Original Article

Gender Differences in the J-Shaped Association between Serum Uric Acid Levels and the Incidence of Hypertension

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Background: Reports regarding the risk of hypertension (HT) in hyperuricemic persons were widely varied due to difference in definition, gender, and genetic of studied population. The authors then conducted a study to elucidate this risk in a group of Thai people stratified by serum uric acid (SUA) concentration and gender.

Objective: To evaluate the effect of SUA on the future 8-year risk of developing HT.

Materials and Methods: The persons aged at least 15 years old without HT who visited for physical checkup to Primary Care Unit, General Practice Clinic, General Heath Examination Clinic, and Private General Practice Clinic of Songklanagarind Hospital between March and April 2008 were included in the present study. Medical records were reviewed until end of the study in March 2016 or until HT was diagnosed and treated. SUA concentration was categorized in to eight categories starting from less than 2.9 to more than 8.8 mg%. The incidences of HT were calculated and reported in term of person-time incidence. The association between SUA and HT was analyzed and reported in terms of incidence rate ratio (IRR) using multivariate Poisson regression model.

Results: After a median 6.8-year follow-up (interquartile range 3.7, 7.4), the study identified 309 and 195 incident cases of HT among 1,873 women and 1,019 men respectively. The person-time incidences both in men and women shown J-shaped relation with SUA concentration with inflection points at 4.9 to 5.8 mg% and 2.9 to 3.8 mg%, respectively. Multivariate Poisson regression analysis showed the similar relationship pattern of association between SUA and HT both in men and women.

Conclusion: The results of the present study provide evidence that SUA has the different 8-year risk of developing HT at both high and low concentration. This effect was also different between gender.

Keywords: Longitudinal study, Uric acid, Hyperuricemia, Essential hypertension

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Hypertension (HT) is a global public health challenge due to its high prevalence and increase risk of stroke and cardiovascular diseases. Thus, identifying modifiable risk factors of HT is urgently required for preventive measures plan.

Serum uric acid (SUA) has been shown as a risk of HT but the relative risk varies among studies ranging from 1.08 to 2.19[(1)]. This phenomenon may due to genetic markers because HT and hyperuricemia are both genetically related[(2-5)]. Other causes of this variation may due to definitions used for classification hyperuricemia in man and woman. To the best of our knowledge, there was no previous report concerning incidence of HT in Thai people with asymptomatic hyperuricemia. Lack of this information leading to uncertainty whether treatment of asymptomatic hyperuricemia is cost-effective. The authors then conducted a retrospective cohort study to determine the risk of developing HT after SUA determined in the persons visited to the four primary care units of a university hospital for routine physical checkup.

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Materials and Methods

Setting

The present study was conducted in the

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four outpatient departments of Songklanagarind Hospital, a university hospital belonging to Prince of Songklanagarind University. The study included Primary Care Unit, General Practice Clinic, General Heath Examination Clinic, and Private General Practice Clinic.

Study population and samples

The adult persons (age older than 15 years old) without HT who visited the hospital for routine physical checkup between March and April 2008.

Studied variables

Variables included body weight, height, gender, age, the follow-up clinic, uric-lowering agent, history of diabetes mellitus (DM), dyslipidemia, gout, lipid profile, HT, SUA, and estimated glomerular filtration rate (eGFR; Cockcroft and Gault equation). The sample size for gender group was estimated with the formula $n = [(Z_{1-\alpha/2}+Z_{1-\beta})^2][\pi_1(1-\pi_1) + \pi_2(1-\pi_2)] / d^2$. Where n is the minimal sample sized required for each gender group; $Z_{1-\alpha/2}$ is Z value at probability of 0.05 and $Z_{1-\beta}$ is Z value at probability of 0.8; π_1 is probability of HT in male = 0.2 and π_2 is probability of HT in female = 1.5; d is the mean difference between two group = 0.05. By this formula the estimated minimal sample size is 1,208 for each group.

Data collection

Medical records of the persons 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) died, and 3) end of study date in April 2016.

Statistical analysis

Since SUA is related closely with gender[6], statistical analyses were carried out separately by gender with R-Program version 2.11. Continuous data of baseline characteristics were presented in terms of arithmetic mean and intergroup comparisons were performed using two-sample Student t-test statistics with unequal variances. Categorical variables were described in term of percentage and test hypothesis for difference by Pearson chi-square test. The precision of data was assessed and reported in term of 95% confidence interval (CI) using Gaussian statistics for continuous data or exact binomial statistics for discrete data.

During the analysis for incidence of HT, concentration of SUA was categorized in to eight categories starting from less than 2.9 to more than 8.8 mg%. Risks of HT by SUA categories were calculated and reported in term of person-time incidence and illustrated with line graph. Person-time incidences were calculated by dividing number of hypertensive persons with number of person-years at risk. The association between SUA and HT was analyzed and reported in term of incidence rate ratio (IRR) using univariate and multivariate Poisson regression models. Only variables that associated significantly with HT from univariate analysis were included in the multivariate model. To cope with collinearity in regression analysis caused by highly related variables, the authors used the variables reduction method[7]. All serum lipids were replaced with diagnosis of dyslipidemia. Uric acid lowering drug was used instead of gout. The 95% CIs of person-time incidences and IRRs was derived from exact Poisson statistics. The IRRs by SUA categories with corresponding 95% CI were illustrated with line graph. The J-shaped relationship were assessed by mean of R2 of quadratic trend.

Results

After a median 6.8-year follow-up (IQR 3.7, 7.4), the present study identified 309 and 195 incident cases of HT among 1,873 women and 1,019 men, respectively. Comparison of characteristics of studied samples between men and women are shown in Table 1. The study included more women than men, but the age and body mass index of men were more than women. Other putative risk factors for HT were more common in men such as DM, dyslipidemia, gout, uric lowering drug used, and chronic kidney disease more than second stage.

The person-year incidences of HT with 95% CIs in each group of SUA are illustrated in Figure 1 and 2. The incidence declined from 2.2/100 person-years in SUA concentration of less than 2.9 mg% group to 1.5/100 person-years in 2.9 to 3.8 mg% group and then raised in stepwise fashion in the higher SUA groups. This phenomenon was also found in men with the inflection pointed at the SUA concentration 4.9 to 5.8 mg%. Among categories of SUA concentration, the lowest incidence of HT in women (1.5/100 person-years; 95% CI 1.1 to 2.1) was lower than in men (2.2/100 person-years; 95% CI 1.6 to 3.4), but not significantly different (p=0.1, exact Poisson statistics).

The association between various factors including SUA and HT derived from univariate analysis are shown in Table 2[8-13]. The variables that are statistically significant associated with incidence of HT were recruited into the multivariate Poisson regression

Table 1. Description and comparison of the studied samples baseline characteristics with corresponding 95% CI

Characteristics	Overall (n=2,892) Mean (95% CI)	Women (n=1,873) Mean (95% CI)	Men (n=1,019) Mean (95% CI)	p-value
Age (year)	49.8 (49.4 to 50.2)	49.1 (48.6 to 49.6)	51.1 (50.5 to 51.8)	<0.0001[a]
Body mass index (kg/m^2)	24.1 (23.9 to 24.2)	23.9 (23.7 to 24.1)	24.3 (24.0 to 24.5)	0.02[a]
Diagnosis (%)				
Diabetes mellitus	5.5 (4.7 to 6.4)	4.3 (3.4 to 5.3)	7.8 (6.3 to 9.6)	<0.001[b]
Dyslipidemia	32.4 (30.7 to 34.1)	27.0 (25.0 to 29.0)	42.4 (39.4 to 45.5)	<0.001[b]
Gout	1.8 (1.3 to 2.3)	0.5 (0.3 to 1.0)	4.0 (3.0 to 5.4)	<0.001[b]
ULD used	2.5 (2.0 to 3.2)	0.5 (0.3 to 1.0)	6.2 (4.9 to 7.8)	<0.001[b]
Blood chemistry				
TC	217.5 (216.0 to 219.0)	216.6 (214.8 to 218.5)	219.1 (216.6 to 221.7)	0.1[a]
TG	120.8 (118.2 to 123.4)	105.5 (102.9 to 108.1)	149.1 (143.8 to 154.4)	<0.0001[a]
HDL-C	55.7 (54.8 to 56.6)	59.6 (58.5 to 60.8)	50.0 (48.7 to 51.3)	<0.0001[a]
LDL-C	149.7 (147.4 to 152.0)	151.4 (148.5 to 154.3)	147.3 (143.4 to 151.1)	0.09[a]
eGFR	86.3 (85.4 to 87.1)	86.9 (85.9 to 87.9)	85.1 (83.6 to 86.6)	0.04[a]
Serum uric acid	5.3 (5.2 to 5.4)	4.6 (4.5 to 4.7)	6.6 (6.5 to 6.7)	<0.0001[a]
Chronic kidney disease (%)				0.004[b]
Stage 1	38.9 (37.2 to 40.7)	40.2 (37.9 to 42.5)	36.6 (33.6 to 39.6)	
Stage 2	51.5 (49.6 to 53.3)	51.5 (49.2 to 53.8)	51.5 (48.4 to 54.6)	
Stage >2	9.6 (8.5 to 10.7)	8.3 (7.1 to 9.7)	11.9 (9.9 to 14.0)	

ULD=uric acid lowering drug; TC=total serum cholesterol; TG=serum triglyceride; HDL-C=high density lipoprotein cholesterol; LDL-C=density lipoprotein cholesterol; eGFR=estimated glomerular filtration rate by Cockcroft and Gault equation; CI=confidence interval

[a] Two-sample t test with unequal variances, [b] Pearson chi-square test

model. The strength of association between SUA and HT is displayed in Figure 3 and 4. The IRRs of HT in men and women shown a similar J-shaped trend as the incidence rates in men and women respectively. The R2 for quadratic trends of incidences of HT in men and women were equal to 0.927 and 0.946, and of the IRRs to 0.957 and 0.948, respectively.

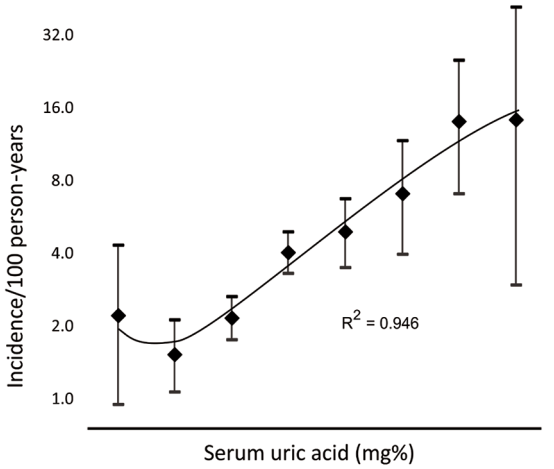
Discussion

HT has become public health burden worldwide. Pathogenesis of HT is a complex interplay of genetic, age, gender, obesity, lipid profile, renal function, environment, and hormonal factors.

SUA is the final enzymatic product of purine nucleotides catabolism. It has been long recognized that uric acid is associated with HT, but the causal relationship remains controversial[14]. Many observational studies try to elucidate the effect of SUA on HT, but the results varied between reports[15]. The discrepancy of the results may be due to the rules applied for categorization of SUA, the genetic diversity of studied population, or failure to control interaction with gender. Lack of information regarding effect of SUA on HT lead healthcare provider in trouble making decision whether to treat hyperuricemia or not.

The authors conducted a study to evaluate the effect of SUA on HT in a group of people residing in the southern part of Thailand. The study avoids the SUA-gender interaction by separately analyze by gender. To assess for the effect at different concentration levels, the authors divided SUA into eight groups with 1 mg% class intervals to include the lowest SUA concentration.

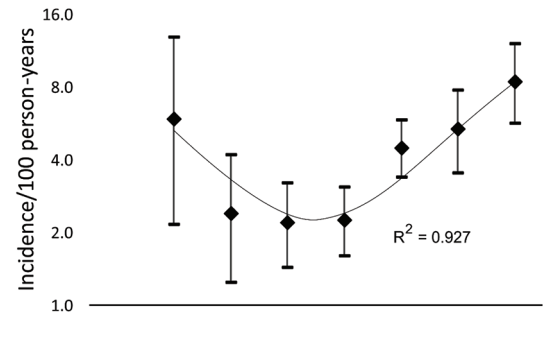
The present study demonstrated the J-shaped association patterns between SUA concentration and incidence rates of HT consistently in men and in women with R equal to and respectively. The incidence of HT increased continuously as the SUA increased from 2.9 mg% to 3.8 mg% in women and 4.9 mg% to 5.8 mg% in men. On the other hand, incidence also increased with the SUA lower than these (Figure 1, 2). After adjusting for potential confounding effect from



	<2.9	2.9-3.8	3.9-4.8	4.9-5.8	5.9-6.8	6.9-7.8	7.9-8.8	>8.8
Incidence	2.2	1.5	2.2	4.0	4.9	7.1	14.1	14.3
LL	1.0	1.1	1.8	3.3	3.5	4.0	7.0	3.0
UL	4.3	2.1	2.7	4.9	6.7	11.7	25.2	41.8

Figure 1. Incidence rates of hypertension with corresponding 95% CI in women stratified by serum uric acid concentration. In addition, quadratic trend of J-shaped association and R^2 of the predictive performance.

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



	<2.9	2.9-3.8	3.9-4.8	4.9-5.8	5.9-6.8	6.9-7.8	7.9-8.8	>8.8
Incidence	-	5.9	2.4	2.2	2.3	4.5	5.4	8.5
LL	-	2.2	1.3	1.4	1.6	3.4	3.6	5.7
UL	-	12.9	4.2	3.2	3.1	5.9	7.8	12.2

Figure 2. Incidence rates of hypertension with corresponding 95% CI in men stratified by serum uric acid concentration. In addition, quadratic trend of J-shaped association and R^2 of the predictive performance.

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

other putative risk factors, the association between SUA and HT remained the same J-shaped patterns (Figure 3, 4). The J-shaped relation between SUA and HT that varied between published reports may in part be due to detail of SUA classification, age, gender, and country (Table 2). J-shaped was not only found in HT incidence, it was found in other condition[16-22].

Even though the J-shaped association of uric acid demonstrated in many researches, the mechanism is not clearly understood. The authors proposed that uric may play both harmful and beneficial roles depending on intracellular or extracellular location, level of concentration, gender, and hydrophilic environment[23]. The authors also proposed that the paradox may be extracellular SUA oxidizes endothelium of blood vessel leading to vascular stiffness and HT[24,25]. Decrease in extracellular SUA concentration to a critical level will decrease intracellular uric acid and consequently compromise the antioxidant capacity that protect the endothelium lining.

What is already known on this topic?

SUA has been shown as a risk of HT but there is no available report published about Thai people. Pathogenesis of HT is a complex interplay of genetic, age, gender, obesity, lipid profile, renal function, environment, and hormonal factors. Difference in classification of SUA concentration result in variation of the association between uric acid and risk of HT.

What this study adds?

The relation between SUA concentration and the risk of HT is a J-shaped relation. The incidence of HT increases continuously both in high serum and low level of SUA concentration. The effect of SUA on the risk of HT is different among men and women. The smallest risk in men and in women are at 4.9 to 5.8 mg% and 2.9 to 3.8 mg%, respectively.

Conflicts of interest

The authors declare no conflict of interest.

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Table 2. Published reports regarding the association between concentration level of serum uric acid and incidence of hypertension

Author	Country	Gender	Measurement						
Zhang, et al.[8]	China	Men	SUA (mg%)	<4.2	4.2 to 4.9	>4.9 to 5.7	>5.7		
			RR	1.0	0.97	1.23	1.39		
		Women	SUA (mg%)	<3.6	3.6 to 4.2	>4.2 to 4.8	>4.8		
			RR	1.0	1.49	1.58	1.85		
Wei, et al.[9]	China	Both	SUA (mg%)	<4.66	4.66 to 5.53	5.53 to 6.46	>6.46		
			HR	1.0	1.103	1.043	1.350		
Yang, et al.[10]	Taiwan	Men	SUA (mg%)	<6.2	6.2 to 7.1	7.2 to 8.0	>8.0		
			HR	1.00	1.14	1.21	1.41		
		Women	SUA (mg%)	<4.4	4.4 to 5.2	5.3 to 6.1	>6.1		
			HR	1.0	1.77	1.18	1.64		
Shankar, et al.[11]	Singapore	Men	SUA (mg%)	<4.4	4.4 to 5.5	>5.5 to 6.6	>6.6		
			HR	1.0	1.06	1.22	1.48		
		Women	SUA (mg%)	<4.4	4.4 to 5.5	>5.5 to 6.6	>6.6		
			HR	1.0	1.16	1.30	1.71		
Leiba, et al.[12]	Israel	Men	SUA (mg%)	<2	2 to <3	3 to <4	4 to <5	5 to <6	6 to <6.9
			OR	1.11	to	1.0	1.21	1.36	1.54
		Women	SUA (mg%)	<2	2 to <3	3 to <4	4 to <5	5 to <6	6 to <6.9
			OR	0.70	1.0	1.15	1.34	1.66	1.76
Forman, et al.[13]	HPFS	Men <60 years	SUA (mg%)	2.4 to 5.1	5.2 to 5.9	6.0 to 6.7	6.8 to 11.5		
			RR	1.0	1.30	1.07	1.57		
		Men ≥60 years	SUA (mg%)	2.4 to 5.1	5.2 to 5.9	6.0 to 6.7	6.8 to 11.5		
			RR	1.0	0.72	1.17	0.98		

HPFS=Health Professionals Follow-Up Study; SUA=serum uric acid; HR=hazard ratio; RR=relative risk; OR=odds ratio

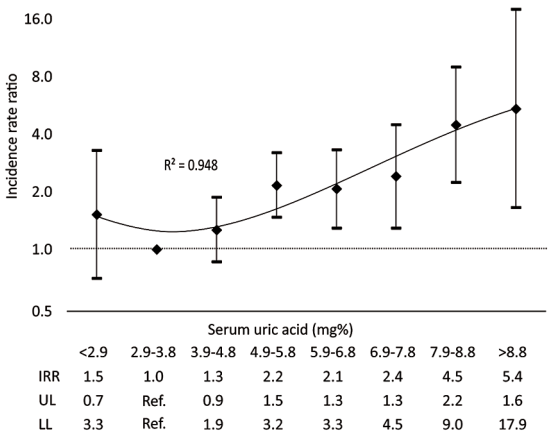

Figure 3. Incidence rate ratios of hypertension with corresponding 95% CI in women stratified by serum uric acid concentration, resulting from multivariate Poisson regression analysis. In addition, quadratic trend of J-shaped association and R^2 of the predictive performance.

IRR=incidence rate ratio; UL=upper limit of 95% confidence interval; LL=lower limit of 95% confidence interval

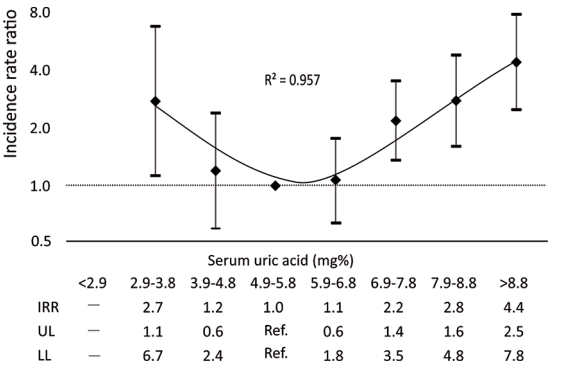

Figure 4. Incidence rate ratios of hypertension with corresponding 95% CI in men stratified by serum uric acid concentration, resulting from multivariate Poisson regression analysis. In addition, quadratic trend of J-shaped association and R^2 of the predictive performance.

IRR=incidence rate ratio; UL=upper limit of 95% confidence interval; LL=lower limit of 95% confidence interval

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