Original Article

The Relationship of Serum Uric Acid Concentrations of 6.8 mg% or Less on the Future Risks of Hypertension: A Retrospective Cohort Study

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Objective: To determine the relationship between serum uric acid (SUA) concentrations of 6.8 mg% or less on the future risk of hypertension (HT).

Materials and Methods: People aged at least 15 years old, without HT, who visited for physical checkups, either at the Primary Care Unit, General Practice Clinic, General Health Examination Clinic, or the Private General Practice Clinic of Songklanagarind Hospital, between July and December 2008, were included in the present study. Medical records were reviewed until the end of March 2016, either until HT was diagnosed or treatment with any HT drugs started. SUA was categorized into five categories, starting from less than 2.9 to 6.8 mg%. The incidences of HT were reported in terms of person-time incidence. The association between SUA and HT was analyzed and reported in terms of hazards ratios (HRs), using Cox proportional hazards regression model.

Results: After a median of 7.3 years follow-up, with an interquartile range 3.2 years, the study identified 240 and 109 incident cases of HT among 2,253 females and 821 males, respectively. The relationship between SUA and incidence of HT appeared to be a U-shaped association, with the bottom of the curves at 4.9 to 5.8 mg% for males, whereas, in females the relationship between SUA and incidence of HT appeared to be an exponential relationship. In multivariate analysis, comparing each 1 mg% increase in SUA, were 1.3 (95% CI 1.2 to 1.5, p<0.01) in females and 1.0 (95% CI 0.8 to 1.3, p=0.99) in males for hypertensive incident.

Conclusion: The results showed that higher SUA concentrations in female gender increase exponentially on HRs of HT. Nonetheless, this effect was not found in males. U-shaped association was found between low SUA concentrations and the person-time incidences of HT in male patients. However, the relationship was not statistically significant in multivariate analysis.

Keywords: Cohort study, Uric acid, Hypouricemia, Essential hypertension

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Hypertension (HT) has become a major problem for global public health. It is the leading risk of death, disabilities, strokes, and cardiovascular diseases. Hence, identifying modifiable risk factors of HT are urgently required for preventive measure plans[1]. The pathogenesis of HT is a complex interplay of genetic, age, sex, obesity, lipid profile, renal function, environment, and hormonal factors[2-4].

Serum uric acid (SUA) is the end enzymatic product of purine nucleotide catabolism. In general, higher SUA levels are found in males versus females, with older age, higher blood pressure, increased cholesterol and creatinine (Cr) levels, and with a higher body mass index[3]. It has been long recognized that uric acid is associated with cardiovascular diseases, such as metabolic syndrome, diabetes mellitus (DM), and obesity[3,4]. However, the causal relationship with HT remains controversial[4,5]. From meta-analysis's, it was found that SUA is positively associated with the risk of hypertensive incidence, but this varies among studies, ranging from 1.08 to 2.19[6]. Variations may be due to different definitions used for

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the classification levels of SUA for both males and females. Some studies, with adjusted multivariable for standard HT risk factors, show that SUA is not associated with incidence of HT[7]. The physiologic definition of normouricemia is a concentration of serum urate below 6.8 mg%, because this level defines the saturation point of sodium urate salt[8]. Currently, there is no definition appropriate for hypouricemia[9-13], due to the critical levels of SUA concentrations have yet to be classified. Therefore, the authors performed this longitudinal study, in a retrospective cohort study design, with multivariable analyses that included SUA concentrations less than or equal to 6.8 mg%, so as to analyze the independent association between SUA and risk for incidence HT.

Materials and Methods

Setting

The present study was conducted in four outpatient departments of Songklanagarind Hospital, a tertiary referral hospital, medical school and research center in Southern Thailand. The study included data from the Primary Care Unit, General Practice Clinic, General Health Examination Clinic, and Private General Practice Clinic.

Study population and samples

Inclusion criteria:

1. Adults (aged 15 years old or older) without HT, who visited the hospital for a routine physical checkup, between July and December 2008.
2. Serum uric acid level of 6.8 mg% or less, at first visit.
3. Patients who followed up for more than one visit.

Exclusion criteria:

1. Prior diagnosis of HT
2. Follow-up of less than two visits

Sample size

The authors used the standard formula to determine the sample size of the cohort study[14].

$n = \{z^2_{\alpha/2} * [(1–P_1)/P_1 + (1–P_2)/P_2]\} / [In(1–\varepsilon)]^2$

The required, total sample size could be driven by plugging the above values in the formula as follow: P_1=28%, P_2=24%, α=0.05

$n = \{z^2_{0.05/2} * [(1–0.28)/0.28 + (1–0.24)/0.24]\} / [In(1–0.1)]^2$

Calculated sample size (n) = 1,982

Studied variables

The variables included body weight, height, sex, age, uric lowering agent (ULD), history of DM, dyslipidemia, gout, lipid profile, HT, SUA, and estimated glomerular filtration rate (eGFR; Cockcroft and Gault equation).

Data collection

Medical records of the people attending the aforementioned clinics were reviewed. Data were collected until any of the following conditions occurred 1) diagnosis or treatment of HT was made, 2) death, 3) the patient ceased follow-ups, or 4) end of study date in March 2016. The data was recorded using Microsoft Excel.

Statistical analysis

Analyses were performed using Stata MP version 13.1 software. Statistical analyses were carried out separately by gender. Continuous data of baseline characteristics were presented in terms of arithmetic mean, whilst intergroup comparisons were performed using two-sample t-test statistics, with unequal variances. Categorical variables were described in terms of percentage and test hypothesis for the difference by Pearson chi-square test and Fisher's exact test. The precision of data was assessed and reported in terms of a 95% confidence interval (CI), using Gaussian statistics for continuous data, or exact binomial statistics for discrete data. During the analysis, the incidence of HT coupled with the concentration of SUA were categorized into five categories starting from less than 2.9 to 6.8 mg%. Age was categorized into three groups (less than 40 years, 40 to 60 years, and more than 60 years). The risk of HT by SUA categories were calculated, and reported in terms of person-time incidence, then illustrated with a line graph. Person-time incidences were calculated by dividing the number of hypertensive people with the number of person-years at risk. The association between SUA and HT was analyzed and reported in terms of incidence rate (IR) per 100 person-years using Poisson Regression models. The IR by SUA categories with a corresponding 95% CI were illustrated with a graph. The survival analysis used Kaplan-Meier categorized concentrations of SUA of less than 3.9 mg%, 3.9 to 6.8 mg% in males and less than 4.9 mg%, 4.9 to 5.8 mg%, and 5.9 to 6.8 mg% in females.

Univariate and multivariate analysis used Cox proportional hazards model for the association between various risk factors, and the future development of HT. Only variables that were significantly associated with HT from univariate analysis ($p<0.2$) were included in the multivariate model, via backward stepwise. To

Table 1. Description and comparison of the studied samples baseline characteristics

Characteristics	Overall (n=3,074)	Female (n=2,253)	Male (n=821)	p-value
	Mean±SD	Mean±SD	Mean±SD	
Age (years)	48.2±10.9	47.6±10.6	49.8±11.4	<0.001[a]
Body mass index (kg/m^2)	23.8±3.6	23.8±3.8	24±3.2	0.069[a]
Diagnosis, n (%)				
Diabetes mellitus	79 (2.6)	44 (2.0)	35 (4.3)	<0.001[b]
Dyslipidemia	287 (9.3)	201 (8.9)	86 (10.5)	0.190[b]
Gout	7 (0.2)	0 (0.0)	7 (0.9)	<0.001[c]
Uric lowering drug	7 (0.2)	5 (0.2)	2 (0.2)	<0.911[b]
Blood chemistry				
Total cholesterol (mg%)	217.4±40.3	217.8±40.1	219.1±40.9	0.363[a]
Triglyceride (mg%)	112.3±60.6	106.0±60.4	129.7±78.6	<0.001[a]
eGFR (mL/minute)	90.2±35.6	83±30.3	110.1±41.1	<0.001[a]
Serum uric acid (mg%)	4.7±1.0	4.4±0.9	5.6±0.8	<0.001[a]
Chronic kidney disease, n (%)				<0.001[b]
Stage 1	1,334 (43.4)	792 (35.2)	542 (66)	
Stage 2	1,158 (37.7)	953 (42.3)	205 (25.0)	
Stage >2	582 (18.9)	508 (20.5)	74 (9.0)	

SD=standard deviation; eGFR=estimated glomerular filtration rate

[a] Two-sample t-test with unequal variances, [b] Pearson chi-square test, [c] Fisher's exact test

cope with collinearity in regression analysis, caused by highly related variables, the authors used the variables reduction method. All serum lipids were replaced with a diagnosis of dyslipidemia, Cr and GFR were replaced with chronic kidney disease (CKD) stage, whilst body weight and height were replaced with body mass index (BMI). For the analysis, the hazards ratios (HRs), and a p-value of less than 0.05 was considered to indicate statistical significance.

Ethical approval

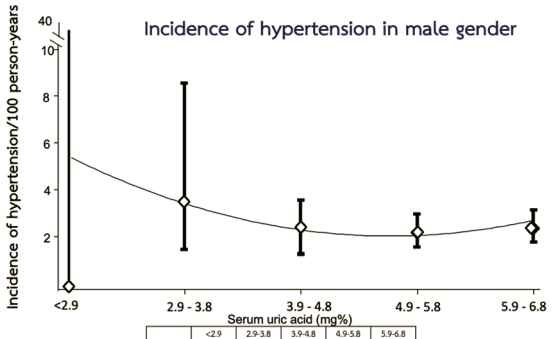
The study protocol was approved by the Ethics Committees of the Faculty of Medicine, Prince of Songkla University (EC: 60-161-09-1). Because, of the observational nature of the study written informed consent was not required.

Results

After including eligible samples from the hospital database of 4,471 samples, the authors excluded 1,397 samples from the study by following the exclusion criteria. Finally, 3,071 samples were included for the analysis. After a median of 7.3 years follow-ups (IQR 3.2), the study identified 240 and 109 incident cases of HT, among 2,253 females and 821 males, respectively. Comparison of characteristics of the studied samples between males and females are shown in Table 1. The baseline characteristics had found a significant difference between female and male participants in all putative variables risk factors for HT, with the exceptions of BMI, the percentage of prior dyslipidemia, and total cholesterol (TC). The variables were more common in males than females.

The person-year incidences of HT with a 95% CI in each group of SUA are shown in Figure 1 and 2. The incidence in female participants declined from 4.2 per 100 person-years in the SUA concentration 5.9 to 6.8 mg% group to 1 per 100 person-years in the less than 2.9 mg% group, and each stepwise lower SUA groups have a declined incidence of HT. On the other hand, in male participants, the lowest incidence of HT was at the SUA concentrations of 4.9 to 5.8 mg% (3.1 per 100 person-years; 95% CI 1.6 to 3.4). The predicted trend line, which is shown in the figure, used Poisson Regression models. The survival curves, based on a Kaplan-Meier analysis of the diagnosed HT end point, is provided in Figure 3 and 4 for males and females, respectively.

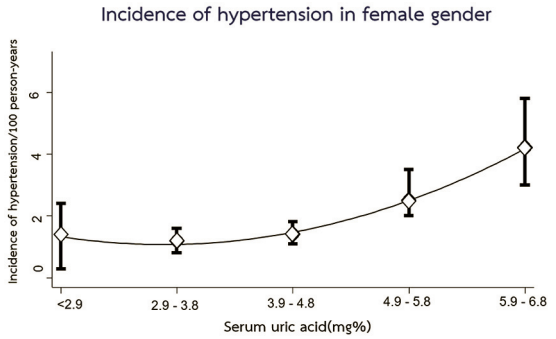
The association between various factors, including, SUA and HT derived from the univariate



	<2.9	2.9-3.8	3.9-4.8	4.9-5.8	5.9-6.8
incidence	0	3.9	2.2	2.1	2.3
LL	0	1.4	1.2	1.5	1.7
UL	40	8.5	3.5	2.9	3.1

Figure 1. Incidence rates of hypertension, with a corresponding 95% confidence interval (CI) in male patients, is stratified by serum uric acid concentration.

Incidence=incidence/100 person-years; UL=upper limit of 95% CI; LL=lower limit of 95% CI



	<2.9	2.9-3.8	3.9-4.8	4.9-5.8	5.9-6.8
incidence	1	1.2	1.4	2.5	4.2
LL	0.3	0.8	1.1	2	3
UL	2.4	1.6	1.8	3.2	5.8

Figure 2. Incidence rates of hypertension, with a corresponding 95% CI in female patients, is stratified by serum uric acid concentration.

Incidence=incidence/100 person-years; UL=upper limit of 95% CI; LL=lower limit of 95% CI

and multivariate analyses are shown in Table 2 and 3 in HRs with a 95% CI, p-value and C-statistics. The variables that were both statistically and significantly associated with incidence of HT were included into the multivariate Cox proportional hazard regression model. The strength of association between SUA and HT is displayed in Figure 5 and 6. The adjusted HRs 95% CI comparing each 1mg% increase in SUA were 1.3 (1.2 to 1.5, p<0.01) in females and 1.0 (0.8 to 1.3, p=0.99) in males, for incident HT.

Discussion

The present study shows that the relationship

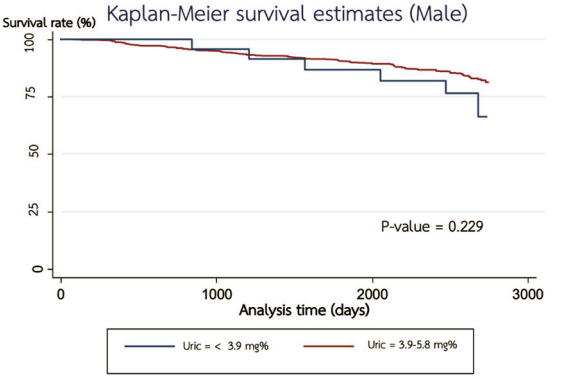


Figure 3. Kaplan-Meier survival curves for diagnosed hypertension in males.

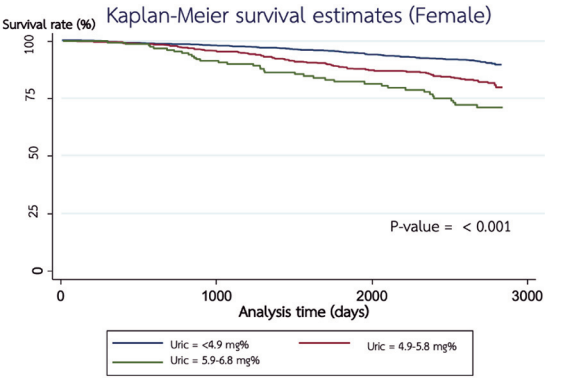


Figure 4. Kaplan-Meier survival curves for diagnosed hypertension in females.

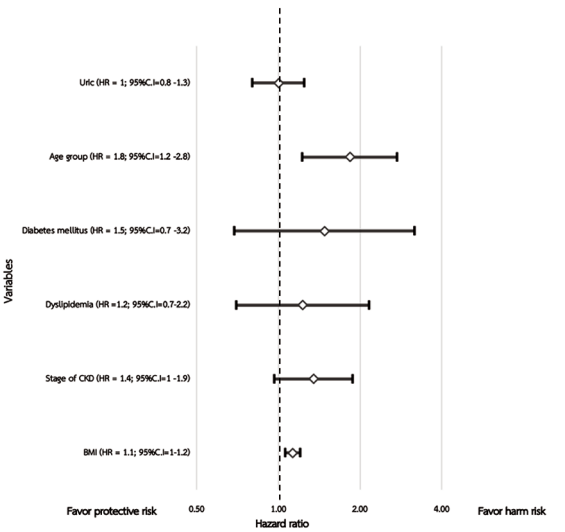


Figure 5. Forest plots of multivariate analysis using Cox proportional hazards model for the male gender.

Table 2. Univariate analysis, using Cox proportional hazards model for the association between various risk factors, and the future development of HT

	Univariate		
Variable	HR (95% CI)	p-value	C-statistics
Uric	1.4 (1.2 to 1.5)	<0.001	60%
Uric groups (1 mg%)	1.4 (1.2 to 1.5)	<0.001	59%
<2.9 mg%	1	Reference	
2.9 to 3.8 mg%	1.3 (0.5 to 3.2)	0.606	59%
3.9 to 4.8 mg%	1.5 (0.1 to 3.7)	0.374	
4.9 to 5.8 mg%	2.4 (1.0 to 5.9)	0.053	
5.9 to 6.8 mg%	2.9 (1.2 to 7.1)	0.032	
Female	1	Reference	
Male	1.3 (1 to 1.6)	<0.046	52%
Age (years)	1.06 (1.05 to 1.07)	<0.001	69%
Age group			
<40 years	1	Reference	
40 to 60 years	3 (2 to 4.4)	<0.001	64%
>60 years	7.3 (4.8 to 11.1)	<0.001	
Diabetes mellitus	2 (1.3 to 3.3)	0.004	51%
Dyslipidemia	2.7 (2 to 3.5)	<0.001	56%
Uric lowering drug	3.8 (0.9 to 15.1)	0.738	50%
Gout	1.4 (0.2 to 10.1)	0.127	50%
Total cholesterol	1.01 (1.005 to 1.01)	<0.001	60%
Triglyceride	1.002 (1.002 to 1.005)	<0.001	64%
Creatinine (mg%)	2.8 (1.5 to 5.2)	0.006	53%
eGFR (mL/minute)	1 (0.99 to 1)	0.670	49%
Stage of CKD	1.1 (1 to 1.2)	0.080	52%
Body weight (kg)	1.04 (1.03 to 1.1)	<0.001	64%
Body height (cm)	1.01 (0.99 to 1.02)	0.260	51%
BMI (kg/m^2)	1.1 (1.1 to 1.2)	<0.001	65%

HR=hazards ratio; CI=confidence interval; eGFR=estimated glomerular filtration rate; CKD=chronic kidney disease; BMI=body mass index

Table 3. Multivariate analysis, using Cox proportional hazards model for the association between various risk factors, and the future development of HT classified by gender

	Multivariate		
Variable	HR (95% CI)	p-value	C-statistics
Male			68%
Uric (1 mg%)	1 (0.8 to 1.3)	0.991	
Age group	1.8 (1.2 to 2.8)	<0.001	
DM	1.5 (0.7 to 3.2)	0.315	
Dyslipidemia	1.2 (0.7 to 2.2)	0.473	
Stage of CKD	1.4 (1 to 1.9)	0.080	
BMI (kg/m^2)	1.1 (1 to 1.2)	<0.001	
Female			76%
Uric (mg%)	1.3 (1.2 to 1.5)	<0.001	
Age group	2.2 (1.6 to 2.9)	<0.001	
DM	0.8 (0.4 to 1.6)	0.554	
Dyslipidemia	2.2 (1.6 to 3)	<0.001	
Stage of CKD	1.1 (0.9 to 1.4)	0.348	
BMI (kg/m^2)	1.1 (1.1 to 1.2)	<0.001	

HR=hazards ratio; CI=confidence interval; DM=diabetes mellitus; CKD=chronic kidney disease; BMI=body mass index

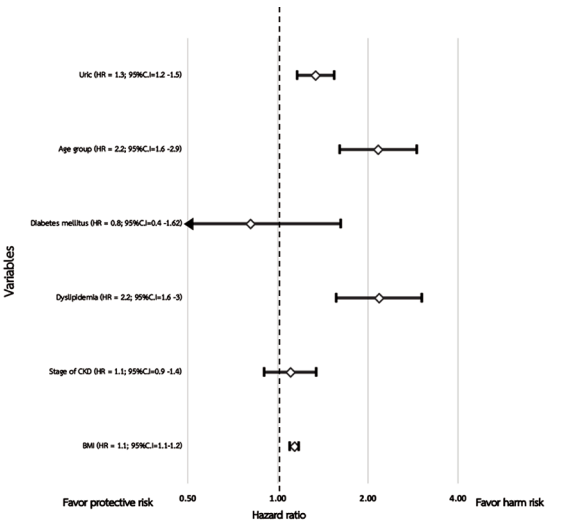


Figure 6. Forest plots of multivariate analysis using Cox proportional hazards model for the female gender.

between low SUA concentrations and HT is different between genders. The impact of higher SUA on HT remained independent only in females. Therefore, comparison with a previous, large cohort study, that included participants within the accepted normal range (less than 6.9 mg%) of SUA, related to an increased risk of HT being strongly indicated in females (adjusted odds ratio 1.15; 95% CI 1.01 to 1.30)[9]. Although the authors did not find any harmful risk factors between decreased SUA and HT in females, several studies have shown that extremely low SUA may be related to a decline in the glomerular filtration rate[15], increasing cardiovascular mortality[16,17], especially in kidney transplant recipients[18].

The authors proposed that uric acid may play

both harmful, and beneficial roles in different conditions. The lowest risk of HT in females is a SUA level at less than 2.9 mg%, howbeit, the authors' suggestion was to keep SUA levels at less than 4.9 mg%. This might be appropriate because below this level, the HRs of incidence of HT was indifferent (Figure 2, 4), however, it might be a harmful risk factor for other diseases. For male patients, the authors suggest keeping SUA levels below 5.8mg%, and the lowest risk on HT was a SUA between 4.9 mg% and 5.8 mg% (Figure 1). However, the authors would caution that when the SUA was below 3.9 mg%, there was a quadratic trend with inflection points at 3.9 mg% (Figure 1, 3).

Limitations of the present study were that it was a retrospective cohort study, wherein the criteria for diagnosed HT was obtained from medical records of ICD-10, and prescribed HT drugs, but in practice, HT was diagnosed by measured blood pressure. This retrospective study was also limited by the incompleteness of information from medical records such as history of smoking along with exercise status, which are important factors for the development of HT.

For implication, the authors suggest a prospective study to clarify the relationship between SUA and HT, or other metabolic diseases such as DM, dyslipidemia and cardiovascular diseases, which could readjust the optimal term of normouricemia, or hypouricemia.

Conclusion

The results of the present study show that higher SUA concentrations in the female gender increases exponentially on HRs of HT. This effect is different between genders. A quadratic trend of U-shaped association between a low SUA concentration, and the incidence of HT found in the male gender was observed. However, the results were not statistically significant.

What is already known on this topic?

Currently, there is no appropriate definition for hypouricemia because the critical level of SUA concentration has yet to be classified. Therefore, the authors performed this longitudinal study in a retrospective cohort study design so as to analyze the independent association between SUA and risk for incident HT.

What this study adds?

Higher SUA concentrations in females increase exponentially on HRs of HT.

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Conflicts of interest

The authors declare no conflict of interest.

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