ORIGINAL ARTICLE

Effects of Low-dose Aspirin on Serum Uric Acid among Asymptomatic Hyperuricemia Patients with Cardiovascular Risk Factors

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Objective: Several drugs can cause hyperuricemia including low-dose aspirin (LDA), which is commonly prescribed for primary prevention of cardiovascular disease. The effect of LDA on serum uric acid (SUA) level in asymptomatic hyperuricemia patients needed exploration. The authors' aim was to determine the prevalence of a significant change in the SUA level and onset of any new acute gouty attack in asymptomatic hyperuricemia patients with cardiovascular risk factors as indicated by taking LDA.

Materials and Methods: An experimental study was performed in 128 Thai asymptomatic hyperuricemia patients with cardiovascular risks at Srinagarind Hospital, Khon Kaen University, Thailand, between October 2016 and October 2017. Both clinical and laboratory assessments were performed before and after taking LDA for 2 weeks.

Results: Data analysis was performed on the 120 patients who completed the present study. Seven patients were excluded because of being lost to follow-up, and another was withdrawn because of having an acute gouty attack. The mean SUA level at baseline was 7.5 mg/dl. After 2 weeks of LDA, 75.8% of the participants had a significantly decreased SUA level. Only 4.2% of participants had an increased SUA level. One of our participants experienced an acute gouty attack at the first metatarsophalangeal joint after LDA initiation.

Conclusion: The influence of 2 weeks of LDA on the SUA level was demonstrated in asymptomatic hyperuricemia patients with cardiovascular risks. The SUA level showed an unexpected, significant decrease in two-third of the study population, and less than 1% of the participants experienced an acute gouty attack after 7 days of aspirin initiation.

Keywords: Low-dose aspirin; Gouty arthritis; Uric acid; Hyperuricemia

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Hyperuricemia is the result of interactions among multiple factors, including sex[1], age[2], genetics[3], lifestyle[4], and environment[5]. Several studies have suggested that hyperuricemia is associated with many diseases, including diabetes mellitus[6], hypertension[7], stroke[8], dyslipidemia, chronic kidney disease[9], cardiovascular events, and heart failure[10-12]. Hyperuricemia is considered to be a precursor of gout as the deposition of urate crystals in the joints results in an acute inflammatory response. Deposition in the soft tissue can lead to tophi. Gout and hyperuricemia represent a serious health issue, and can result in a significant socioeconomic loss. In recent in epidemiological studies, an increasing trend in the prevalence of hyperuricemia and gout have been observed[13-15] and both diseases have become public health problems needing redress.

Aspirin is a non-steroidal anti-inflammatory drug (NSAID). The use of low-dose and very low dose (mini-dose) aspirin for the prevention of thrombosis has been greatly expanded during the last decade. Aspirin administered to men in a sufficiently large dosage (5 to 6 or more grams per day) causes marked uricosuria, characterized by substantial inhibition of tubular reabsorption of the filtered urate. In smaller dosages (1 to 2 g per day) salicylate exerts a contrary effect, i.e., retention of urate[16]. Aspirin has been shown to be effective in reducing cardiovascular morbidity and mortality in high-risk patients who have experienced myocardial infarction (MI) or stroke[17] and is recommended as a secondary prevention strategy for individuals with multiple atherosclerosis risk factors[18]. Patients at a relatively high risk for the development of vascular disease might also be expected to derive substantial benefit from regular aspirin administration.

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The relative risks for developing hyperuricemia have been reviewed and include diet, alcohol consumption, metabolic syndrome, and some drugs that influence hyperuricemia (i.e., long-term use of low-dose aspirin for chronic conditions). Hyperuricemia caused by long-term low-dose aspirin may be one of many conditions linked to hypertension, dyslipidemia, and disordered glucose metabolism—all of which play a causal role in the pathogenesis of cardiovascular disease. As such, uric acid may be merely a marker of risk for cardiovascular disease. The effect of low-dose aspirin in serum uric acid has been studied less so the severity of any association with serious hyperuricemia cannot be predicted. The authors, thus, set out to determine (a) the prevalence of significant changes in SUA level in asymptomatic hyperuricemia patients related to aspirin compared to baseline, and (b) the incidence of new onset acute gouty arthritis in asymptomatic hyperuricemia patients while taking the low-dose aspirin

Materials and Methods

An experimental study was performed in asymptomatic hyperuricemia with or without metabolic syndrome and followed-up at both the Out- or In-patient Units at Srinagarind Hospital, Khon Kaen University, Thailand, between October 2016 and October 2017. The population included all patients diagnosed as having asymptomatic hyperuricemia and an indication of low-dose aspirin therapy for primary and secondary prophylaxis of cardiovascular diseases.

The authors excluded patients having (a) Type I Diabetes; (b) a history of gouty attacks; (c) a history of alcohol consumption within 1 week before blood testing for serum uric acid; (d) a history of alcoholic addiction; (e) risks for aspirin side-effects (i.e., current active peptic disease, congestive heart failure, hemorrhagic stroke, history of gastrointestinal bleeding or bleeding tendency); (f) using prohibited medication (i.e., anticoagulants, aspirin, NSAIDs, and urate-lowering agents); (g) history of aspirin or NSAIDs allergy; and, (h) uncontrolled/severe medical problems (i.e., asthma, angina pectoris, hepatitis, or renal diseases [serum creatinine ≥1.5 mg/dL or GFR ≤50 ml/min]. We also excluded patients receiving (a) co-medications that may have a drug interaction with aspirin (i.e., phenytoin, warfarin clopidogel, endoxaban, steroid, dypyridamole, metoplolol, methothraxate, emthambutol, pyrazinamide, and diuretics), or (b) co-medications that may influence the serum uric acid level (i.e., thiazide, ethambutol and pyrazinamide, Lasix). The authors withdrew patients who (a) were unable to attend follow-up or who refused blood collection at the 2nd visit (i.e., 2 weeks after taking aspirin); (b) had had an adverse reaction to aspirin within 2 weeks of taking aspirin; and, (c) were not able to take regular aspirin and/or were using <80% of total dose aspirin in 2 weeks.

Subjects entered into the study were ruled out for any of the exclusion criteria and assessed at baseline. Assessment included medical history, demographic data, and physical examination. Serum uric acid, renal function test, and liver function test were investigated using standard methods before the first dose of aspirin treatment. All patients were asked to take one 81-mg tablet of aspirin orally in the morning after breakfast for 2 weeks for primary or secondary prevention of cardiovascular disease. Before starting aspirin, patients were advised to report any adverse effects related to the aspirin therapy during the study. Any adverse drug reaction or event and any new onset of acute gouty attack were reported during the 2 weeks of follow-up. The patients were re-evaluated for serum uric acid and others blood chemicals at the 2nd visit (after 2 weeks of aspirin). The glomerular filtration rate (GFR) was calculated using the Cockcrof-Gault formula: (140-years of age) x body weight/serum creatinine (mg/dl) x72, corrected by x0.85 for women[19]. Patients were also classified according to their renal failure staging 19 before and after aspirin treatment. The blood samples were kept in blood tubes without heparin and sent to the laboratory for testing. If the assays could not be completed within a few hours, the serum or plasma was at +2 to +8°C until tested. The samples were run as part of a multi-analysis biochemistry panel.

A diagnosis of hyperuricemia was defined by serum uric acid above 6.8 mg/dl. Normo-uricemia was defined by serum uric acid ≤6.8 mg/dl[20]. The definition of gout followed the diagnosis criteria of the American College of Rheumatology[21]. A significant increase of serum uric level was fulfilled when the serum uric level increased by >1.0 mg/dl from baseline based on recent studies[22]. Fifty to 100 mg/day constituted low-dose aspirin while a high dose meant >1 g/day[23]. Metabolic syndromes included hypertension, type II diabetes, dyslipidemia, abdominal obesity (BMI ≥30 kg/m^2).

Ethics approval and consent to participate

The Human Research Ethics Committee of Khon Kaen University approved the study as per the Helsinki Declaration and the Good Clinical Practice Guidelines (HE591367). All eligible patients signed informed consent before entry the study.

Statistical analysis

Patient baseline characteristics were summarized using descriptive statistics. Categorical data were presented as proportions or percentages. Continuous data were presented as means (±SD) or medians with interquartile range (IQR), as appropriate. A rise in the level of uric acid was determined with its respective 95% confidence interval

(95% CI); changes before and after low-dose aspirin therapy were determined and analyzed using the Paired Student's t-test. The incidence of new onset gouty arthritis was investigated with it 95% CI. All p-values were two-tailed (statistical significance was set at $p<0.05$). All statistics were analyzed using STATA version 11.2 (Stata Corp. College Station, TX, USA).

Results

The study comprised 128 patients with asymptomatic hyperuricemia. Seven patients were excluded from the study analysis due to their being lost to follow-up. One of the patients who withdrew experienced a new acute gouty attack at the first metatarsophalangeal joint during the study period. Her SUA at baseline was 7.4 mg/dl with normal renal function. She had underlying hypertension and dyslipidemia but no family history of gouty arthritis.

The majority of the study population were male (78%). The median age of participants was 58.5 (IQR 53.4 to 65.5) years, 58.5 (IQR 53.6 to 64.6) for males vs. 59.9 (IQR 52.5 to 69.5) for females. The types of comorbidity identified in the study population included dyslipidemia (92.4%), hypertension (80%), diabetes mellitus 24.2%, and obesity (23.3%). All patients were receiving multiple drug therapies for their respective associated diseases (Table 1).

The study population had good renal function at baseline with an average eGFR of 72.5 ml/min/1.73 m^2. At baseline, the median SUA was 7.5 mg/dl (IQR 7.15 to 7.95); 7.6 mg/dl (IQR 7.2 to 8.0) among males and 7.2 mg/dl (IQR 6.7 to 7.9) among females. Other baseline characteristics were listed in Table 2. About 97% of the patients had more than one risk factor for cardiovascular disease; 39, 46, and 11% had 2, 3, and 4 risk factors, respectively. Low-dose aspirin was prescribed for cardio-protection for all of these patients (Table 3).

After 2 weeks of low-dose aspirin administration, the mean level of SUA among all participants was slightly decreased compared to the baseline in both males and females (Figure 1). Serum creatinine (Cr) and blood urea nitrogen (BUN) was stable during the study period (Table 4).

All participants were classified into 3 groups according to the change in SUA level after aspirin treatment: Stable if within the range of baseline SUA ±1 mg/dl; Decreased

Table 1. Baseline demographics

Variable	n=120	Percentage (100%)
Age (years); mean (IQR)	58.5 (53.6 to 64.6)	100
Male (years)	58.5 (53.4 to 65.5)	
Female (years)	59.9 (52.5 to 69.5)	
Sex male: female	3.6: 1	94: 26
Dyslipidemia	111	92.4
Hypertension	96	80
Diabetes mellitus	29	24.17
Obesity	28	23.3
Recent Ischemic stroke	2	1.67
Benign prostate hypertrophy	1	0.83
Smoking	54	45
Antidiabetic therapy (n=29)		
Metformin with glipizide	12	41.4
Metformin	11	38
Glipizide	1	3.5
Insulin	1	3.5
Metformin with glipizide and insulin	1	3.5
Diet control	3	10.3
Antihypertensive treatment (n=96)		
CCB (amlodipine)	44	45.8
ACE-Is (enalapril)	29	30.2
ACE-Is + CCB	10	10.4
ARBs (losartan)	4	4.16
ARBs + CCB	1	1.04
Alpha-Blocker (doxazocin)+ CCB	2	2.08
Life style modification	6	6.25
Lipid-lowering therapy (n=111)		
Simvastatin	71	63.7
Atorvastatin	16	14.4
Simvastatin with gemfibrozil	9	8.1
Gemfibrosil	5	4.5
Atorvastatin with gemfibrozil	1	0.99
Life style modification	9	8.1

ACE-Is=angiotensin converting enzyme inhibitors; ARBs=angiotensin II receptor blockers; CCB=calcium channel blocker

Table 2. Baseline clinical and laboratory data of asymptomatic hyperuricemia patients

Variable	n=120	Mean (IRQ)
BMI (kg/m^2)	25.92	25.92 to 28.53
Fasting plasma glucose (mg/dl)	102	93 to 113.5
HbA1C (%)	5.6	0 to 6.2
Serum creatinine (mg/dl)	1.03	0.88 to 1.17
BUN (mg/dl)	12.38	10 to 15
GFR (ml/ min)	72.5	64.02 to 85.05
Serum uric acid in male (mg/dl)	7.6	7.2 to 8
Serum uric acid in female (mg/dl)	7.2	6.7 to 7.9
Proteinuria	9	7.5%
CHO (mg/dl)	180.5	151.5 to 210
TG (mg/dl)	153.5	113.5 to 245.5
HDL (mg/dl)	46	38 to 54.5
LDL (mg/dl)	109.5	88 to 133

Proteinuria trace proteinuria by urine dipstick test for proteinuria

BMI=body mass index; HbA1C=hemoglobin A1c; BUN=blood urea nitrogen; GFR=glomerular filtration rate; CHO=cholesterol; TG=triglyceride; HDL=high density lipoprotein; LDL=low density lipoprotein

if less than baseline SUA-1 mg/dl; and, Increased if more than baseline SUA+1 mg/dl. Approximately two-thirds (75.8%) of the study patients were classified in the decreased SUA group, while 4.2% and 20%, respectively, were in the increased and stable SUA group (Table 5). The decrease in SUA was not statistically significant when comparing between males and females (p=0.62). The use of concomitant drugs with an uricosuric effect and the change of SUA are presented in Table 5.

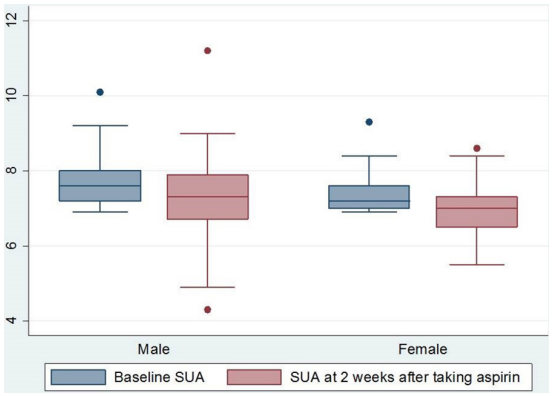

Figure 1. Effect of low-dose aspirin in asymptomatic hyperuricemia on serum uric acid.

Discussion

Low-dose aspirin at a dosage of 75 to 325 mg/day is currently used for platelet aggregation inhibition in many patients, and cardiovascular protection among healthy individuals. No data have been published vis-à-vis the effect of low-dose aspirin among patients with asymptomatic hyperuricemia.

Salicylate is known to influence the uric acid balance and renal function, and was once a popular anti-inflammatory agent for many rheumatic diseases[24]. Yu et al. found that at higher doses (>3 gm/day), salicylate increases renal uric acid excretion, while at lower doses (1 to 2 g/day), it may cause uric acid retention. A paradoxical effect of salicylate on SUA was thus demonstrated in that different levels of excretory

Table 3. Number of cardiovascular risk factors in asymptomatic hyperuricemia patients

Variable	n=120	Percentage (%)
One risk factor	4	3.33
Two risk factors	47	39.17
Three risk factors	55	45.83
Four risk factors	13	10.83
Five risk factors	1	0.83

Risk factors: diabetes, hypertension, obesity, dyslipidemia, smoking

Table 4. Comparison of serum uric acid and renal function at baseline and at 2 weeks after taking low-dose aspirin

	Male		p-value	Female		p-value	Baseline total mean (IRQ)	After 2 weeks total mean (IRQ)	p-value
	Baseline	After 2 weeks		Baseline	After 2 weeks				
Serum uric acid (mg/dl)	7.6 (7.2 to 8.0)	7.3 (6.7 to 7.9)	0.001	7.2 (6.7 to 7.9)	7 (6.5 to 7.3)	0.008	7.5 (7.15 to 7.95)	7.2 (6.7 to 7.9)	<0.001
Serum creatinin (mg/dl)	1.095 (0.97 to 1.2)	1.05 (0.97 to 1.18)	0.67	0.85 (0.76 to 0.95)	0.865 (0.81 to 1.0)	0.2	1.03 (0.88 to 1.17)	1.025 (0.9 to 1.145)	0.33
BUN	12.75 (10.2 to 15.2)	12.05 (10.2 to 15.5)	0.36	10.8 (9.4 to 13.6)	13.85 (10.2 to 16.3)	0.03	12.35 (10 to 15)	12.3 (10.2 to 15.65)	0.80

The p-value <0.05 statistic significant

Table 5. Concomitant drug use and the change of serum uric acid after 2 weeks of aspirin treatment

Variable	Change in serum uric acid					
Total, n=120	Decrease[1], n=91 (75.8%)		Stable[2], n=24 (20%)		Increase[3], n=5 (4.2%)	
Sex, n (%)	Male	Female	Male	Female	Male	Female
	70 (74)	21 (80.7)	20 (21.27)	4 (15.38)	4 (4.2)	1 (3.8)
Enalapril	20		6		0	
Atorvastatin	13		4		0	
Simvastatin + gemfibrosil	7		2		0	
Gemfibrosil	3		2		0	
Losartan	2		2		0	
Atorvastatin + gemfibrosil	1		0		0	
Losartan + amlodipine	1		0		0	
Losartan + gemfibrosil	1		0		0	

[1] Decrease=SUA at the end of treatment < baseline SUA-1 mg/dl; [2] Stable=SUA at the end of treatment = baseline SUA ±1 mg/dl; [3] Increase=SUA at the end of treatment > baseline+1 mg/dl

salicylate influence the tubular reabsorption of excretory uric acid[24]. Yu et al. also demonstrated the influence of different doses of salicylate on probenecid uricosuria[24].

Recently, Louthrenoo et al. studied the effect of mini-dose aspirin on renal function and renal acid uric handling in healthy young adults with normal renal function. The results showed that 300 mg aspirin/day (not 60 mg/day) resulted in significantly decreased uric acid and creatinine clearance by the end of the second week of aspirin therapy. Uric acid clearance, not creatinine clearance, did not return to normal 1 week after aspirin withdrawal; notwithstanding, both doses of aspirin had no significant effect on SUA and serum creatinine[25].

Caspi et al. studied the effect of low-dose aspirin in elderly patients without gout, on hyperuricemia and abnormal renal function (serum Cr >1.6)[22]. There was a significant decrease in uric acid excretion with slightly increased SUA and decreased renal function even after mini-dose aspirin therapy (75 mg/day). Two studies on the effect of mini-dose aspirin on SUA investigated patients with diabetes and ischemic heart disease. They demonstrated that long-term use of low-dose aspirin caused hyperuricemia in both groups of patients[26]. By contrast, a study on the effect of low-dose aspirin on SUA and urinary uric acid excretion in gouty arthritis patients treated with allopurinol or benzbromarone did not show any negative results[27].

The target population of this study included persons (a) with metabolic syndrome with asymptomatic hyperuricemia, at risk for cardiovascular diseases requiring prophylaxis treatment with low-dose aspirin that may influence SUA level. The study showed that taking low-dose aspirin for 2 weeks had a minimal effect on SUA; however, the mean SUA level after treatment was significantly lower than the baseline SUA level (7.5 vs. 7.2 mg/dl. p=0.001). Our results contradicted results from other studies[22,26]. When the treatment outcome measure was considered individually-about two-thirds of the participants had a significant decreased SUA level (< baseline SUA-1) after taking aspirin, while only 4.2% had an increased SUA level (> baseline SUA+1).

The mechanism by which the SUA level is lowered after taking low-dose aspirin among metabolic syndrome patients with asymptomatic hyperuricemia needs to be elucidated. The authors hypothesize an abnormal tubular transport system of uric acid (without renal failure) with co-treatment of metabolic syndrome may explain the phenomenon. The authors did not measure urine uric acid excretion but research has demonstrated that the angiotensin II receptor antagonist, losartan, fibrate, and atorvastatin have an uricosuric effect, increasing renal excretion of uric acid[28-32]. The suppression of salicylate on uricosuric effect of probenecid and sulfinpyrazone have also been demonstrated[24,33]. Once concomitant medications have stabilized prior to entering a study period, low-dose aspirin should result in a higher level of SUA. Notwithstanding, Choi et al. found that low-dose aspirin did not influence the level of SUA or urinary uric acid excretion among patients with gouty arthritis treated with allopurinol or benzbromarone[27]. A satisfactory explanation is still needed for the discrepant effect of aspirin on SUA concentration in this subset of patients.

One of our participants experienced an acute gouty attack during low-dose aspirin initiation. She was excluded from the SUA level analysis because she stopped taking aspirin prior to the end of the study. No predictor of acute gouty attack was identified; neither a strikingly high baseline SUA level nor a positive family history of gout. The authors' study demonstrated a less than 1% chance of a gouty attack after aspirin initiation in asymptomatic hyperuricemic patients; however, the sample size was too small to conclude the prevalence of the complication. Zhang et al. also found that a recurrent gouty attack was increased two consecutive days after using low-dose aspirin[34].

Study limitations included: 1) sample size of the study was calculated upon the previous report of changing SUA level after taking low dose aspirin, that was too small to identify the prevalence of gouty attack after drug initiation. 2) Urinary excretion of uric acid was not performed during study period, thus the authors could not explain the possible interaction between low dose aspirin and allowed concomitant medications that may explain the decrease in SUA level. 3) The patient who had gouty attack was loss to follow-up, then the authors could not classify the change of SUA level at the time of gouty attack.

Conclusion

The present study demonstrated the influence of low-dose aspirin on the SUA level in asymptomatic hyperuricemia patients with metabolic syndrome. The mean SUA level was decreased significantly in this subpopulation, so that a gouty attack occurred in less than 1%. This observation contradicts several reports in which low-dose aspirin blocked urinary uric acid excretion, with or without any increase in the SUA level, and none decreased the SUA level. The authors postulate this may due to the interaction between low-dose aspirin and concomitant drugs used to treat metabolic syndrome that may influence urine uric acid excretion. Further study is needed to elucidate whether the effect of LDA on SUA was transient or long-term, and the mechanism.

What is already known on this topic?

Aspirin in a large dosage (5 to 6 or more grams per day) causes marked uricosuria, characterized by substantial

inhibition of tubular reabsorption of the filtered urate. In smaller dosages (1 to 2 g per day) salicylate exerts a contrary effect, i.e., retention of urate.

What this study adds?

After 2 weeks of low-dose aspirin administration, the mean level of SUA was slightly decreased compared to the baseline in both males and females in asymptomatic hyperuricemia patients with cardiovascular risks, so that a gouty attack occurred in less than 1%.

The mechanism by which the SUA level is lowered after taking low-dose aspirin among metabolic syndrome patients with asymptomatic hyperuricemia is still unknown.

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Conflicts of interest

The authors declare no conflict of interest.

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