Relationship Between Hyperuricemia and Apolipoprotein AI in Chinese Healthy People: a Cohort Study

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Research

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Abstract

Background: Hyperuricemia is an independent risk factor for various cardiovascular diseases. However the association of plasma uric acid and Apolipoprotein AI among Chinese healthy people is still unclear.

Aims: To evaluate the relationship between blood uric acid and Apolipoprotein AI level in Chinese healthy people.

Method: A total of 3501 normal healthy subjects who were undergone physical examination were divided into hyperuricemia (HUA) group and normouricemia (NUA) group.

Result: Apo AI (1.33±0.21 vs. 1.47±0.26) and HDL-c (1.12±0.27 vs. 1.36±0.33) decreased significantly in HUA group than NUA group. LDL-C(2.81±0.77 vs. 2.69±0.73),Apo B(0.96±0.20 vs. 0.89±0.20), FBG(5.48±0.48 vs. 5.36±0.48) and HOMA-IR(2.75±1.92-3.91±vs. 2.18±1.50-3.12) was significantly higher in HUA group than NUA group. Increased plasma UA was correlated with decreased HDL-c(r=-0.289, P<0.01 ) and Apo AI(r=-0.236, p<0.01).

Conclusion: Hyperuricemia was associated with decreased plasma Apolipoprotein AI and HDL-c. Inhibiting Apolipoprotein AI may be one of the mechanisms of UA involved in the progression of cardiovascular disease.

Introduction

A large number of studies have shown that hyperuricemia is closely related to cardiovascular disease. It has been known that hyperuricemia is associated with a significant increased risk of hypertension, coronary heart disease (CHD) and congestive heart failure (CHF)\textsuperscript{1–3}. In addition, another study found that serum uric acid is an independent predictor for cardiovascular disease-related death, including chronic, acute and subacute forms of CHF, CHD and stroke\textsuperscript{4,5}. These related to the deposition of urate crystals in the vascular endothelium, and the dissolution of urate promotes lipid peroxidation, thus increasing oxidative stress and inflammatory response, resulting in vascular endothelial dysfunction\textsuperscript{6,7}.

Dyslipidemia is also an independent risk factor of cardiovascular disease. High-density lipoprotein cholesterol(HDL-c) is a cardiovascular protective factor\textsuperscript{8}. Apolipoprotein(apo)A-I is the principal protein of HDL-c\textsuperscript{9}. Previous studies have found that hyperuricemia is closed related to HDL-C and apo A-I. Hyperuricemia is often accompanied by abnormal lipid metabolism, including low HDL-C level\textsuperscript{10}. Moreover it was found that the ratio of apolipoprotein-B to AI are strongly associated with serum uric acid levels in US people\textsuperscript{10}. However, because the participants of most previous studies with hyperuricemia had comorbidities such as diabetes, hypertension or cardiovascular diseases, finding the role of uric acid under the condition of comorbidity become a difficulty. In the present study, we studied the relationship between hyperuricemia and APO A1 in normal healthy Chinese subjects.
Methods

Design and participants

A total of 3501 healthy individuals over 20 years and under the age of 80 years were enrolled in this study. All participants had undergone a routine physical examination at Beijing Chao-yang Hospital Affiliated to Capital Medical University from March 2012 to October 2014. The exclusion criteria were individuals with hypertension, diabetes, pre-diabetes, cancer, liver or renal function impairment, coronary artery disease or systemic inflammatory disease. Participants who took lipid-lowering agents were also excluded. HUA was defined by the plasma UA level $\geq 420\text{mol/L}$ in men and $\geq 360\text{mol/L}$ in women\textsuperscript{[11]}. We divided the participants into two groups: the NUA group (subjects without hyperuricemia) and the HUA group (subjects with hyperuricemia). The protocol of this study was approved by the Ethics Committee of the Beijing Chao-yang Hospital Affiliated to Capital Medical University.

Physical and biochemical measurement

Height, weight, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were measured. BMI was calculated as weight (kg)/height (m)$^2$.

Blood samples were collected from the vein after a 12-h fasting period. Each sample of participants was stored at $\sim80^\circ\text{C}$. HDL-c and low-density lipoprotein cholesterol (LDL-c) were measured by the direct assay on an autoanalyser(Hitachi 7170). Triglyceride (TG) level was measured by glycerol lipase oxidase reaction, and total cholesterol(TC) levels were measured by enzymatic cholesterol oxidase method on a Hitachi 7170 autoanalyser. Serum uric acid(UA) level was measured by enzymatic assay. ApoAI and apolipoprotein B (ApoB) were analysed by immune turbidimetry. The concentration of fasting insulin (FINS) and fasting blood glucose(FBG) was measured at the central chemistry laboratory in Beijing Chao-yang Hospital.

Homeostasis model assessment of $\beta$-cell function (HOMA-$\beta$) was calculated as $20\times\text{FIN}/(\text{FBG}-3.5)$

Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as $\text{FINS (µIU/mL)} \times \text{FBG (mmol/L)}/22.5$

Statistical methods

SPSS version 21.0 was used for all statistical analysis in the present study. Continuous variables with normal distributions were shown as mean $\pm$ standard deviation (SD). Continuous variables with skewed distributions were expressed as median with upper and lower quartiles. The Student t-test and non-parametric test were applied to analyze the differences between the groups. The continuous variables of abnormal distribution were expressed as the median of upper and lower quartiles, and analyzed by nonparametric test. Discontinuous variables were given as percentage and analyzed by chi-square test. To analyze the relationship between blood uric acid and Apolipoprotein AI level or other metabolism
indexes, linear regression and logistic regression analysis was performed for correlation analysis. Statistical significance was considered to be defined as $P < 0.05$.

**Results**

Clinical characteristics of the HUA and NUA group

Table 1 showed the clinical characteristics between HUA and NUA groups. There were 2868 and 633 individuals in each NUA and HUA groups. The proportion of male in the HUA group was significantly higher than that in the NUA group. BMI, SBP and DBP increased significantly in HUA groups than in NUA groups ($P < 0.01$). In the aspect of lipid metabolism, participants in HUA had a significant higher level of TG, LDL-c and apo B and lower HDL-c and Apo AI in comparison with those in the NUA group ($P < 0.01$). Also, the HUA group had a significant higher concentrations of FBG and FIN due to higher HOMA-$\beta$ and HOMA-IR in participants in the HUA group ($P < 0.01$).
### Table 1
comparison of Characteristics between NUA and HUA

| Parameters   | NUA group (n = 2868) | HUA group (n = 633) | P value |
|--------------|----------------------|---------------------|---------|
| **Age, y**   | 45.2 ± 11.6          | 41.5 ± 11.9         | < 0.01  |
| **Gender, male%** | 41.00               | 95.10               | < 0.01  |
| **BMI, kg/m²** | 23.49 ± 2.85        | 25.42 ± 2.47        | < 0.01  |
| **SBP, mmHg** | 118.4 ± 11.9        | 122.7 ± 10.6        | < 0.01  |
| **DBP, mmHg** | 71.5 ± 8.8          | 75.0 ± 8.5          | < 0.01  |
| **TG, mmol/l** | 1.05(0.76–1.51)    | 1.57(1.12–2.32)     | < 0.01  |
| **LDL-C, mmol/l** | 2.69 ± 0.73      | 2.81 ± 0.77         | < 0.01  |
| **HDL-C, mmol/l** | 1.36 ± 0.33      | 1.12 ± 0.27         | < 0.01  |
| **Apo AI, g/l** | 1.47 ± 0.26        | 1.33 ± 0.21         | < 0.01  |
| **Apo B, g/l** | 0.89 ± 0.20        | 0.96 ± 0.20         | < 0.01  |
| **FBG, mmol/l** | 5.36 ± 0.48        | 5.48 ± 0.48         | < 0.01  |
| **FINS, ulU/ml** | 9.11(6.41–12.74) | 11.31(8.01–16.12) | < 0.01  |
| **HOMA-IR**   | 2.18(1.50–3.12)     | 2.75(1.92–3.91)     | < 0.01  |
| **HOMA-β**    | 99.64(72.14-137.56) | 112.74(81.23-165.71)| < 0.01  |
| **UA, umol/l** | 300.88 ± 64.71     | 474.13 ± 55.47      | < 0.01  |
| **CRE, umol/l** | 61.73 ± 12.62    | 76.65 ± 10.82       | < 0.01  |

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; UA, uric acid; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; Apo A1, apolipoprotein A1; LDL-c, low-density lipoprotein cholesterol; Apo B, apolipoprotein B; FBG, fasting blood glucose; FINS, fasting insulin; CRE, creatinine.

Correlation between UA and Apo AI or other metabolic indexes

Multiple linear regression analysis was used to prove the correlation between UA and metabolic index. After adjusting for age, BMI and SBP, FBG was positively associated with UA (r = 0.046, P < 0.05) and Apo AI was inversely associated with UA significantly (r = -0.236, P < 0.01). Also, it was found that HDL-c was inversely associated with UA (r = -0.289, P < 0.01).

Multiple logistic regression analysis for the association of HUA and Apo AI
To further explore whether there was significantly association of HUA and Apo AI, multiple logistic regression analysis was applied. Low Apo AI was associated with HUA significantly after adjusting for age, sex, BMI and glucose (P = 0.01, OR: 0.508, 95%CI: 0.305 to 0.848). We also found high HOMA-IR was correlated to HUA (P = 0.016, OR: 1.094, 95%CI: 1.017 to 1.177). However, there was no significant correlation between HUA and FBG or HOMA-β.

**Discussion**

At present, a large number of studies have found that HUA is closely related to cardiovascular disease. For example, it can affect vascular endothelium, increase the risk of hypertension\[12\]\[13\], heart failure\[14\] and increase the risk of cardiovascular disease, including coronary heart disease\[15\], myocardial infarction\[5,16\]. Although many studies on the mechanism partly explain the relationship between UA and cardiovascular disease, it is not completely clear. Moreover, hyperuricemia is often accompanied by other diseases. At present, a large number of people who study uric acid and metabolic or cardiovascular diseases often have other metabolic or cardiovascular comorbidities or even metabolic syndrome. It is difficult to purely study the relationship between UA and specific risk factors or protective factors of cardiovascular disease. The characteristic of this study is to study in healthy people without diabetes, hypertension or metabolic syndrome, to clarify the relationship between UA and apo AI, one of the cardiovascular protective factors\[17\]. The result plays a certain role in the occurrence and development mechanism of UA in cardiovascular disease.

The present study explored the association between UA and Apo AI in healthy people without diabetes, hypertension or metabolic syndrome. We found that in the HUA group, the Apo AI and HDL-c were higher than that in the NUA group. In the further analysis, HUA was found associated with decreased plasma Apolipoprotein AI and HDL-c independently. The results may suggest that hyperuricemia may promote the progress of the cardiovascular disease by reducing the levels of ApoA1 and HDL-C. Other previous studies are similar to our study\[18\]. Kuwabara et al.\[13\] conducted a prospective study on Japanese patients with hyperuricemia but without typical symptoms and other complications. The study found that the incidence of cardiovascular related metabolic disorders such as abnormal lipid metabolism and hypertension in the asymptomatic hyperuricemia group was significantly higher than that in the normal UA group after five years of follow-up. A sub-analysis of the NHANES III study also found that HDL-c and apo-B to apo-AI were linearly positively associated with uric acid levels. However, different from our study, the participants included patients with diabetes, hypertension and other complications, and no significant correlation between apo AI and UA after adjusting for related factors\[10\].

At present, the mechanism of the interaction of uric acid with HDL-C and apo-AI is not completely clear. Animal studies have found that high uric acid can reduce the level of phospholipids of HDL subclasses, and induce the increase of fractional catabolic rate FCR significantly, resulting in decreased HDL-C and apo AI levels\[19\]\[20\]. Other studies have found that high UA is also closely related to small and dense HDL-C. At the same time, HDL-C volume is negatively correlated with fibrinogen concentration\[21\], and HUA
was negatively correlated with large HDL-C level[^15], which may present a mechanism that contribute to arteriosclerosis. There are different relationships between HUA and different subclasses of HDL-C[^22], HUA and HDL2, which are associated with alcohol consumption[^23], waist circumference, smoking, and exercise had a negative correlation. However, HUA and HDL3 which only associated with alcohol consumption had a positive correlation. Moreover, most studies only studied the relationship between HDL and UA; the mechanism of the interaction between apo-AI and UA needs to be further explored.

In addition, instead of lipoprotein, the result of the current study showed that other metabolic index correlated to UA, including FBG and HOMA-IR. Similar to this study, many studies have found that HUA is closely related to insulin resistance and hyperglycemia[^24–26]. Long term follow-up studies confirmed that hyperuricemia is an indicator for predicting abnormal glucose metabolism. Krishnan et al.[^27] conducted a 15-year follow-up study on young people without diabetes. They found that the risk of developing diabetes, insulin resistance and prediabetes in the hyperuricemia group within 15 years was significantly higher than that in the non-hyperuricemia group. A 5.3-year follow-up study of the Chinese population also confirmed that HUA and is closely related to the development of hypertension[^28]. The mechanisms are complex; uric acid can reduce IR by promoting mitochondrial oxidative stress and NO bioavailability[^29,30]. However, hypouricemic drugs such as Allopurinol can reduce uric acid, improve insulin resistance and systemic inflammation in patients with hyperuricemia[^31]. On the contrary, IR can induce hyperuricemia by inhibiting uric acid excretion through increasing renal tubular sodium reabsorption[^32].

The limitations of our study include that this is a cross-sectional study, and it is impossible to determine the causal relationship. A follow up study can be carried out next to further explore the relationship between UA, apoAI and cardiovascular disease. This study is calculated based on the data of a small number of subjects who receive health examination which had selection bias, and more large-scale studies will be carried out in the future.

**Conclusion**

In conclusion, Hyperuricemia was associated with decreased plasma Apolipoprotein AI and HDL-c independently. Inhibiting Apolipoprotein AI may be one of the mechanisms of UA involved in the progression of cardiovascular disease.

**Abbreviations**

CHD, coronary heart disease; CHF, congestive heart failure; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; UA, uric acid; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; Apo A1, apolipoprotein A1; LDL-c, low-density lipoprotein cholesterol; Apo B, apolipoprotein B; FBG, fasting blood glucose; FINS, fasting insulin; CRE, creatinine; HOMA-IR, Homeostasis model assessment of insulin resistance; HOMA-β, Homeostasis model assessment of β-cell function.
Declarations

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Ethics approval

The protocol of this study was approved by the Ethics Committee of the Beijing Chao-yang Hospital Affiliated to Capital Medical University.

Consent for publication

Participants were informed of data sharing with their name and identity hidden per consent.

Availability of data and materials

All data generated or analyzed are included in this paper

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

J.L. and G.W. are responsible for the design of the study. Y.A., X.D. and X.C are responsible for data collection. Y.D. and J.L. are responsible for data analysis and drafting of the manuscript. Both authors read and approved the final manuscript.

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Figures
Figure 1

Bar graph of Lipid metabolism indices (A. HDL-c; B. Apo A1; C. LDL-c; D. Apo-B) mean value with SD intervals between NUA and HUA groups. *P< 0.05, **P< 0.01 UA, uric acid; HDL-c, high-density lipoprotein cholesterol; Apo A1, apolipoprotein A1; LDL-c, low-density lipoprotein cholesterol; Apo B, apolipoprotein B.
Figure 2

Bar graph of glucose metabolism indices (A. FBG; B. INS; C. HOMA-IR; D. HOMA-β) mean value with SD intervals or median with quartiles between NUA and HUA groups. *P < 0.05, **P < 0.01 FBG, Fasting blood glucose; INS, insulin; HOMA-IR, Homeostasis model assessment of insulin resistance; HOMA-β, Homeostasis model assessment of β-cell function.
Figure 3

The correlation between plasma UA and the levels of apoAl (A) and HDL-c (B). Plasma UA was negatively correlated with apoAI and HDL-C, and this negative correlation was still observed after adjustments for age and BMI levels.