

Assessing the effects of low dose aspirin on uric acid and renal function in healthy adults

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ABSTRACT

Objective: To evaluate the effects of low daily aspirin doses on uric acid (UA) level and renal functions in healthy adults.

Methods: Healthy adults were randomized to receive 100 mg (n= 33), or 300 mg (n = 31) aspirin daily for one month. Laboratory tests included measurement of blood urea nitrogen (BUN), serum creatinine, and uric acid (UA) levels. Urine creatinine, urea and uric acid excretion were measured in a 24 h collection of urine, 24 hours urine uric acid, creatinine clearance (Ccr), were measured at baseline and then after 4 weeks of therapy.

Results: After 4 weeks of therapy, 100 and 300 mg/d dosage, aspirin caused a 7% and 12% decrease in the rate of UA excretion respectively ($P < 0.05$). Patients at the dosage 300 mg/d but not the 100mg/day had an increase in serum levels of uric acid (UA), creatinine and urea with a significant decrease in 24 hour creatinine clearance and urinary urea excretion ($P < 0.05$) when compared with the baseline.

Conclusion: Because of the effects of 300 mg dose aspirin, in the lowering of kidney function and the potential of aspirin to cause dose-dependent impairment of renal function, patients taking low-dose aspirin therapy should be monitored for the development of impaired renal function.

Keywords: Low dose aspirin, renal function, healthy adult.

الخلاصة

الهدف: تقييم تأثيرات جرعات الأسبيرين المتدنية اليومية على مستوى الحامض البولي ووظائف الكلى في البالغين الأصحاء.

الطريقة: أعطى الأسبيرين عشوائياً (ثلاث و ثلاثون شخصاً أعطوا 100 ملغم، واحد و ثلاثون شخصاً أعطوا 300 ملغم) الى البالغين الأصحاء يومياً لمدة 4 أسابيع. شمل الفحص المختبري كمية الحامض البولي، يوريا نتروجين، كرياتينين في مصل الدم، طرح الكرياتينين، الحامض البولي واليوريا نتروجين في الـ 24 ساعة بول قبل وبعد 4 أسابيع من إعطاء الأسبيرين.

النتائج: ان جرعة الـ 100 ملغم و الـ 300 ملغم أسبيرين يومياً تسببت بـ 7% و 12% نقصان في نسبة طرح الحامض البولي على التوالي بعد 4 أسابيع. على أية حال، مرضى العينة 300 ملغم وليس 100 ملغم كان عندهم زيادة في مستويات الحامض البولي، الكرياتينين واليوريا في مصل الدم مع نقص معنوي في طرح الكرياتينين واليوريا مقارنة مع ما قبل العلاج.

الاستنتاج: بسبب تأثير جرعة الـ 300 ملغم أسبيرين يومياً في ضعف الوظيفة الكلوية وإمكانية الأسبيرين في تسبب ضعف وظيفة الكلية المعتمد على الجرعة. المرضى اللذين يأخذون جرعة منخفضة من علاج أسبيرين يجب متابعة حالتهم لأي تطور يضاعف الوظيفة الكلوية.

Treatment with low-dose aspirin (acetylsalicylic acid) offers beneficial effects on patients with atherothrombotic vascular disease⁽¹⁾. The therapeutic efficacy of low-dose aspirin is due to irreversibly acetylating cyclooxygenase-1 (COX-1), and thereby reduces thromboxane A₂ produced by platelets. TxA₂ is a potent inducer of platelet aggregation and vasoconstriction⁽²⁾.

Although aspirin is generally a very well-tolerated drug, like most medications it carries a risk of significant adverse effects, many of which are dose-related⁽³⁾. Aspirin has a biphasic effect on urate excretion (that is, antiuricosuria at low doses and uricosuria at high doses)⁽⁴⁾. Minimal doses of salicylate (75, 150, and 325 mg daily) were shown to increase serum uric acid levels⁽⁵⁾. On the other hand, in high doses (as may be used to treat rheumatoid arthritis), aspirin blocks reabsorption of uric acid by the kidneys, resulting in a lowering of the blood level of uric acid^(6,7). The changing of uric acid levels above or below normal levels could possibly lead to unwanted side effects⁽⁸⁾.

Hyperuricemia has long been associated with renal disease. Approximately 20 to 60% of patients with gout have mild or moderate renal dysfunction; indicating a possible link between an elevated uric acid level and renal disease⁽⁹⁾. Also, an elevated uric acid has been reported to predict the development of renal insufficiency in individuals with normal renal function⁽¹⁰⁾.

Several studies have identified the value, in populations, of serum uric acid concentration in predicting the risk of cardiovascular events⁽¹¹⁻¹³⁾.

In an experimental hyperuricaemic rat model study, Kang et al⁽¹⁴⁾ provided evidence that uric acid may be a true mediator of renal disease and progression.

A possible mechanism by which uric acid may worsen the progression of kidney disease is by the activation of the renin angiotensin system (RAS). The RAS has been identified as a contributor to the progression of renal disease by increasing both systemic and glomerular pressure and by directly causing the fibrosis of renal and vascular cells^(14,15).

Low dose aspirin has been reported to be a risk factor of hyperuricemia⁽⁵⁾. Therefore the present study was designed to assess the effects of the daily use of low dose aspirin on uric acid and renal functions in healthy adult.

Subjects and methods

Subjects

The study group consisted of 64 healthy adult volunteers. There were 31 men and 33 women aged 30 to 50 years, mean 39±6.9 (SD). Healthy volunteers were asked to complete a questionnaire to detect the history of urinary tract infection (UTI), renal stone, hematuria, and renal stones in the family. Any one with one of these abnormalities was excluded from the study. They were randomly assigned to 1 of 2 groups: one group received 100 mg/day (n=33, 16 females and 17 males) and the other 300 mg/day (n=31, 16 females and 15 males). Aspirin (was given as Aspin® (SDI) enteric-coated tablet) for 4 weeks. The doses selected for investigation in this trial (100 and 300 mg) reflect the current, most frequently used for cardioprotection.

All study participants had 24-h urinary and fasting blood samples collected prior to dosing and 4 weeks following aspirin treatment, for measurement of serum creatinine, uric acid and urea concentrations and 24-hour urinary excretion of creatinine, uric acid, and urea.

Laboratory assessment of creatinine, uric acid, and urea

Creatinine was determined by standard laboratory procedures⁽¹⁶⁾ utilizing a commercial kit (Syrbio). Uric acid and urea levels were measured enzymatically with commercially available kits (Biolabo for uric acid measurement by the Tietz method⁽¹⁷⁾; BioMerieux for urea measurement by the Fawcett and Scott method⁽¹⁸⁾).

Clearances of creatinine, uric acid and urea were calculated as the products of urine concentrations and 24-hour urine collection divided by the serum concentrations and expressed as ml/min using the following formulas for calculations:

1. Creatinine clearance= urinary creatinine (mg/dl) × 24-hour urine collection (ml)/

serum creatinine (mg/dl $\times 1440$ (min in 24hr)).

2. Uric acid clearance= urinary uric acid (mg/dl) \times 24-hour urine collection (ml) / serum uric acid (mg/dl) multiplied by 1440.
3. Urea clearance= urinary urea (mg/dl) \times 24-hour urine collection (ml) / serum urea (mg/dl) multiplied by 1440.

Statistical analysis

Comparison of kidney function parameters before and after aspirin therapy was done by paired t-test and the unpaired t-test to compare the differences between the 2 groups. Pearson correlation was applied to evaluate the correlations of serum parameters with urine parameters. Gender differences were evaluated to see if the effect of acetyl salicylic acid varied according to sex.

Results

100 mg/d of aspirin did not significantly affect serum uric acid, creatinine and urea levels, whereas it significantly decreased by 21% and 6.74% 24h urinary uric acid fraction and uric acid clearance rate respectively (Table1).

While 300 mg/d aspirin, caused a significant elevation in serum uric acid, creatinine and urea levels, with a significant reduction in the 24h-urinary fractional excretion, and the 24 urine uric acid, creatinine clearance (Table1).

The percent increase in serum uric acid in 300mg/d of-aspirin users was 3-fold compared with 100 mg/d -aspirin users (300mg/d -aspirin users versus 100 mg/d -aspirin users, $6.12 \pm 4.29\%$ versus $2.14 \pm 4.24\%$, $P < 0.05$).

A significant correlation between the changes from baseline to week 4 in both creatinine and uric acid clearance was documented ($r = 0.278$, $P < 0.042$) (Figure 1).

After 4 weeks of 300 and 100 mg/d aspirin administration (Figure 2), women exhibited a higher percent change of serum creatinine compared with the men ($9.34 \pm 7.48\%$ versus $2.86 \pm 3.91\%$, $P < 0.05$ and $2.66 \pm 1.79\%$ versus $1.0 \pm 1.58\%$, $P < 0.05$ respectively). The percent of decline in 24h creatinine clearance with 300 mg/d aspirin administration was greater in women compared with men (women, $-9.8 \pm 5.12\%$; men, $-4.78 \pm 6.1\%$; $P < 0.05$).

Table (1): Treatment with low doses of aspirin and alteration in uric acid and renal function parameters in serum and 24h urine.

	Aspirin 100 mg/day (no.33)			Aspirin 300 mg/day (no.31)		
	Baseline	After 4 weeks	% change	Baseline weeks	After 4	% change
Serum Uric Acid (mg/dl)	5.01 \pm 1.09	5.04 \pm 1.04	2.14 \pm 4.24	5.09 \pm 1.06	5.31 \pm 1.01*	6.12 \pm 4.29 §
Fractional Excretion of Uric Acid(mg/dl)	46.69 \pm 15.03	31.82 \pm 10.4*	-21.26 \pm 20.4	40.73 \pm 12.16	22.11 \pm 9.13*	-38.3 \pm 13.42 §
Uric Acid Clearance (ml/min)	8.32 \pm 1.34	7.45 \pm 1.37*	-6.74 \pm 6.1	8.47 \pm 1.45	7.08 \pm 1.42*	-12.41 \pm 7.24 §
Serum Creatinine (mg/dl)	1.04 \pm 0.23	1.06 \pm 0.21	1.16 \pm 5.01	0.96 \pm 0.19	1.04 \pm 0.17*	4.43 \pm 4.15 §
Urine Creatinine (mg/dl)	131 \pm 28	128 \pm 25	-2.94 \pm 9.07	109 \pm 15	98 \pm 13*	-11.66 \pm 7.95 §
CrCl (ml/min)	108 \pm 16	106 \pm 14	-1.13 \pm 4.89	106 \pm 13	97 \pm 11*	-8.61 \pm 6.54 §
Serum Urea (mg/dl)	29.79 \pm 6.37	30.13 \pm 6.69	1.05 \pm 3.1	29.74 \pm 4.79	31.46 \pm 3.92*	3.76 \pm 2.86 §
Urine Urea (mg/dl)	1865 \pm 312	1836 \pm 318	-1.63 \pm 5.6	1816 \pm 391	1693 \pm 271*	-8.18 \pm 6.15 §

Data are mean \pm (SD) * $P < 0.05$ versus baseline;

§ Values are number (percentage) $P < 0.05$ versus 100 mg/day aspirin.

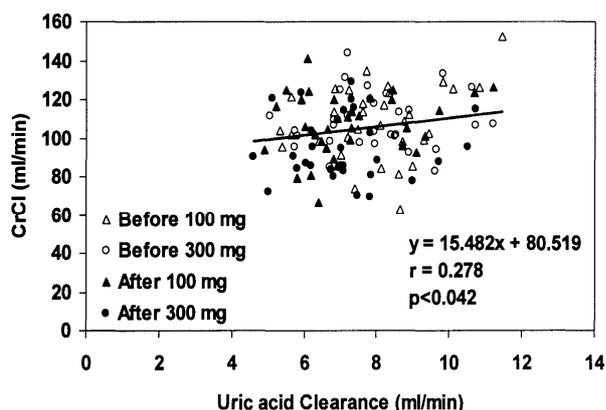
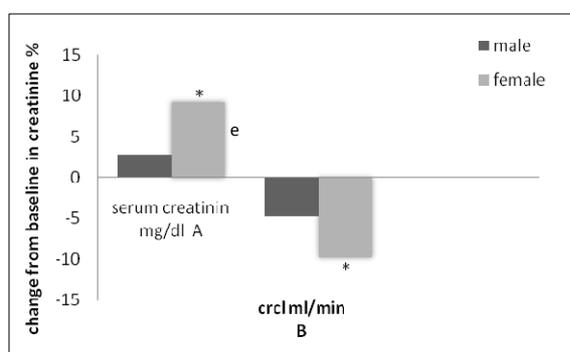


Fig. (1): Correlation of 24h-creatinine clearance with 24h-uric acid clearance before and after 4 week aspirin treatment.



*P<0.05

Fig. (2): Sex difference A- in percentage change serum creatinine level B- percentage change 24h creatinine clearance after 4 week 300 mg/d aspirin treatment.

Discussion

In this study, low-dose aspirin has been shown to produce a dose-dependent depression of renal function in healthy adults. After 4 weeks of treatment there was a significant increase (from baseline to end of study) in serum uric acid, creatinine and urea levels in aspirin 300 mg/d users, but not with 100 mg per day aspirin users, with a marked reduction in creatinine clearance rate and urine urea. However at both doses of aspirin, a significant reduction in the fractional excretion of uric acid and uric acid clearance were observed.

Comparing our results with those of previous studies, Louthrenoo et al⁽¹⁹⁾ found that both 300 mg/d and 60 mg/d doses of aspirin decreased the fractional excretion of uric acid

after 2 weeks of therapy. A relatively significant decreased uric acid clearance and creatinine clearance was found in those who were on 300 mg/day aspirin therapy only. While serum creatinine and uric acid concentration, remained stable during both drug administration periods. The important differences between these studies included aspirin dosages and duration of therapy.

A related result on the effects of the current low dose aspirin regimens (75–325 mg/day) for cardiovascular disease prevention were previously studied in two groups of elderly patients^(20,21). They found that these doses of aspirin were capable of inducing a significant decrease in both creatinine and uric acid excretion within 1–2 weeks. One week after the drug was withdrawn, uric acid excretion returned to normal while creatinine clearance remained low. In another trial Segal et al⁽²²⁾ reported that Mini-dose aspirin, even at a dosage of 75 mg/day, caused significant changes in renal function and UA handling within 1 week in a group of elderly inpatients, mainly in those with preexisting hypoalbuminemia. In contrast, when Low doses (100 mg/day) of aspirin were administered in gouty arthritis patients treated with allopurinol or benzbromarone for 4 weeks did not influence serum uric acid level or urinary uric acid excretion⁽²³⁾.

Small doses of aspirin can increase the level of uric acid in the blood⁽²⁴⁾, via effects on the urate/anion transport mechanism in the renal proximal tubule⁽²⁵⁾; conditions that cause a reduction in the glomerular filtration rate, a decrease in the excretion of uric acid, or an increase in overall tubular absorption^(12,26). This seems to be the case for the association of hyperuricemia with impaired GFR^(27,28).

Low-doses of aspirin are associated with an increase in serum uric acid levels⁽⁵⁾, and it is suggested that raising uric acid levels can stimulate the renin-angiotensin-system accelerating the development of renal microvascular disease, which could be mediated by its effect to upregulate angiotensin-1 receptors on vascular smooth muscle cells⁽²⁹⁾ and thereby predispose the patient to renal disease progression^(30,31).

The relation of serum uric acid to development of renal impairment in healthy individuals has been reported in clinical studies. Iseki et al⁽¹⁰⁾ followed 6403 adults and found that a uric acid of 8.0 mg/dl conferred a 2.9-fold risk in men and a 10.4-fold risk in women for developing elevated creatinine after controlling for multiple risk factors.

A recent epidemiologic study⁽³²⁾, determined the risks of elevated levels of uric acid, on the progress of new-onset kidney disease in healthy individuals. During follow-up examinations, the researchers assessed glomerular filtration rates. They reported that individuals in the slightly elevated uric acid group were 1.26 times as likely to develop kidney disease as those in the low uric acid group. The odds of developing kidney disease among volunteers in the elevated uric acid group were 1.63 times greater than that of individuals in the low uric acid group.

In this study, creatinine clearance and serum creatinine were found to be higher among women as compared to that in men indicating that women are at higher adverse effect on renal function. This may be because of the sex differences in acetylsalicylic acid pharmacokinetics and pharmacodynamics that may affect aspirin dosing and efficacy. Women are reported to have slower clearance of acetylsalicylic acid and, therefore, higher circulating levels⁽³³⁾. There is also a study suggesting that the clinical efficacy of aspirin may be sex-dependent⁽³⁴⁾. Uric acid plays a role in platelet adhesiveness⁽³⁵⁾; this relationship between serum uric acid and risk in aspirin-treated patients has prompted speculation that treatment-mediated elevation of serum uric acid might attenuate some of their potential benefits on platelet and endothelial function to increase the risk of vascular related events.

In conclusion our results agree with those of previous research in that aspirin causes a dose-dependent impairment of renal function. A dosage of 300 mg/day aspirin was found to induce a significantly higher changes in renal function and secretion of uric than 100 mg/day. The dosage of 100 mg/day aspirin can be used with more safety during the

treatment. The observation, however, did not suggest to neglect a careful laboratory examination when low dose aspirin is added to therapy in order to ensure their safety.

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