables was evaluated by univariate and multivariate logistic regression models.

Results. A dose-response relationship was observed for the prevalence of MetS and uric acid quartiles. Subjects in the second, third and fourth quartile of uric acid had a 2.23-fold, 2.25-fold and 4.41-fold increased risk, respectively, of MetS than those in the first uric acid quartile (p for trend <0.001). Furthermore, each 1 mg/dl increment of serum uric acid level had a 1.38-fold increased risk of MetS (OR 1.38; 95% CI, 1.14-1.69; p=0.001).

Conclusions. Our present study demonstrated that elevated uric acid was positively associated with the prevalence of MetS in elderly women. Further random control trials are needed to elucidate the effectiveness of treatment of hyperuricaemia in reducing the incidence of MetS in elderly women.

Keywords: Uric acid; Metabolic syndrome; Elderly women

1 Introduction

Metabolic syndrome (MetS) consists of a range of risk factors including obesity, hyperglycaemia, high blood pressure, high triglycerides, and low high-density lipoprotein cholesterol [1]. MetS is associated with increased risk of type 2 diabetes mellitus (DM), cardiovascular disease, cardiovascular mortality and all-cause mortality [2, 3], and is regarded as a critical public health and clinical challenge given its high prevalence in developing and developed countries [4, 5]. Hence, detection and intervention against MetS as early as possible are necessary for preventing the progression of MetS related diseases and reducing the public health burden in the world.

Uric acid (UA) is the end product of purine metabolism in humans[6]. Recent studies have demonstrated that elevated UA may be a predictor for MetS in different populations [7-10]. However, results of these studies are controversial, and research on the relationship between UA and MetS in elderly populations is insufficient. The prevalence of MetS is much higher in elderly populations, especially in women [11, 12], and previous studies showed that MetS was associated with higher cardiovascular risk in women than men [13, 14]. Therefore, we conducted a cross-sectional study to investigate the relationship between UA and MetS and its components in elderly women.

2 Methods

2.1 Subjects

Our present study enrolled 468 Han Chinese elderly women (aged 60-90 years) who visited for an annual health examination in Linyi People’s Hospital from March 2016 to October 2016. All subjects completed a physical check-up according to a standardized protocol. Written informed consent was obtained from all participants. The study was approved by the Ethics Committee of Linyi People’s Hospital and was conducted in accordance with the guidelines of the Helsinki Declaration.
2.2 Data collection and laboratory measurement

Trained nurses administered standardized questionnaires to obtain general information, including age, past illness history, history of drug treatment, smoking, drinking, etc. Height was measured without shoes by calibrated height metres, and weight was measured to the nearest 0.1 kg. Waist circumference (WC) was measured between the iliac crest and rib cage with a non-elastic tape. Body mass index (BMI) was evaluated by the formula weight (kg)/height$^2$ (m$^2$). Blood pressure was measured 3 times with an automated sphygmomanometer in the seated position after at least 5 minutes of rest.

Venous blood samples after overnight fasting were obtained from the antecubital vein and were then sent to the hospital laboratory for analysis. Laboratory parameters, including fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), creatinine, UA and liver function index (Alanine aminotransferase, Aspartate transaminase) were measured enzymatically on an automatic analyser (Architect Ci8200, Abbott Co., Illinois, USA). All laboratory assessments were performed by trained clinical laboratory technicians, according to the standard operating procedures of the hospital laboratory.

2.3 Definition of MetS

We used the 2009 harmonizing definition criteria of MetS[15]: central obesity: WC≥ 80 cm in Asian women; high blood pressure: systolic blood pressure (SBP) ≥ 130 mmHg, diastolic blood pressure (DBP) ≥85 mmHg, or use of antihypertensive drugs; high TG: TG ≥150 mg/dl; low HDL-C: HDL-C<50 mg/dl in women; and hyperglycaemia: FPG ≥100 mg/dl or use of antidiabetic agents.

2.4 Statistical analysis

Continuous variables are described as the mean with standard deviation (SD), and Student’s t-test or one-way ANOVA was used to compare the difference in characteristics between the two groups or multiple groups. Categorical variables were summarized as numbers and percentages and were compared using the chi-square test. Univariate and multivariate logistic regression analyses were performed to evaluate the crude and adjusted ORs for MetS and its components according UA quartile. All statistical tests were two-sided, and p-value <0.05 was considered significant. All statistical analyses were conducted using SPSS software 18.0 (SPSS Inc., Chicago, IL, USA).

3 Results

3.1 Differences in characteristics between the MetS and Non-MetS groups

A total of 468 female subjects were enrolled in our present study, and the main characteristics are shown in Table 1. Among these, 161 subjects were diagnosed with MetS

| Table 1: Characteristics of the study populations |
|-----------------------------------------------|
| MetS (n=161) | Non-MetS (n=307) | P value |
| Age (year) | 69.34±7.11 | 70.60±6.76 | 0.065 |
| BMI (kg/m$^2$) | 26.37±3.08 | 22.85±2.52 | <0.001 |
| WC (cm) | 84.39±9.85 | 73.12±8.05 | <0.001 |
| HBP | 124(77.0%) | 124(40.4%) | <0.001 |
| DM | 54(33.5%) | 37(12.1%) | <0.001 |
| SBP (mmHg) | 139.32±15.12 | 131.24±17.26 | <0.001 |
| DBP (mmHg) | 79.27±9.59 | 77.10±9.82 | 0.023 |
| TG (mg/dl) | 239.13±131.57 | 139.54±86.58 | <0.001 |
| TC (mg/dl) | 216.12±47.35 | 206.14±38.62 | 0.015 |
| LDL-C (mg/dl) | 62.06±17.86 | 74.14±18.54 | <0.001 |
| HDL-C (mg/dl) | 110.85±36.16 | 103.14±29.16 | 0.013 |
| FPG (mmol/L) | 6.47±2.02 | 7.77±2.17 | 0.001 |
| ALT (IU/L) | 24.77±14.58 | 21.64±14.17 | 0.025 |
| AST (IU/L) | 24.62±14.58 | 24.19±8.80 | 0.634 |
| Uric acid (mg/dl) | 5.72±1.49 | 5.03±1.28 | <0.001 |
| Creatinine (mg/dl) | 0.74±0.18 | 0.74±0.17 | 0.905 |
| eGFR | 77.09±27.29 | 76.63±23.37 | 0.849 |
| No of MetS components | 3.36±0.48 | 1.36±0.68 | <0.001 |

Abbreviations: BMI: body mass index; WC: waist circumference; TG: triglyceride; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; FPG: fasting plasma glucose; ALT: alanine aminotransferase; AST: aspartate aminotransferase; eGFR: estimated glomerular filtration rate.
according to the criteria, and the overall incidence of MetS was 34.4%. There was no significant difference in mean age (69.34 years vs 70.60 years, p=0.065), AST (24.62 IU/L vs 24.19 IU/L, p=0.634) or creatinine level (5.72 mg/dl vs 5.04 mg/dl, p=0.897) between the MetS and non-MetS groups. Compared with the non-MetS group, there was a significantly higher prevalence of hypertension (77.0% vs 40.4%, p<0.001) and DM (33.5% vs 12.1%, p<0.001) in the MetS group. Additionally, subjects in the MetS group had significantly greater BMI and WC, higher levels of SBP, TG, TC, LDL –C, FPG, ALT, and uric acid, and a greater number of MetS components (all p values <0.05 or 0.01). In contrast, the MetS group had significantly lower levels of HDL-C than the non-MetS group (62.06 mg/dl vs 74.14 mg/dl, p< 0.001).

### 3.2 Subject characteristics according to uric acid quartiles

We next evaluated general subject characteristics according to uric acid quartile (Table 2). The subjects were categorized into 4 groups based on the following uric acid cut-off values: Q1: ≤4.26, Q2: 4.26-5.12, Q3: 5.12-6.11, and Q4: >6.11. The prevalence of MetS (p for trend <0.001) and hypertension (p for trend =0.017) was significantly increased with the increment of uric acid quartile. Additionally, significantly increased levels of age, BMI, WC, TG, ALT and creatinine were found across uric acid quartiles (all p values for trend <0.05). However, there was no substantial difference in the prevalence of DM, SBP, DBP, TC, LDL-C, FPG, AST across uric acid quartiles (all p values for trend>0.05).

| Table 2: Characteristics of subjects according to quartiles of UA |
|----------------|----------------|----------------|----------------|----------------|----------------|
|                | Q1 (n=117)     | Q2 (n=117)     | Q3 (n=117)     | Q4 (n=117)     | P value        |
| UA quartiles (mg/dl) | ≤4.26          | 4.26-5.12      | 5.12-6.11      | >6.11          |                |
| Age (year)       | 69.21±7.33     | 69.06±6.66     | 69.46±7.03     | 71.37±6.86     | 0.041          |
| BMI (kg/m2)      | 23.14±3.19     | 23.80±2.98     | 23.99±2.85     | 25.32±3.36     | <0.001         |
| WC (cm)          | 74.06±10.23    | 76.17±9.53     | 76.76±9.13     | 81.02±10.76    | <0.001         |
| HBP              | 52(44.4%)      | 57(48.7%)      | 64(54.7%)      | 75(64.1%)      | 0.017          |
| DM               | 22(18.8%)      | 19(16.2%)      | 25(21.4%)      | 25(21.4%)      | 0.717          |
| SBP (mmHg)       | 134.01±17.92   | 134.79±18.70   | 133.21±15.49   | 134.08±15.75   | 0.917          |
| DBP (mmHg)       | 78.25±10.28    | 77.50±10.53    | 78.44±8.71     | 77.19±9.58     | 0.381          |
| TG (mg/dl)       | 137.59±89.28   | 162.48±94.46   | 160.59±85.61   | 234.53±152.03  | <0.001         |
| TC (mg/dl)       | 204.95±35.12   | 209.38±43.05   | 206.60±36.87   | 217.35±50.78   | 0.111          |
| HDL-C (mg/dl)    | 78.39±22.38    | 70.86±18.53    | 67.26±17.37    | 63.43±14.52    | <0.001         |
| LDL-C (mg/dl)    | 100.18±27.34   | 106.59±32.48   | 104.81±29.71   | 111.58±36.71   | 0.053          |
| FPG (mmol/L)     | 5.95±2.54      | 5.54±1.07      | 5.79±1.49      | 5.78±1.38      | 0.329          |
| ALT (IU/L)       | 21.92±13.62    | 20.07±10.64    | 22.97±13.94    | 25.90±17.91    | 0.017          |
| AST (IU/L)       | 23.96±10.32    | 23.03±7.30     | 24.20±7.85     | 26.16±10.57    | 0.064          |
| Creatinine (mg/dl) | 0.67±0.16     | 0.71±0.14      | 0.73±0.16      | 0.84±0.19      | <0.001         |
| eGFR              | 84.93±22.90    | 79.52±25.57    | 77.95±27.59    | 64.76±17.53    | <0.001         |
| MetS              | 22(18.8%)      | 37(31.6%)      | 38(32.5%)      | 64(54.7%)      | <0.001         |
| No of MetS components | 1.68±0.99     | 1.89±1.20      | 2.10±1.07      | 2.53±1.09      | <0.001         |

Abbreviations: BMI: body mass index; WC: waist circumference; TG: triglyceride; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; FPG: fasting plasma glucose; ALT: alanine aminotransferase; AST: aspartate aminotransferase. eGFR: estimated glomerular filtration rate.
3.3 Association between uric acid and the prevalence of MetS

Univariate and multivariate logistic regression analyses were performed to evaluate the association between MetS and uric acid quartile. The detailed results are shown in Table 3. The unadjusted OR for MetS increased from 1.99 (95% CI, 1.09–3.66) for the second quartile to 5.21 (95% CI, 2.89–9.40) for the fourth quartile (p for trend <0.001). In the multivariate logistic analysis, subjects in the second, third and fourth uric acid quartiles had a 2.23-fold, 2.25-fold and 4.41-fold increased risk, respectively, of MetS than those in the first uric acid quartile (p for trend <0.001). Furthermore, each 1 mg/dl increment of serum uric acid level had a 1.38-fold increased risk of MetS (OR, 1.38; 95% CI, 1.14–1.69; p=0.001). One previous study showed that the positive association between acid uric and MetS diminished with age in elderly people[16], and we obtained similar results in our present study: the ORs for MetS in the young old (60-74 years), old (75-84 years) and oldest old (85-94 years) were 1.52, 1.30, and 2.34, respectively, per 1 mg/dl increment of uric acid (detailed results are shown in supplementary material).

3.4 Association between uric acid and the incidence of individual MetS components

We further assessed the association between uric acid and individual MetS components. After adjustment for age, positive associations for uric acid quartile and individual MetS risk components were found for all components, except for hypertensive subjects (Table 4).

| Table 3: Odds ratios (95% CIs) of MetS according to quartiles of UA |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| UA quartiles (mg/dl)            | Q1 (n=117)      | Q2 (n=117)      | Q3 (n=117)      | Q4 (n=117)      | P for trend     |
| Case                           | ≤4.26           | 4.26-5.12       | 5.12-6.11       | >6.11           |                 |
| Model 1                        | 22              | 37              | 38              | 64              | <0.001          |
| Model 2                        | 1               | 1.99(1.09-3.66) | 2.08(1.14-3.80) | 5.21(2.89-9.40) | <0.001          |
| Model 3                        | 1               | 2.01(1.10-3.68) | 2.07(1.13-3.80) | 5.05(2.79-9.13) | <0.001          |
| Per 1mg/dl UA increment         | 1.38(1.14-1.69) |                 |                 |                 | 0.001           |

Model 1: unadjusted OR.
Model 2: adjusted for age.
Model 3: adjusted for age, BMI, ALT, TC, LDL-C, Creatinine.

4 Discussion

The incidence of MetS significantly increases with increasing age. Li et al. [11] performed a meta-analysis including 226,653 Chinese subjects and showed that the prevalence of MetS was 32.4% in subjects ≥60 years old in Mainland China, which is significantly higher than that in populations of subjects less than 60 years old. Moreover, the authors also showed that MetS was more common in post-menopausal females than in elderly males (42.9 vs. 23.0 %). In this study, we investigated the association between uric acid and risk of MetS in elderly women. Our results showed that elevated uric acid was positively associated with MetS and its individual variables in elderly women; compared with subjects in the bottom quartile, the unadjusted MetS OR was 5.21 (95%CI 2.89–9.40) for the highest quartile group. The OR in the fourth quartile was still 4.41-fold higher than that in the first quartile after adjusting for several confounding factors. As to MetS components, our study suggested that uric acid was significantly correlated with central obesity, high TG and low HDL-C, but not with hypertension or hyperglycaemia.

A large number of epidemiological studies have found a positive relationship between serum uric acid levels and the prevalence of MetS. However, it is still controversial whether elevated uric acid levels are a risk factor or just a biomarker in the development and progression of MetS [17, 18]. Recent clinical and animal studies indicated that elevated uric acid levels might play a pathogenic role in the development of MetS [19]. Basic research has confirmed a causal role of uric acid in the onset of MetS and the benefits of lowering uric acid levels in preventing or reversing MetS [9,20,21]. A small randomized, controlled clinical trial has also verified the protective effect of lowering uric acid levels in the development of MetS [22].
potential mechanisms of uric acid in inducing MetS are as follows: First, hyperuricaemia has been shown to induce endothelial dysfunction in both animal and human models [23,24]. Endothelial dysfunction is a hallmark of MetS [25]. Second, uric acid has been shown to inhibit the production and bioavailability of NO [26], which is essential for insulin action [27,28]. Thus, hyperuricaemia could induce or worsen insulin resistance by itself. Indeed, epidemiological studies have shown the predictive value of uric acid in the risk of insulin resistance [29]. In turn, insulin resistance is thought to play a pivotal role in MetS [30]. Additionally, despite being a classic antioxidant, uric acid can promote oxidative stress once inside the cell [31,32]. Hyperuricaemia is also associated with elevated circulating levels of inflammatory cytokines, such as monocyte chemoattractant protein 1, C-reactive protein and tumour necrosis factor-α [31,33,34].

Our present study has several limitations. First, our study design is cross-sectional and we cannot draw a causal relationship between uric acid and MetS in elderly women. Second, the sample size in our study is not large enough. Moreover, we adjusted for several possible confounding factors in exploring the association of uric acid and MetS in our statistical analysis; however, residual confounding effects may still exist. For example, caloric intake, sodium intake, and exercise, etc., were not included in our study, which might lead to potential bias in the results.

In summary, our present study demonstrated that elevated uric acid was positively associated with the prevalence of MetS in elderly women. Further random control trials are needed to elucidate the effectiveness of treatment for hyperuricaemia in reducing the incidence of MetS in elderly women.

**Conflicts of interest:** The authors have no conflicts of interest to declare.

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**Table 4:** Age-adjusted odds ratios of each individual MetS components according to quartiles of UA

|               | Q1 n=117 | Q2 n=117 | Q3 n=117 | Q4 n=117 | P for trend |
|---------------|----------|----------|----------|----------|------------|
| UA quartiles (mg/dl) |          |          |          |          |            |
| ≤4.26         | 30       | 37       | 40       | 60       | <0.001     |
| 4.26-5.12     |          | 1.34(0.76-2.37) | 1.52(0.86-2.67) | 3.21(1.84-5.61) | <0.001     |
| 5.12-6.11     |          |          |          |          |            |
| >6.11         |          |          |          |          |            |
| Central obesity | Case     | 88       | 82       | 95       | 98         |
| Odds ratio    | 1        | 0.76(0.42-1.38) | 1.41(0.74-2.67) | 1.45(0.75-2.82) | 0.102     |
| High blood pressure | Case     | 43       | 48       | 57       | 59         |
| Odds ratio    | 1        | 1.20(0.71-2.04) | 1.63(0.97-2.75) | 1.68(0.99-2.84) | 0.028     |
| Hyperglycemia | Case     | 33       | 53       | 53       | 79         |
| Odds ratio    | 1        | 2.11(1.22-3.63) | 2.12(1.23-3.65) | 5.48(3.12-9.62) | <0.001     |
| High TG       | Case     | 4        | 8        | 11       | 18         |
| Odds ratio    | 1        | 2.01(0.61-7.19) | 2.92(0.90-9.48) | 4.83(1.57-14.80) | 0.002     |
| Low HDL-C     | Case     |          |          |          |            |
| Odds ratio    |          |          |          |          |            |
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