The relationship between leukocyte level and hypertension in elderly patients with hyperuricemia

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Abstract
To evaluate the change of leukocyte level caused by hyperuricemia, and to explore the relationship between leukocyte level and hypertension in elderly patients with hyperuricemia. A cross-sectional study of serum uric acid (UA) level was conducted in 1352 elderly people over 65 years old. The samples were divided into 3 categories according to the tertiles of leukocyte: Tertile 1, leukocyte ≤ 5.2 × 10⁹/L; Tertile 2, leukocyte = 5.3–6.3 × 10⁹/L; Tertile 3, leukocyte ≥ 6.4 × 10⁹/L. Multiple logistic regression models were used for modeling relationships between leukocyte, hyperuricemia and hypertension. Human vascular endothelial cells were treated by different concentrations of UA. The levels of interleukin-1 beta, tumor necrosis factor-α, endothelial nitric oxide synthase, inducible nitric oxide synthase and reactive oxygen species were measured by Western Blot or fluorescence microscope. The levels of leukocyte were higher in elderly patients with hyperuricemia than without hyperuricemia. Hyperuricemia was an independent risk factor of leukocyte in Tertile 3 (odds ratio [OR] = 1.657, 95% confidence interval [CI]: 1.180–2.328). The prevalences of hypertension were higher in elderly patients with hyperuricemia than without hyperuricemia (77.0% vs 63.5%). In the Model 1, hyperuricemia was an independent risk factor of hypertension (OR = 1.536, 95% CI: 1.026–2.302). Leukocyte in Tertile 3 was an independent risk factor of hypertension (OR = 1.333, 95% CI: 1.031–1.724). Expression levels of interleukin-1 beta, inducible nitric oxide synthase and tumor necrosis factor-α were obviously higher in the UA group than the control group, along with the productions of reactive oxygen species. But the expression level of endothelial nitric oxide synthase was obviously lower in the UA group. Hyperuricemia was associated with an increased risk for hypertension. The chronic inflammation caused by hyperuricemia maybe one of important pathogenesis of incident hypertension in patients with hyperuricemia.

Abbreviations: BMI = body mass index, eNOS = endothelial nitric oxide synthase, HDL-C = high density lipoprotein cholesterol, HUVECs = human vascular endothelial cells, IL-1β = interleukin-1 beta, iNOS = inducible nitric oxide synthase, ROS = reactive oxygen species, TNF-α = tumor necrosis factor-α, UA = uric acid, WC = waist circumference.

Keywords: hypertension, hyperuricemia, inflammation, leukocyte

1. Introduction
Hypertension is a long-term condition that the blood pressure in the arteries is persistently elevated. In China, hypertension is very common. In 2017, the prevalence of hypertension reached 37.2% and the rates of treatment and control were extremely low.[1] Hypertension maybe not cause symptoms. However, hypertension is not benign and causes significant target organ damage, such as cardiovascular diseases and stroke.[2,3] Hypertension-related cardiovascular diseases remains the leading cause of death in Chinese adults.[4]

In humans, uric acid (UA) is the final product of purine metabolism. UA played an important role to maintain arterial blood pressure and guarantee sufficient blood supply to important organs.[5] Cross-sectional studies found that hyperuricemia is associated with hypertension in Chinese adults.[6] Cohort studies further confirmed that hyperuricemia can predict the risk of incident hypertension, independent of traditional risk factors.[7–9] Hyperuricemia could induce hypertension by the following mechanisms, including activation of renal epithelial sodium channel, renal oxidative stress, pro-inflammatory pathways, renin-angiotensin-aldosterone system and peripheral insulin resistance.[10–13] Several clinical trials found that lowering of UA may assist reducing blood pressure. UA lowering treatment can lower blood pressure in patients with hyperuricemia, especially in patients with normal renal function or early stage of chronic kidney disease.[14,15]

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Low-grade systemic inflammation is implicated in the pathophysiology of hypertension. Leukocyte levelcount reflected low-grade systemic inflammation. Leukocyte count could independently predict hypertension in Chinese adults.[16] Two studies shown that hyperuricemia correlated with leukocyte count.[17,18] Whether elevated leukocyte in patients with hyperuricemia correlated with hypertension? Very little information is currently available on the relationship between leukocyte and hypertension in hyperuricemia. In our study, we attempted to evaluate the change of leukocyte and related inflammatory factors caused by hyperuricemia and explore the relationship between leukocyte and hypertension in older adults with hyperuricemia.

2. Methods

2.1. Study population

We performed a cross-sectional study about hyperuricemia. All subjects have medical examination in Beichen District of Tianjin between June 2018 and October 2018. All subjects were men and women over 65 years old. The exclusion criteria included the following: subjects with acute and chronic inflammation; subjects with acute gout; subjects with abnormal leukocyte (leukocyte < 4 × 10^9/L or leukocyte > 1 × 10^10/L); subjects with secondary hypertension. This study was approved by the ethics committee of Tianjin Medical University Metabolic Diseases Hospital. All subjects provided written informed consent before study initiation (reference number: DXBYYhMEC2018-17).

2.2. Measurements

Anthropometric measurements, including height, weight, waist circumference (WC) and blood pressure were obtained. WC was accurately measured at the level of midway between the lowest rib and the top of the iliac crest. Blood pressure was measured accurately measured at the level of midway between the lowest rib and the top of the iliac crest. Blood pressure was measured using an automatic blood pressure monitor. Blood pressure was measured using uricase method, fasting plasma glucose concentration was measured using enzymatic assays with an autoanalyzer (Hitachi, Tokyo, Japan). Estimate glomerular filtration rate = 175 × creatinine (mg/dL)−1.234 × age (year)−0.179 (×0.79 if female).[19] The automated hematology analyzer Beckman Coulter LH750 (Beckman Coulter Inc, Brea, CA) was used to evaluate the results of blood routine examinations (including leukocyte count).

2.3. Definition

Hyperuricemia was defined as UA > 420 μmol/L (7 mg/dL).[20] Hypertension was defined as subjects with history of hypertension or systolic blood pressure and/or diastolic blood pressure ≥ 140/90 mm Hg for 3 screenings. Abdominal obesity: WC ≥ 90 cm (male) and 85 cm (female), abnormal glucose metabolism: fasting plasma glucose ≥ 6.1 mmol/L or have been diagnosed with diabetes, hypertriglyceridemia: triglyceride ≥ 1.7 mmol/L, low high density lipoprotein cholesterol (HDLC): HDL-C < 1.04 mmol/L.

2.4. Cells culture and treatment

Human vascular endothelial cells (HUVECs; Beona Chuanglian Biotechnology Co. LTD, Beijing, China) were incubated in high-glucose DMEM medium (Gibco, CA) containing 10% fetal bovine serum (Gibco) at 37°C with 5% CO₂. When the adhering cells reached confluence, passage by trypsin digestion was conducted. After 3 to 5 passages, cells were treated with different concentrations of UA (0, 4, 8, 16 mg/dL) for 24 hours, then cells were collected for western blotting.

2.5. Western blot analysis

HUVECs were collected and lysed with RIPA protein lysis buffer and the protein concentration was investigated by Bio Rad protein assay. Proteins were resolved by 12.5% SDS-PAGE and transferred to nitrocellulose membranes. Membranes were incubated with antibody targeting endothelial nitric oxide synthase (eNOS) (1:500; Abcam, Cambridge, UK), inducible nitric oxide synthase (iNOS) (1:500; Abcam, UK), interleukin-1 beta (IL-1β) (1:1000; Affinity, CA) and tumor necrosis factor-α (TNF-α) (1:1000; Abcam) at 4°C overnight. After washing, the membranes were incubated with secondary antibody (1:4000) in TBST for 1 h at room temperature. ECL Plus detection system was used for immunodetection, and the density of the bands was detected by Image J software (National Institutes of Health, USA).

2.6. Influence of UA on the production of ROS

HUVECs were treated by different concentrations of UA (0, 4, 8, 16 mg/dL) for 12 hours. Then cells were loaded with 10 μM working solution at 37°C for 20 minutes and washed thrice with warm buffer according to the experimental protocol of reactive oxygen species (ROS) assay kit (Beyotime Biotechnology, Shanghai, China). After that, cells were analyzed with a fluorescence microscope.

2.7. Statistical analyses

All analyses were performed using the SPSS 11.5 statistical software (SPSS 11.5 for Windows; SPSS, Inc., Chicago, IL). Values are expressed as mean with standard deviation, and analyzed using GraphPad Prism 8.0 (GraphPad Software, CA). The 2 groups were compared using the Student t test. When equal variances not assumed, t’ test was used. When not normally distributed, the data were expressed as medians with interquartile ranges and were compared using by the Mann–Whitney U test. Comparison of prevalence data was performed by χ² analysis. Multiple logistic regression models were used for modeling relationships between leukocyte, hyperuricemia and hypertension. The one-way analysis of variance for multiple comparison was performed for differences analysis. P < .05 was considered statistically significant.

3. Results

3.1. Clinical characteristics of the subjects

This study enrolled 1352 elderly people (620 males and 732 females), age 72.4 ± 6.4 years. The prevalence of hyperuricemia was 11.9% in our study. The prevalence of hyperuricemia were higher in males than in females (Males 16.1% vs Females 8.3%, χ² = 19.447, P < .001). The levels of hemoglobin, platelet, neutrophil (%), lymphocyte (%) and lymphocyte (10^9/L) were similar between elderly patients with or without hyperuricemia (P > .05). The levels of neutrophil (10^9/L) and lymphocyte (10^9/L) were higher in elderly patients with hyperuricemia than without hyperuricemia (P < .01). The study samples were divided into 3 categories according to the tertiles of leukocyte: Tertile 1 leukocyte ≤ 5.2 × 10^9/L, Tertile 2 leukocyte = 5.3–6.3 × 10^9/L, and Tertile 3 leukocyte ≥ 6.4 × 10^9/L. The frequencies of leukocyte in Tertile 3 were higher in elderly patients with hyperuricemia than without hyperuricemia (Table 1). In multiple logistic regression analysis, leukocyte (Tertile 3) was considered as the dependent variables with sex, age, BMI (0 = BMI < 24 kg/
The results showed that there was no significant difference in TNF-α protein expression between the 4 mg/dL UA group and the control group (P = .0687). Expression levels of IL1-β in the 8 mg/dL UA group and in the 16 mg/dL UA group were obviously higher than that in the control group (P < .0001). Expression levels of IL1-α in the 8 mg/dL UA group and in the 16 mg/dL UA group were obviously higher than that in the 4 mg/dL UA group (P < .0001) (Fig. 1C and F).

The results showed that there was no significant difference in TNF-α protein expression between the 4 mg/dL UA group and the control group (P = .3260). Expression levels of TNF-α in the 8 mg/dL UA group and in the 16 mg/dL UA group were obviously higher than that in the control group (P < .0001). Expression levels of TNF-α in the 8 mg/dL UA group and in the 16 mg/dL UA group were obviously higher than that in the 4 mg/dL UA group (P < .0001) (Fig. 1C and G).

### 3.3. Comparison of ROS content in different UA concentration groups

The results showed that there was no significant difference in ROS content between the 4 mg/dL UA group and the control group (P = .7230). The production of ROS in the 8 mg/dL UA group (P = .0370) and in the 16 mg/dL UA group (P < .0001) were obviously higher than that in the control group (P < .05) (Fig. 1A and B).

#### Table 2

| Variable                  | OR     | 95% CI | P    |
|---------------------------|--------|--------|------|
| Abdominal obesity         | 1.595  | 1.249–2.038 | <.001 |
| Abnormal glucose metabolism| 1.380  | 1.091–1.746 | .007  |
| Hypertriglyceridemia      | 1.404  | 1.105–1.785 | .006  |
| Hyperuricemia             | 1.657  | 1.180–2.328 | .004  |

Elevated WBC was defined as WBC in Tertile 3 (≥6.4 × 10⁹/L). Multiple logistic regression analysis, elevated WBC was considered as the dependent variables in a multiple logistic regression analysis with sex, age, BMI (0 = BMI < 24 kg/m², 1 = BMI 24–27.9 kg/m², 2 = BMI ≥ 28 kg/m²), abdominal obesity, abnormal glucose metabolism, hypertriglyceridemia, low HDL-C and hyperuricemia as independent variables.

BMI = body mass index, CI = confidence interval, HDL-C = high density lipoprotein cholesterol, OR = odds ratio, WBC = white blood cell.

### 3.2. Effect of different concentrations of UA on the expression level of eNOS, iNOS, IL1-β and TNF-α in HUVECs

The results showed that there was no significant difference in eNOS protein expression between the 4 mg/dL UA group and the control group (P = .9639). Expression level of eNOS was obviously lower in the 8 mg/dL UA group (P = .0022) and in the 16 mg/dL UA group (P = .0003) than that in the control group. Expression levels of eNOS tested by Western blot in the 8 mg/dL UA group (P = .0013) and in the 16 mg/dL UA group (P = .0002) were obviously lower than that in the 4 mg/dL UA group. Expression level of iNOS was obviously higher in 4 mg/dL UA group (P = .0021), 8 mg/dL UA group (P = .0210) and 16 mg/dL UA group (P = .0111) than that in the control group. There was no significant difference in iNOS protein expression between the 4 mg/dL UA group, 8 mg/dL UA group (P = .3281) and 16 mg/dL UA group (P = .5393) (Fig. 1C–E).

The prevalences of hypertension were similar between males and females (Males 63.2% vs Females 66.7%, \( \chi^2 = 1.749, P = .186 \)). Patients with hypertension were older than patients without hypertension (\( P < .01 \)). The levels of alanine aminotransferase were similar between 2 groups (\( P > .05 \)). The levels of estimate glomerular filtration rate were lower in older adults with hypertension than without hypertension (\( P < .01 \)). The frequencies of BMI ≥ 28 kg/m², abdominal obesity, abnormal glucose metabolism, hypertriglyceridemia, low HDL-C, hyperuricemia and leukocyte (Tertile 3) were higher in older adults with hypertension than without hypertension (\( P < .01 \)) (Table 3).

The prevalences of hypertension were higher in elderly people with hyperuricemia than without hyperuricemia (77.0% vs 63.5%, \( \chi^2 = 11.447, P = .001 \)). In multiple logistic regression analysis (Model 1), hypertension was considered as the dependent variables with sex, age, BMI abdominal obesity, abnormal glucose metabolism, hypertriglyceridemia, low HDL-C and hyperuricemia as independent variables. Hyperuricemia was an independent risk factor of hypertension (OR = 1.657, 95% confidence interval [CI]: 1.180–2.328, \( P = .004 \) (Table 2).

The risk factors of elevated WBC in older adults.

| Variable                  | OR     | 95% CI | P    |
|---------------------------|--------|--------|------|
| Abdominal obesity         | 1.595  | 1.249–2.038 | <.001 |
| Abnormal glucose metabolism| 1.380  | 1.091–1.746 | .007  |
| Hypertriglyceridemia      | 1.404  | 1.105–1.785 | .006  |
| Hyperuricemia             | 1.657  | 1.180–2.328 | .004  |

Elevated WBC was defined as WBC in Tertile 3 (≥6.4 × 10⁹/L). Multiple logistic regression analysis, elevated WBC was considered as the dependent variables in a multiple logistic regression analysis with sex, age, BMI (0 = BMI < 24 kg/m², 1 = BMI 24–27.9 kg/m², 2 = BMI ≥ 28 kg/m²), abdominal obesity, abnormal glucose metabolism, hypertriglyceridemia, low HDL-C and hyperuricemia as independent variables.

BMI = body mass index, CI = confidence interval, HDL-C = high density lipoprotein cholesterol, OR = odds ratio, WBC = white blood cell.
### Table 3
Clinical characteristics of older adults with or without hypertension.

| Variable                  | Non-hypertension group (n = 472) | Hypertension group (n = 880) | t or χ² | P   |
|---------------------------|----------------------------------|-----------------------------|--------|-----|
| Sex (males/females)       | 228/244                          | 392/488                     | 1.749  | .186|
| Age (yr), mean (SD)       | 71.2 (5.9)                       | 73.1 (6.7)                  | 5.406* | <.001|
| ALT (U/L), mean (IQR)†    | 17.0 (12.0)                      | 17.0 (13.0)                 | 1.031  | .302|
| eGFR (mL/min•1.73 m⁻２), mean (SD) | 96.8 (13.6)                     | 93.0 (15.2)                 | 4.652* | <.001|
| BMI, n (%)                |                                 |                             |        |     |
| <24 kg/m²                 | 190 (40.3)                       | 225 (25.6)                  | 35.434 | <.001|
| 24–27.9 kg/m²             | 173 (36.7)                       | 332 (40.0)                  |        |     |
| ≥28 kg/m²                 | 109 (23.1)                       | 203 (34.4)                  |        |     |
| Abdominal obesity, n (%)  | 245 (51.9)                       | 573 (65.1)                  | 22.424 | <.001|
| Abnormal glucose metabolism, n (%) | 134 (28.4)                     | 435 (49.4)                  |        |     |
| Hypertriglyceridemia, n (%) | 149 (31.6)                     | 343 (39.0)                  |        |     |
| Low HDL-C, n (%)          | 52 (11.0)                        | 171 (19.4)                  |        |     |
| Hyperuricemia, n (%)      | 37 (7.8)                         | 124 (14.1)                  |        |     |
| WBC (Tertile 3), n (%)    | 130 (27.5)                       | 321 (36.5)                  |        |     |

ALT = alanine aminotransferase, BMI = body mass index, eGFR = estimate glomerular filtration rate, HDL-C = high density lipoprotein cholesterol, IQR = interquartile range, SD = standard deviation, WBC = white blood cell.

* When equal variances not assumed, f-test was used.
† When not normally distributed, the data were expressed as medians with interquartile ranges and were compared by using the Mann–Whitney U test.

### 4. Discussion
In this study, we found that hyperuricemia has higher level of leukocyte than patients with normal UA. Elevated leukocyte level induced by hyperuricemia was associated with hypertension in elderly people with hyperuricemia.

As a marker of inflammation, elevated leukocyte count reflected a low-grade systemic inflammation in hyperuricemia.

Table 4
The risk factors of hypertension in older adults (Model 1).

| Variable                  | OR      | 95% CI    | P   |
|---------------------------|---------|-----------|-----|
| BMI                       |         |           |     |
| <24 kg/m²                 | 1.829   | 1.382–2.422 | <.001|
| 24–27.9 kg/m²             | 2.261   | 1.662–3.276 | <.001|
| ≥28 kg/m²                 | 2.319   | 1.812–2.969 | <.001|
| Abnormal glucose metabolism| 1.608   | 1.134–2.280 | .008 |
| Low HDL-C                 | 1.536   | 1.026–2.302 | .037 |

Multiple logistic regression analysis, hypertension was considered as the dependent variable in a multiple logistic regression analysis with sex, age, BMI (0 = BMI < 24 kg/m², 1 = BMI 24–27.9 kg/m², 2 = BMI ≥28 kg/m²), abdominal obesity, abnormal glucose metabolism, hypertriglyceridemia, low HDL-C and hyperuricemia as independent variables.

BMI = body mass index, CI = confidence interval, HDL-C = high density lipoprotein cholesterol, OR = odds ratio.

Table 5
The risk factors of hypertension in older adults (Model 2).

| Variable                  | OR      | 95% CI    | P   |
|---------------------------|---------|-----------|-----|
| BMI                       |         |           |     |
| <24 kg/m²                 | 1.839   | 1.389–2.344 | <.001|
| 24–27.9 kg/m²             | 2.271   | 1.670–3.088 | <.001|
| ≥28 kg/m²                 | 2.256   | 1.762–2.889 | <.001|
| Abnormal glucose metabolism| 1.654   | 1.168–2.341 | .005 |
| Low HDL-C                 | 1.333   | 1.031–1.724 | .028 |
| WBC (Tertile 3)           |         |           |     |

Multiple logistic regression analysis, hypertension was considered as the dependent variable in a multiple logistic regression analysis with sex, age, BMI (0 = BMI < 24 kg/m², 1 = BMI 24–27.9 kg/m², 2 = BMI ≥28 kg/m²), abdominal obesity, abnormal glucose metabolism, hypertriglyceridemia, low HDL-C, hyperuricemia and WBC (Tertile 3) as independent variables.

BMI = body mass index, CI = confidence interval, HDL-C = high density lipoprotein cholesterol, OR = odds ratio, WBC = white blood cell.

Consistent with previous research,[17,18] the frequencies of the highest tertile of leukocyte was higher in elderly people with hyperuricemia. As we known, subjects with hyperuricemia often accompany abdominal obesity, abnormal glucose metabolism, hypertriglyceridemia, etc. These factors were also associated with chronic inflammation. In our study, we adjusted these confounding factors, hyperuricemia still correlated with leukocyte count. Elevated UA can promote the expression of inflammatory proteins by triggering complex proinflammatory cascades that damage cells and tissues.[21] UA lowering treatment can improve systemic inflammation in asymptomatic hyperuricemia.[22]

In whole sample, hyperuricemia was an independent risk factor of hypertension. However, after leukocyte adjusted, the association between hyperuricemia and hypertension disappeared. Among older adults with hyperuricemia, elevated leukocyte was independently associated with hypertension. These results implied that inflammation may be involved in the development of hypertension associated with hyperuricemia in elderly people. Leukocyte was correlated with coronary heart disease risk in Chinese adults aged 40 to 85 years old with hyperuricemia.[23] Similar result was also observed in Japanese men.[24]

To confirm that inflammation is involved in hyperuricemia associated hypertension, we further conducted experiments at the cellular level. Endothelial dysfunction plays an important role in pathogenesis of hypertension. Hyperuricemia caused endothelial dysfunction through inflammation, which may induce hypertension.[25] UA promoted vascular inflammation, which was characterized by up-regulating of cytokines and enhanced monocyte adhesion.[24] Anti-inflammatory intervention can attenuate UA-induced endothelial injury.[27] Therefore, we further verified the effect of high levels of UA on inflammatory factors and endothelial function at the cellular level. In this study, we found that UA could significantly increase the level of IL-1β and TNF-α in HUVECs. Several reports in the literature suggested that the monosodium urate activated several inflammatory mediators, such as IL-1β, IL-6, and TNF-α.[28] TNF-α is most important player in inflammatory reactions, can further activating production of additional inflammatory cytokines.[28] It was reported that endothelial cells damage induced by inflammatory factors plays a key role in the pathogenesis of vascular diseases. The increase of IL-1β and TNF-α induced by UA probably account for vascular endothelium damage. Studies demonstrated that hypertension may develop as a result of increased ROS. Hypertensive effects of oxidative stress are mostly due to endothelial dysfunction resulting from disturbances of vasodilator systems. The eNOS is
a vascular smooth muscle relaxing factor that plays an important role in the regulation of blood pressure. Animal studies have shown that mice genetically deficient in eNOS (eNOS−/−) are hypertensive, indicated that the importance of eNOS to blood pressure regulation. A population-based study with Brazilian women showed that genetic polymorphisms of eNOS were significantly associated with a higher prevalence of hypertension. In the present study, we determined that the high concentration of UA induced intracellular ROS accumulation, increasing iNOS, and reduced eNOS in a dose-dependent manner. Therefore, the results of our external experiment further verified the relationship between white blood cells and hypertension in elderly patients with hyperuricemia, that high levels of UA trigger endothelium impairment and vascular dysfunction by increase the expression of inflammatory cytokines and ROS content, inducing iNOS and reducing eNOS, which may induce hypertension.

In conclusion, the present study demonstrates that hyperuricemia is associated with an increased risk for hypertension. The chronic inflammation caused by hyperuricemia maybe one of important pathogenesis of incident hypertension in patients with hyperuricemia.

5. Limitations

There are 2 limitations to our study. First, because of the cross-sectional design of this study, we could not identify the causal relationship between hyperuricemia, leukocyte and hypertension. Second, the measurement of blood pressure was performed within 1 day. The measurement was not repeated with an interval of several days. Third, it is well known that some antihypertensive agents can affect the level of UA. Antihypertensive agents, such as taking diuretics, were not analyzed in our study.

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