*Original Article*

# Serum Uric Acid and Hypertension in Healthy Adult Thai Populations

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***Objective:*** High serum uric acid has been reported to be a risk factor for hypertension. However, data regarding this association in Thai adults is lacking. We aimed to examine the association between serum uric acid level and the diagnosis of hypertension in healthy Thai adults.

***Materials and Methods:*** This cross-sectional study was conducted at Srinagarind Hospital, a tertiary care setting in Thailand. A total of 1,754 adults who did a health check-up were recruited. The association between serum uric acid level and hypertension, defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg, were analyzed using multivariable logistic regression analysis. Hyperuricemia was defined as serum uric acid level >6 mg/dL.

***Results:*** Prevalence of hyperuricemia and hypertension in the study population was equal at 25.5%. Subjects with hyperuricemia had higher SBP, DBP, and mean arterial pressure (MAP) than in the subject with normal uric acid level. Every 1 mg/dL increment of the uric acid level was significantly associated with hypertension, with the adjusted Odds ratio of 1.23 (95% CI 1.12 to 1.35, p-value <0.01). Hyperuricemia showed significant association with hypertension, with the adjusted Odds ratio of 2.16 (95% CI 1.63 to 2.85, p-value <0.01), after adjusted with potential confounders, including age, sex, body mass index (BMI), fasting plasma glucose (FPG), and estimated glomerular filtration rate (eGFR).

***Conclusion:*** Hyperuricemia is associated with hypertension in healthy Thai adults. Serum uric acid measurement may be a useful additional parameter in identifying patients at a high probability of having hypertension.

***Keywords:*** Uric acid; Hyperuricemia; Hypertension; Thailand

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High serum uric acid is a risk factor for cardiovascular morbidity and mortality[1]. Asymptomatic hyperuricemia is frequently prevalent in patients with increase cardiovascular risks, including obesity, chronic kidney disease (CKD), diabetes mellitus (DM), and hypertension (HT)[2-6]. Recently, the association between serum uric acid and the prevalence of HT has received widespread attention. The relationship between hyperuricemia and hypertension has been reported in various epidemiological studies[7-9]. In Asian populations, high serum uric acid level has been reported to be a risk factor for hypertension in many cohorts including participants from healthy Chinese[10,11], Japanese[12], and Bangladeshi[13] cohorts. In contrast, no association between high serum uric acid level and hypertension has been reported in some other cohorts[14,15]. There are still some arguments about the causal relationship of serum uric acid and hypertension, whether uric acid is a true risk factor or just solely a marker of hypertension[16]. Two previous randomized controlled studies showed that urate-lowering therapy help reduces blood pressure in adolescents, suggesting that hyperuricemia may play a causal role in the development of hypertension[17,18]. However, the exact relationship between uric acid and hypertension remains unclear. Conflicting results from many pieces of evidence, especially studies from different countries and different patient settings, further complicates this controversial issue. To our knowledge, no studies have been conducted to investigate the relationship between serum uric acid and the prevalence of hypertension in Thai adults. Therefore, this study aimed to explore whether hyperuricemia is associated with hypertension in healthy adults in Thailand.

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## Materials and Methods

### *Study sample*

This cross-sectional study included healthy adults aged 15 to 90 years who underwent a health check-up in 2017 at Srinagarind Hospital, a tertiary care setting in Thailand. Individuals with a history of taking medications that could affect blood pressure or serum uric acid (including glucocorticoids, contraceptive pills, neuropsychiatric agents, and antihypertensive agents) were excluded. Subjects who

had been previously diagnosed with HT, DM, gout, liver disease, and CKD were also excluded from the study. The remaining 1,754 participants were included in the final analysis.

### *Data collection*

The health check-up process consisted of a thorough history taking and physical examination which were applied in all subjects. Each participant's body weight (BW) and standing height (without shoes) were measured using an electronic balance (accuracy 0.1 kg) and a stadiometer (nearest 0.1 cm), respectively. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Blood pressure (BP) was measured after the participant had been seated and resting for at least five minutes. Average blood pressure was calculated from 2 measurements. Mean arterial blood pressure (MAP) was calculated by the summary of SBP and 2 folds of DBP divided by 3. Serum samples of uric acid level, plasma glucose (FPG), serum creatinine, total cholesterol (TC), and triglyceride (TG) were collected in the morning after participants had fasted for 12 hours. Serum uric acid was measured with an autoanalyzer using a phosphotungstic acid reagent[19]. Fasting plasma glucose level was measured using the glucose oxidase method, while serum creatinine, TC, and TG were measured using enzymatic methods with an automatic autoanalyzer (Cobas Integra 800; Roche Diagnostics, Mannheim, Germany). The estimated glomerular filtration rate (eGFR) was calculated by using CKD-EPI creatinine equation 2009[20].

### *Operational definition*

Subjects were categorized into hypertension and normotension using systolic BP (SBP) and diastolic BP (DBP) according to JNC 8 criteria[21]. Hypertension was defined by SBP ≥140 mmHg and/or DBP ≥90 mmHg while normotension was defined by SBP <140 mmHg and DBP <90 mmHg. Hyperuricemia was defined by a serum uric acid level of greater than 6.0 mg/dL[22]. Diabetes mellitus and chronic kidney disease were defined by FPG ≥126 mg/dL and eGFR ≤60 mL/min, respectively. Hypercholesterolemia and hypertriglyceridemia were defined as TC ≥200 mg/dL and TG ≥150 mg/dL, respectively. Obesity was defined as BMI ≥25 kg/m$^2$.

### *Statistical analyses*

All statistical analyses were performed using R (de Micheaux, Drouilhet, & Liquet, 2014). Descriptive statistics were calculated between the normouricemia and hyperuricemia groups separately. Data were presented as median (IQR) and proportions for continuous and categorical variables, respectively. Wilcoxon rank-sum test and Chi-square were used to calculate the p-value as appropriate. Logistic regression analysis was performed to calculate the odds ratio (OR) and 95% confidence interval (95% CI) between serum uric acid level and the prevalence of hypertension. The odds of hyperuricemia and hypertension were also analyzed using univariable and multivariable logistic regression with stepwise elimination to assess confounding and effect modification. The p-value less than 0.05 was considered statistically significant.

## Results

Overall, 616 men and 1,138 women had been recruited into the study. Baseline characteristics of subjects are shown in Table 1. 448 individuals (25.5%) were classified

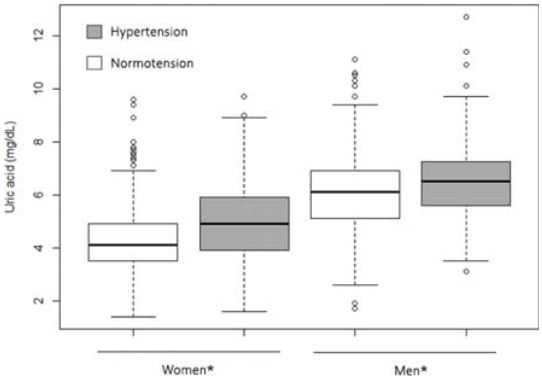
**Table 1.** Characteristics of study participants according to uric acid status

| | Total n=1,754 | Hyperuricemia n=448 | Normouricemia n=1,306 | p-value |
|---|---|---|---|---|
| Male, % | 616 (35.1) | 341 (76.1) | 291 (21.1) | <0.01* |
| Age, years | 47.0 (41.0, 55.0) | 52.0 (45.0, 60.0) | 45.0 (40.0, 52.0) | <0.01* |
| BMI, kg/m$^2$ | 23.7 (21.7, 26.1) | 25.1 (23.0, 27.8) | 23.2 (21.3, 25.5) | <0.01* |
| SBP, mmHg | 120.0 (110.0, 130.0) | 120.0 (110.0, 130.0) | 110.0 (110.0, 120.0) | <0.01* |
| DBP, mmHg | 80.0 (70.0, 80.0) | 80.0 (78.5, 90.0) | 70.0 (70.0, 80.0) | <0.01* |
| MAP, mmHg | 90.0 (83.3, 96.7) | 103.3 (100.0, 106.7) | 83.3 (83.0, 93.3) | <0.01* |
| FPG, mg/dL | 86 (80, 94) | 90 (82, 101) | 85 (79, 93) | <0.01* |
| eGFR, mL/min | 93.8 (79.7, 105.9) | 86.2 (72.1, 99.9) | 95.8 (82.9, 107.2) | <0.01* |
| Cholesterol, mg/dL | 209 (182, 236) | 216 (190, 241) | 206 (180, 234) | <0.01* |
| Triglyceride, mg/dL | 109.0 (73.0, 161.0) | 134.0 (91.0, 194.0) | 99.0 (68.8, 149.3) | <0.01* |
| Uric acid, mg/dL | 4.9 (3.9, 6.1) | 6.9 (6.4, 7.7) | 4.3 (3.6, 5.1) | <0.01* |
| Hypertension, % | 448 (25.5) | 196 (43.8) | 252 (19.3) | <0.01* |

Data are presented as median (IQR) and proportions for continuous and categorical variables, respectively. Wilcoxon rank-sum test and Chi-square were used to calculate the p-value as appropriate.
* Statistically significant

into the hyperuricemia group while 1,306 individuals (74.5%) were classified into the normouricemia group. Most of the subjects in the hyperuricemia group were men (72.1%). The median age of the total subjects was 47 years old. The median age of individuals with hyperuricemia was greater than normouricemia. Median BMI was 23.7 kg/m$^2$ for total subjects with higher BMI in hyperuricemia as compared to normouricemia. The hyperuricemia group had higher SBP, DBP, MAP, FPG, TC, and TG but lower eGFR than the normouricemia group. The median uric acid level was 6.9 and 4.3 mg/dL in the hyperuricemia group and normouricemia group, respectively.

Hypertension was diagnosed in 448 subjects. (25.5%) After subjects were categorized according to hypertensive status. We found that median serum uric acid level was greater in hypertensive subjects as compared to normotensive subjects in both men and women (Figure 1). Hyperuricemia was found in 196 subjects (43.8%) in the hypertensive group which was significantly greater than in the normotensive group (p<0.01). Every 1 mg/dL increment of serum uric acid was significantly associated with an increased risk of hypertension (OR 1.46 [95% CI 1.36 to 1.57]). After adjusting for age and sex (model 1), the OR (95% CI) were 1.32 (1.21 to 1.44). In model 2, after additionally adjusting BMI, the OR (95% Cl) were 1.22 (1.12 to 1.33). In model 3, the association remained nearly unchanged even after further adjustment with FPG and eGFR (Table 2). Hyperuricemia significantly increased the risk of hypertension (OR 3.25 [95% CI 2.58 to 4.10]). After adjusting for age, sex and other important metabolic diseases including obesity, DM, CKD, hypercholesterolemia, and hypertriglyceridemia with stepwise elimination, hyperuricemia remained a significant risk of hypertension (OR 2.16 [95% CI 1.63 to 2.85]) with CKD, hypercholesterolemia, and hypertriglyceridemia removed from the model (Table 3).




* p<0.01 in both women and men group

**Figure 1.** Serum uric acid level in hypertensive and non-hypertensive groups by gender.

## Discussion

In the present study, the authors found that increased serum uric acid is significantly associated with hypertension in healthy Thai adults aged 15 to 90 years old. This finding is in agreement with 2 meta-analyses conducted by Wang et al and Grayson et al which reported that every 1 mg/dL increment of uric acid level can increase the risk for incident hypertension (pooled relative risks (RRs) 1.15 [95% CI 1.06 to 1.26] and 1.13 [95% CI 1.06 to 1.20], respectively)[5,6]. Age may be considered to be an important factor that affects the relationship between uric acid and HT in some studies. For example, an association of uric acid with HT has been reported only in a certain age group in Korean adults (aged <60 years) and Chinese adults (aged 41 to 50 years)[10,23]. However, our findings from multivariable analysis suggested that uric acid is an independent risk factor of hypertension regardless of age. Whether age-related such a relationship is from the differences in ethnicity needs to be further investigated.

Uric acid is considered to be a biologically active molecule that may induce oxidative stress under certain inflammatory conditions, a concept known as the prooxidant

**Table 2.** Univariable and multivariable logistic regression analysis of serum uric acid level in association with hypertension

| | Hypertension | | |
|---|---|---|---|
| | Odds ratio (OR) | 95% CI | p-value |
| Serum uric acid, per 1 mg/dL increased | | | |
| Crude | 1.46 | 1.36 to 1.57 | <0.01* |
| Model 1 | 1.32 | 1.21 to 1.44 | <0.01* |
| Model 2 | 1.22 | 1.12 to 1.33 | <0.01* |
| Model 3 | 1.23 | 1.12 to 1.35 | <0.01* |

Model 1 adjusted for age and sex; Model 2 adjusted for age, sex, and BMI; Model 3 adjusted for age, sex, BMI, FPG, and eGFR.
* Statistically significant.

**Table 3.** Univariable and multivariable logistic regression analysis with stepwise elimination of metabolic diseases including hyperuricemia in association with hypertension

| | Hypertension | | | |
|---|---|---|---|---|
| | Crude OR (95% CI) | p-value | Adjusted OR+ (95% CI) | p-value |
| Hyperuricemia | 3.25 (2.58 to 4.10) | <0.01* | 2.16 (1.63 to 2.85) | <0.01* |
| Age, every 1 year increase | 1.07 (1.06 to 1.09) | <0.01* | 1.06 (1.05 to 1.07) | <0.01* |
| Male sex | 2.27 (1.83 to 2.83) | <0.01* | 1.35 (1.03 to 1.77) | 0.027* |
| Obesity | 2.69 (2.16 to 3.36) | <0.01* | 1.95 (1.54 to 2.48) | <0.01* |
| Diabetes mellitus | 4.59 (2.94 to 7.27) | <0.01* | 3.02 (1.87 to 4.93) | <0.01* |
| Chronic kidney disease | 2.59 (1.55 to 4.30) | <0.01* | - | |
| Hypercholesterolemia | 1.51 (1.21 to 1.89) | <0.01* | - | |
| Hypertriglyceridemia | 2.04 (1.63 to 2.56) | <0.01* | - | |

+ Variables entered into the model: age, male sex, obesity, diabetes mellitus, chronic kidney disease, hypercholesterolemia, hypertriglyceridemia, hyperuricemia. Removed from the model: chronic kidney disease, hypercholesterolemia, hypertriglyceridemia.
* Statistically significant

urate redox shuttle theory[24]. This pro-inflammatory property of uric acid may lead to HT through various mechanisms. Arterial stiffness, especially in renal arteriopathy[25], may be one of the possible pathways between hyperuricemia and HT, but a clear association between increased uric acid level and vascular alterations has not been established[26]. There is evidence that hyperuricemia causes hypertension and renal injury with stimulation of the renin-angiotensin system and inhibition of neuronal nitric oxide synthase[27]. It also induces microalbuminuria that is associated with increased risk of HT[28].

The present study is the first study in Thailand that assesses the relationship between uric acid status and the prevalence of HT with a large number of recruited subjects and the adjustment of potential numerous confounding metabolic factors. However, some limitations in the present study are worth mentioning. First, the cross-sectional design of this study may preclude the cause-effect relationships between uric acid concentrations and HT being assumed. Second, the uric acid level is related to various factors such as high-protein dietary, alcohol content, high cell turnover rate, enzyme defect in purine metabolism, decrease excretion, increase absorption from the gastrointestinal tract. These conditions are potential confounders. In this study, we did not evaluate the dietary history and alcoholic consumption. However, all participants had been previously healthy without any known underlying disease, which can be assumed that conditions such as congenital enzymatic defect or abnormal uric acid absorption and metabolism are less likely.

## Conclusion

We found that hyperuricemia is an independent risk factor associated with hypertension in Thai adults. Prospective studies are necessary to confirm these results that could also identify serum uric acid level cut-off values for defining categories of patients at risk for developing HT. Also, a further large-scale study is warranted to evaluate whether uric-lowering treatment can help prevent hypertension.

## What is already known on this topic?

High serum uric acid is associated with the risk for hypertension in studies from various ethnicities.

## What this study adds?

Elevation of the uric acid level was positively associated with the diagnosis of hypertension among Thai adults. Serum uric acid measurement may be a useful additional parameter in identifying patients at a high probability of having hypertension.

## Declarations

### *Ethics approval*

The Human Research Ethics Committee of Khon Kaen University reviewed and approved the study per the Helsinki Declaration and the Good Clinical Practice Guidelines (HE611278).

### *Consent for publication*

All of the authors consent to publication and grant the publisher exclusive license of the full copyright.

### *Availability of data and material*

Data availability on reasonable request.

### *Author's contribution*

SC designed the study, performed statistical analysis, and drafted the manuscript. SD collected the data.

CP performed conceptualization of the research and commented on the manuscript.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## Potential conflicts of interest

The authors declare no conflict of interest.

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