Original Article

Association of Hyperuricemia with Low Dose Aspirin Use in Middle Aged and Elderly Population

Adil Khan, Dania Faisal and Nimra Khan

ABSTRACT

Objective: To study association between low dose aspirin and serum uric acid level in middle age and elderly population of Karachi.

Study Design: Cross-sectional study

Place and Duration of Study: This study was conducted at the Department of Medicine, Fatima Hospital, Baqai Medical University, Karachi from 15th December 2022 to 15th February 2023.

Materials and Methods: A sample of 366 participants, aged more than 40 years, who had cardiovascular diseases or were at increased risk of cardiovascular disease were included in study. They were divided into two groups on basis of aspirin use:1) Those who are using low dose aspirin for more than one month 2) Those who have never used aspirin or did not take it for more than one month. After a brief physical examination, blood sample were taken for serum uric acird, lipids & blood sugar level. Data was analysed using appropriate statistical test, to observe difference in uric acid level and some other parameters in two groups on basis of aspirin useo

Results: Prevalence of hyperuricemia was significantly lower in individuals using low dose aspirine for more than one month. (11.2% Vs 39.79% p = 0.003). Asprin use was also not associated with renal dysfuntion. Better renal functions were observed in aspirin users as compared to non-aspirin users. (eGFR 104.68±14.23 Vs 99.70±15.28 p = 0.001). Hyperuricemia was significantly associated with metabolic conditions like higher BMI, diabetes mellitus and hypercholesterolelmia.

Conclusion: Use of low dose aspirin for primary or secondary prevention of cardiovascular diseases is not associated with hyperuricemia in middle aged and older population.

Key Words: Hyperuricemia, low dose aspirin, uric acid level

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INTRODUCTION

Uric acid is the end product of purine catabolism. Uric acid levels depend on the balance between purine input, either endogenous synthesis or dietary ingestion, and renal and GI elimination of uric acid.(1)Hyperuricemia is defined as serum uric acid (SUA) level > 7mg/dl in males and 6mg/dl in females. However, a person with elevated SUA level may not have any symptoms and signs, a condition traditionally referred to as asymptomatic hyperuricemia.[2] A number of epidemiological studies studies have found a link between serum uric acid level and numerous cardiovascular disorders, such as hypertension, coronary artery disease, and vascular dementia[3].

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Hyperuricemia is also associated with diabetes, obesity, metabolic syndrome, and chronic kidney disease. [4]. Long term use of drugs like thiazide diuretics and low dose aspirin also cause impaired renal excretion of uric acid. For the primary andsecondary prevention of cardiovascular events, low-dose aspirin is frequently advised[5]. The commonly prescribed doses in Pakistan, such as 300mg ("Full strength") or 75mg ("baby aspirin"), can impair renal excretion of uric acid and may result in hyperuricemia theoretically. It remains a valid concern of patients about the side effects of drugs, specially those used for long term period, as it may affect them physically as well as financially. Considering hyperuricemia being a risk factor for cardiovascular diseases and the physiological association between cardioprotective aspirin and hyperuricemia makes, it important to determine the clinical association between low dose aspirin and hyperuricemia. Therefore we conducted this study in order to determine if low dose aspirin use for at least one month is associated with increased serum uric acid in middle aged and elderly individuals who have arteriosclerotic cardiovascular diseases (ASCVD) or are at least at increased risk of ASCVD.

MATERIALS AND METHODS

This research is cross-sectional. Patients who visited the outpatient clinic from 15th December 2022 to 15th February 2023, Department of Medicine, Fatima Hospital,Baqai Medical University, who were older than 40 and had cardiovascular risk factors or coronary artery disease, were considered for inclusion. Participants were included if they had stable coronary artery disease or/and underwent percutaneous coronary intervention and/or had diabetes mellitus, hypertension, dyslipidemia, obesity, a family history of cardiovascular disease, or active smoking. There were two groups created from these patients:

1) Having taken low-dose aspirin (75 mg daily) for at least a month
2) Never taken aspirin or did not take it in the last one month.

Patients who had the following description were disqualified:

1) Those on diuretics, allopurinol, febuxostat, immuno-suppressants, fenofibrate, cytotoxic chemotherapy, and anti-tubercular medications, which can all impact uric acid levels.
2) Those with child-pugh class C chronic liver disease
3) Those with chronic renal disease whose eGFR is less than 30 ml per minute per 1.73 m2.

The Baqai Medical University, Karachi's ethics committee approved the study idea.

The Sample Size: The sample size was calculated using the Open Epi website[11]. According to studies, 39% of the Pakistani population has hyperuricemia. Consequently, a sample size of at least 366 people was determined, with a 5% likelihood of Type I error[2].

Data Collection: All patients have provided their informed permission. Using a self-reporting questionnaire, information on variables like age, gender, underlying medical conditions, and drug history was gathered. A professional staff member measured blood pressure, weight, height and sampled blood. Antecubital vein was used to collect blood samples, which were then analyzed for biochemical values. They comprised total cholesterol(TC), triglycerides(TG), high density lipoprotein (HDL-C), low density lipoprotein(LDL-C), alanine transaminase (ALT), serum creatinine, serum uric acid (SUA), and random blood glucose(RBS) level. The chronic kidney disease epidemiology collaboration's (CKD-EPI) creatinine cystatin equation was used to calculate the estimated glomerular filtration rate (eGFR)[(6)], and the Cockcroft-Gault equation was used to calculate creatinine clearance[(7)].

Data Analysis: Data analysis was done using SPSS version 22. For statistical significance, the chi-square test was used after computing the frequencies for categorical variables. Shapiro Wilk test was used to determine whether continuous variables were normally distributed or not. While normally distributed data were expressed as mean (±SD - standard deviation) and were examined with an independent t-test, non-normally distributed data were provided as median (IQR: Inter-quartile range) and were analyzed using the Mann-Whitney U-test. Statistical significance was taken as $p < 0.05$.

RESULTS

Basic characteristics of study participants: A total 366 participants were included in study. 46.4%(n=170) were using low dose aspirin and 53.6%(n=196) were not taking it. The characteristics of descriptive variables are summarized in table1.

Subgroup Analysis categorized by aspirin use: spirin use more likely associated with co-morbidities such diabetes mellitus($p<0.001$) & coronary heart disease ($p<0.001$). 59.4% of aspirin user were hypertensive ($p=0.222$), but use of antihypertensive was statistically significantly associated with aspirin use. Hyperuricemia was more common in participants not taking aspirin($p=0.003$). Continous variables are like age, weght, BMI, blood glucose, TG,TC,HDL-C,LDL-C, serum creatinine, creatinine clearance and eGFR are also presented in table 1. Use of low dose aspirin is more possibly associated with older age($p = 0.001$), higher BMI ($p<0.01$) and higher blood glucose ($p = 0.008$). Levels of blood lipids were better controlled in low dose aspirin group, possibly due to concomitant use of statins in this group and diet modification after risk identification. eGFR was slightly better in low dose aspirin group.

Table No.1: Baseline characteristics on basis of low dose aspirin use

Variables	Aspirin Use		p-value	Total
	Yes n = 170(46.4%)	No n = 196 (53.6%)		
Age, yrs	58(10)	51(13)	0.001	54(11)
Males, n(%)	103(60.4%)	134(68.4%)	0.12	237 (64.8%)
Weight (Kg)	63(5)	66(5)	<0.028	65(9)
BMI, Kg/m^2	24.59±1.91	23.2±1.36	<0.01	23.84±1.78
Active smoking, n (%)	13(7.6%)	30(15.3%)	0.023	43(11.7%)
Hypertension, n (%)	101(59.4%)	104(53.1%)	0.222	205 (56%)
Diabetes mellitus, n (%)	67(39.4%)	45(23%)	0.001	112(30.6%)
Coronary heart disease,n(%)	137(79.4%)	41(20.9%)	<0.001	176(48.1%)

SUA stratification(hyperuricemia) n (%)	19(11.2%)	78(39.79%)	0.003	64(17.5%)
Previous PCI, n(%)	22(12.9%)	3 (1.5%)	<0.001	25 (6.8%)
ACEIs use, n(%)	16(9.4%)	2(1%)	<0.001	18(4.9%)
ARBs use, n (%)	98(57.6%)	54(27.6%)	<0.001	152(41.5%)
Beta blocker use, n(%)	28(16.5%)	22(11.2%)	0.145	50(13.7%)
Statins use, n(%)	56(32.9%)	17(8.7%)	<0.001	73(19.9%)
CCB use, n(%)	42(24.7%)	23(11.7%)	0.001	65(17.8%)
Blood Glucose	159.7(44)	148(38)	0.008	131(57)
TG,mmol/L	130.5±56.43	136.42±60.72	0.336	133.67±58.76
TC, mmol/L	159.6(19.5)	176.17(20.2)	<0.001	165(24)
HDL-C, mmol/L	36.1±6.38	42.68±9.69	<0.001	39.62±8.93
LDL-C, mmol/L	79.1±13.35	95.22±9.5	<0.001	87.73±8.94
Creatininine	0.67(0.27)	0.68(0.15)	0.430	0.64(0.27)
Ccr	128.17±82.64	119.27±30.96	0.163	123.41±60.78
eGFR	104.68±14.23	99.70±15.28	0.001	102.36±14.92

Table No.2: Sample characteristics on basis of hyperuricemia

Variables	**Uric Acid Level**		p-value
	Normal(269)	**Hyperuricemia(97)**	
Age, yrs	56(10)	52(13)	0.001
Males, n(%)	173(57.3%)	64(66%)	0.768
Weight(Kg)	65(19)	66(8.5)	0.093
BMI, Kg/m^2	23.99±1.83	23.45 ± 1.59	0.011
Active smoking, n (%)	5(1.7%)	38(39.2%)	<0.001
Hypertension, n (%)	141(52.4%)	64(66%)	0.021
Diabetes mellitus, n (%)	48(17.8%)	64(66%)	<0.001
Coronary heart disease,n(%)	116(43.1%)	60(61.9%)	<0.002
Aspirin use n (%)	151(56.1%)	19(19.6%)	<0.001
Previous PCI, n(%)	4(1.5%)	21(21.6%)	<0.001
ACEIs use, n(%)	0	18(18.6%)	<0.001
ARBs use, n (%)	88(32.7%)	64(66%)	<0.001
Beta blocker use, n(%)	9(3.3%)	41(42.3%)	<0.001
Statins use, n(%)	37(13.8%)	36(37.1%)	<0.001
CCB use, n(%)	23(8.6%)	42(43.3%)	<0.001
Blood Glucose	131(86)	131(50)	0.360
TG,mmol/L	132.76 ± 58.38	136.19 ± 60.05	0.632
TC, mmol/L	165(24)	165(32)	0.009
HDL-C, mmol/L	38.97± 8.59	41.43± 9.64	0.02
LDL-C, mmol/L	88.14 ± 14.19	92.16 ± 12.44	<0.001
Creatininine	0.65(0.39)	0.64(0.27)	0.751
Ccr	124.78±66.19	119.59±42.34	0.472
eGFR	103.39±14.59	99.52±15.49	0.028

Subgroup Analysis categorized by SUA: As shown in Table 2, participants using low dose aspirin , has lesser prevalence of hyperuricemia.(56.1% vs 19.6%, p <0.001). Hyperuricemia was more commonly associated with hypertension(p=0.021), Diabetes mellitus(p<0.001) and coronary heart disease(<0.001). Hyperuricemia is more commonly associated with older age (p= 0.001) and higher BMI(0.011). Total cholesterol(0.009) and LDL cholesterol(<0.001) were higher in hyperuricemia group.

DISCUSSION

Low dose aspirin usually 75mg/day is commonly and popularly used for treatment and prevention of cardiovascular and cerebrovascular diseases[5]. Studies have been conducted and protocols are developed extensively regarding aspirin efficacy but few studies are conducted on clinical effects of aspirin on serum uric acid level despite having physiologic basis. No regional research on this could be found. Once information about the connection between serum uric acid level and cardiovascular morbidity became available, it became crucial to investigate the interaction between aspirin use and serum uric acid level. Our present research investigates whether or not low-dose aspirin therapy can affect serum uric acid levels. The clinical effects of low-dose aspirin use on serum uric acid levels are still debatable.

In a study on a small group of 49 elderly adults, Caspi D et al. discovered that daily aspirin administration of 75mg gradually reduced uric acid excretion over the course of weeks 1, 2, and 3 while slightly but significantly raising blood uric acid levels[8]. Using more participants, Zhang P et al. shown that two weeks of low dose aspirin treatment (50 mg and 100 mg daily) in 446 older people did not result in hyperuricemia[9]. Jia Ran Li et al. found that consuming low dose aspirin for more than a month resulted in a small decrease in serum uric acid levels(10). In our study eGFR was slightly better in patients using low dose aspirin (104.68±14.2399 vs 70±15.28) and Asprine using group had lesser prevalence of hyperuricemia. (11.2% vs 39.79% ; p = 0.003). This suggests that multiple factors are involved in serum uric acid level management.

Urine contains 70% of the uric acid that is eliminated, and the kidneys play a significant role in controlling the level of uric acid. Variation in baseline renal functional capacity may be associated to difference in effects of aspirin on blood uric acid. In Caspi's study, the typical creatinine clearance was 47 ml/min[8]. The average creatinine clearance, however, was 75 ml/min in the Jia Ran Li research and 79 ml/min in the Zhang P group[9, 10]. Also, the creatinine clearance rate was higher in our study. (123.41±60.78). It might be because we included middle-aged people with cardiovascular risk in addition to elderly people. Many human investigations have looked at aspirin's longterm nephrotoxicity. In a prospective randomised research conducted through another study, 439 patients receiving high dose aspirin and suffering from osteoarthritis or rheumatoid arthritis ranged in age from 20 to 83. At the conclusion of the research, no appreciable rise in serum creatinine levels was seen. More sensitive tests of renal function or concentration capacity were not used in this investigation. Okada S. et al. observed 1075 patients with Type II diabetes mellitus on low dose aspirin for eight years as part of the JPAD study (Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes). They discovered that long-term low-dose aspirin administration had no effect on eGFR.[11] Aspirin has been shown to improve renal function following coronary bypass surgery by Gerrah R et al[12]. Goicoechea et al evaluated 116 individuals with CKD stages 3 to 4 and discovered that long-term aspirin therapy (mean follow-up period 64.816.4 months) may be a preventative measure against the advancement of renal disease[13]. Aspirin use was not significantly linked to a deterioration in renal function in our study. Better creatinine clearance (128.17±82.64 vs 119.27±30.96) and eGFR (104.68±14.23 vs 99.70±15.28) was observed in aspirin using group.

Recent years have seen a lot of research on how aspirin affects the metabolism of uric acid. Human renal apical organic anion efflux transporter MRP4 is involved in aspirin mediated uric acid excretion. It is a uric acid unidirectional efflux pump that is ATP-dependent. At first, several scientists hypothesised that aspirin at low doses prevents MRP4-mediated urate excretion in human embryonic kidney cells. Eventually, it was shown that aspirin boosted uric acid excretion by causing MRP4 to overexpress[14]. According to research by Massimi I. et al., low dose aspirin has the ability to activate a positive transcriptional regulation of the MRP4 transporter gene in human cells, enhancing excretion of both uric acid and aspirin[15]. Some clinical research showed the manifestation of this molecular pathway. After taking low dose aspirin for more than a month, hyperuricemic people showed a small decrease in blood uric acid, according to Run Li et al[10]. After using aspirin, they did not see an increase in uric acid excretion from the urine. In a prospective case-crossover research, Zhang et al. discovered a link between frequent gout attacks and low-dose cardioprotective aspirin use. Serum uric acid was not tested before and after aspirin administration in this trial; instead, data were submitted by study participants through online questionnaires[16]. Long ago, it was disproved that using aspirin would cause a deterioration in renal function.. Inhibiting thromboxane at low doses, according to other studies, may help to halt the progression of renal impairment[17]. Better renal functions were observed in aspirin using group in our study. On the other hand creatinine clearance (119.59±42.34 vs 124.78±66.19) and eGFR (119.59±42.34 vs 124.78±66.19) were slightly decreased in hyperuricemia group. This not only disproves the notion that using aspirin causes kidney function to decline, but it also demonstrates that using aspirin does not cause uric acid levels to rise. On the other side, hyperuricemia may be influenced by variables like BMI, total cholesterol, LDL cholesterol, and eGFR.

CONCLUSION

The study showed daily use of 75mg aspirin per day for more than one month is not associated with hyperuricemia. SUA level were slightly low in aspirin using group. This demands more research about pharmacological role of aspirin in lowering SUA level. Hyperuricemia was more significantly associated with BMI, diabetes mellitus and hypercholesterolemia in our study.

Author's Contribution:

Concept & Design of Study:	Adil Khan
Drafting:	Dania Faisal
Data Analysis:	Nimra Khan
Revisiting Critically:	Adil Khan, Dania Faisal
Final Approval of version:	Adil Khan

Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Copur S, Demiray A, Kanbay M. Uric acid in metabolic syndrome: Does uric acid have a definitive role? Eur J Internal Med 2022.
2. Qudwai W, Jawaid M. Frequency of uric acid levels symptomatic and asymptomatic hyperuricemia among the Pakistani population. Mid East J Fam Med 2017;15:52-7.
3. Maloberti A, Giannattasio C, Bombelli M, Desideri G, Cicero A, Muiesan M, et al. Hyperuricemia and risk of cardiovascular outcomes: the experience of the URRAH (uric acid right for heart health) project. High Blood Pressure Cardiovascular Prevention 2020;27: 121-8.
4. Ali N, Miah R, Hasan M, Barman Z, Mou AD, Hafsa JM, et al. Association between serum uric acid and metabolic syndrome: a cross-sectional study in Bangladeshi adults. Scientific Reports 2020;10(1):1.
5. Raber I, McCarthy CP, Vaduganathan M, Bhatt DL, Wood DA, Cleland JG, et al. The rise and fall of aspirin in the primary prevention of cardiovascular disease. The Lancet 2019;393 (10186):2155-67.
6. Umeukeje EM, Koonce TY, Kusnoor SV, Ulasi II, Kostelanetz S, Williams AM, et al. Systematic review of international studies evaluating MDRD and CKD-EPI estimated glomerular filtration rate (eGFR) equations in Black adults. Plos One 2022;17(10):e0276252.
7. Šečić D, Turohan A, Begić E, Rebić D, Pepić E, Begić Z, et al. Serum Creatinine versus Corrected Cockcroft-Gault Equation According to Poggio Reference Values in Patients with Arterial Hypertension. Int J Applied Basic Med Research 2022;12(1):9.
8. Caspi D, Lubart E, Graff E, Habot B, Yaron M, Segal R. The effect of mini-dose aspirin on renal function and uric acid handling in elderly patients. Arthritis & Rheumatism: Official J Am Coll Rheumatol 2000;43(1):103-8.
9. Zhang P, Wang H, Chen X, Liang W, Liu W, Liu M. Effect of low-dose aspirin on serum uric acid levels in Chinese individuals over 60: subanalysis of a multicentre randomized clinical trial. Eur Rev Med Pharmacol Sci 2020;24(5):2719-24.
10. Li JR, Fan Y, Liu ML. Association Between Low-Dose Aspirin and Uric Acid in the Elderly: An Observational Retrospective Cross-Sectional Study. Int J General Med 2021:3635-43.
11. Okada S, Morimoto T, Ogawa H, Sakuma M, Matsumoto C, Soejima H, et al. Effect of aspirin on cancer chemoprevention in Japanese patients with type 2 diabetes: 10-year observational follow-up of a randomized controlled trial. Diabetes Care 2018;41(8):1757-64.
12. Gerrah R, Elami A, Stamler A, Smirnov A, Stoeger Z. Preoperative aspirin administration improves oxygenation in patients undergoing coronary artery bypass grafting. Chest 2005;127(5):1622-6.
13. Goicoechea M, de Vinuesa SG, Quiroga B, Verde E, Bernis C, Morales E, et al. Aspirin for primary prevention of cardiovascular disease and renal disease progression in chronic kidney disease patients: a multicenter randomized clinical trial (AASER Study). Cardiovascular Drugs and Therapy. 2018;32:255-63.
14. Xu L, Shi Y, Zhuang S, Liu N. Recent advances on uric acid transporters. Oncotarget 2017;8(59): 100852.
15. Massimi I, Ciuffetta A, Temperilli F, Ferrandino F, Zicari A, Pulcinelli FM, et al. Multidrug resistance protein-4 influences aspirin toxicity in human cell line. Mediators of inflammation. 2015;2015.
16. Zhang Y, Neogi T, Chen C, Chaisson C, Hunter DJ, Choi H. Low-dose aspirin use and recurrent gout attacks. Annals Rheumatic Diseases 2014;73(2):385-90.
17. Rade JJ, Barton BA, Vasan RS, Kronsberg SS, Xanthakis V, Keaney Jr JF, et al. Association of thromboxane generation with survival in aspirin users and nonusers. J Am Coll Cardiol 2022;80(3):233-50.