ORIGINAL ARTICLE

ASSOCIATION OF HYPERURICEMIA WITH THE PRESENCE AND SEVERITY OF CORONARY ARTERY DISEASE IN PATIENTS UNDERGOING CORONARY ANGIOGRAPHY

Ammar Akhtar[1], Muhammad Zubair Zaffar[1], Rashid Minhas[1], Hadi Yousuf Saeed[1], Gul Zaman Khan Niazi[1]

[1]Chaudhary Pervaiz Elahi Institute of Cardiology, Multan, Pakistan

Objectives: To determine the association of hyperuricemia with the presence and severity of coronary artery disease in patients undergoing coronary angiography.

Methodology: This case control study was carried out in the Department of Cardiology, Chaudhary Pervaiz Elahi Institute of Cardiology, Multan for six months. Total number of 292 patients (146 cases with coronary artery disease and 146 controls with normal coronary arteries) having age 40-60 years of both genders were included in this study. Coronary angiography was performed using standard angiographic techniques. After undergoing coronary angiography, patients with 50% luminal stenosis or more in any one of the coronary arteries were labeled case group. Patients with normal coronaries or less than 50% luminal stenosis in any one of the coronary vessels were taken as control group. Serum uric acid was advised and value was noted along with the basic demographic data and established risk factors of coronary artery disease.

Results: Mean age was 50.79±6.08 years. Mean serum uric acid was 7.54±3.60 mg/dl. Hyperuricemia was diagnosed in 94 (64.40%) patients with significant CAD (case group) and in only 59 (40.40%) in control group. The odds ratio was 2.66 (95% CI 1.66 to 7.28) with p-value of <0.001. Triple vessel disease was diagnosed in 66.7% patients with hyperuricemia and in only 33.3% patients without hyperuricemia [OR 4.0 (2.09-7.64), p-value <0.001].

Conclusion: There is a significant association between the presence and severity of coronary artery disease with hyperuricemia.

Keywords: hyperuricemia, coronary artery disease (CAD), coronary angiography, serum uric acid

Citation: Akhtar A, Zaffar MZ, Minhas R, Saeed HY, Niazi GZK. Association of Hyperuricemia with the Presence and Severity of Coronary Artery Disease in Patients Undergoing Coronary Angiography. Pak Heart J. 2021;54(02):157-161. DOI: https://doi.org/10.47144/phj.v54i2.2092

INTRODUCTION

The end oxidation product of purine metabolism is uric acid.[1] Increased levels of serum uric acid, hyperuricemia, are linked with multiple diseases like gout, hyperlipidemia, hypertension, resistance to insulin, diabetes and coronary artery disease.[2] Coronary artery disease (CAD) is the leading cause of death in developed as well as in developing world.[3] The literature has reported that there is one coronary event in every 34 seconds and one death in every one minute and 24 seconds.[4] Since a long time a there is quest to find out the risk factors so that managing them could help to lessen the burden of CAD.

Gertler and colleagues postulated hyperuricemia as a risk factor for coronary artery disease in 1950's[5] and since then it has been a topic of debate. Kuwabara concluded that hyperuricemia in patients with cardiovascular risk factors like hypertension is considered as a risk factor for cardiovascular disease and appropriate intervention must be done at an early stage.[6] Gagliardi et al reported that hyperuricemia is independently associated with coronary artery calcification presence and severity.[7] At the same time there are many studies which showed the contradictory results.[8,9] Similarly there are studies which concluded further workup is needed for developing hyperuricemia as an independent risk factor and whether to modify it or not.[10-12]

Our institute is the largest referral cardiology hospital of South Punjab region of Pakistan with a large catchment area. The rationale to design this study is that the available evidences shows contradictory results of different studies in different populations, As our population differs from others in terms of lifestyle, daily routine activity, fast food and meat consumption, we designed this study to see the association of hyperuricemia not only with the presence of CAD but to find out if there is association between hyperuricemia and the severity of CAD in the population of South Punjab. This study will help clinicians and cardiologists to look whether hyperuricemia is a potential risk factor for coronary artery or not and encourage more research

in future to see if managing hyperuricemia could reduce the risk of CAD or not.

METHODOLOGY

The case-control study was decided to carry out at the Department of Cardiology, Chaudhary Pervaiz Elahi Institute of Cardiology, Multan from 10th of July 2020 to 9th of January 2021. Patients with luminal stenosis of greater than 50% in at least one of the coronary arteries assessed at coronary angiography were labeled as coronary artery disease (Case group). Patients with normal coronary arteries or luminal stenosis of less than 50% in any of the coronary arteries were labeled as control group. Sample size was calculated via Open Epi software. By keeping 95% of confidence level, 80% of power of study, ratio of control to cases 1:1, proportion of hyperuricemia in controls at 47% and proportion of hyperuricemia in cases at 64%,[13] total sample size of 292 was calculated consisting of 146 cases and 146 controls. After approval from Ethical Review board and taking informed consent 292 consecutive patients both male and females of any age were included in the study. Patients having on and off history of chest pain on exertion, acute or chronic ST-T changes on electrocardiography, pathological Q waves on ECG or evidence for stress induced ischemia on exercise tolerance testing of less than 3 months duration were subjected to coronary angiography. Patients with heart failure determined by history and examination like shortness of breath, paroxysmal nocturnal dysnea or pulmonary congestion, hematological or oncological disorders (leukemia) and chronic infections like TB determined through medical records, patients taking diuretics, uric acid lowering drugs (allopurinol), recent major surgical procedure or trauma, patients with nephropathy either acute or chronic determined by serum creatinine > 2 mg/dl and medical record and patients with previous percutaneous or surgical revascularization on history and medical record were excluded from the study.

The femoral or radial approach was used to perform coronary angiogram following institutional protocols. The presence of CAD was labeled if any one of the epicardial arteries has more than 50% luminal stenosis. The severity of CAD was determined by clinical vessel score. The patients who had either no coronary lesions or less than 50% luminal stenosis were in control group. The angiograms having one, two or three major epicardial coronary arteries involvement with more than 50% luminal obstructions were labeled as mild, moderate or severe disease respectively. Left main stem (LMS) disease was labeled as 1 vessel. All the coronary angiographies were reported by two consultant cardiologist with at least 5 years post fellowship experience. After undergoing coronary angiography, patients were categorized into two groups: cases & controls as defined earlier. One hundred forty six (146) patients for cases and 146 patients for control group were enrolled in the study. Now under aseptic conditions, blood sample for uric acid level was drawn and was determined by using standard chemical analyzer in pathology laboratory. Serum uric acid >7.0 mg/dl in men and >6.0 mg/dl in women determined by chemical analyzer was deemed positive to label hyperuricemia. Basic demographic data like age, gender, body mass index along with established risk factors of coronary artery disease like hypertension, family history of coronary artery disease, diabetes, dyslipidemia and smoking was collected. Patient was labeled smoker if he or she has history of smoking 100 cigarettes in his or her lifetime and who currently smokes cigarettes. Hyperlipidemia was labeled if plasma total cholesterol level was ≥200 mg/dL, LDL-cholesterol level ≥130 mg/dL, triglyceride level ≥200 mg/dL, and HDL-cholesterol level ≤40 mg/dL, or history of use of lipid lowering drugs for more than 3 months at the time of the study. Patients were considered to have hypertension if they had documented arterial pressure of more than 140/90 mmHg or were being treated with antihypertensive medications for two or more years. Patients were considered diabetics if they were having history of use of insulin or oral hypoglycemic agents for two or more years. Patients who had no idea of their diabetic status was considered diabetics if they have fasting blood glucose >126 mg/dL. Positive family history was labeled if there was history of coronary artery disease in a parent or sibling under the age of 55 for men and 65 for women. Patients having body mass index of 30kg/m^2 or more was considered obese. All the data was collected on a preformed proforma.

Statistical package for social sciences (SPSS) version 23 was used to enter and analyze the collected data. Quantitative variables like age and serum uric acid were represented by mean and standard deviation. Categorical variables were represented by frequencies and percentages like gender, hyperuricemia (yes, no), presence of diabetes mellitus (yes, no), hypertension (yes, no), dyslipidemia (yes, no), family history of CAD (yes, no), obesity (yes, no) and smoking (yes, no), CAD (yes, no) and severity (mild, moderate or severe). Odds ratio with 95% confidence interval was calculated to determine the association between hyperuricemia, presence of coronary artery disease and its severity as per objective. Data was stratified

on age, gender, presence of diabetes mellitus, hypertension, family history of CAD, dyslipidemia and smoking to control confounding and effect modification. Post stratification odds ratio with 95% confidence interval was also reported. A p value ≤ 0.05 was taken as significant which is calculated via Chi-Square test.

RESULTS

Total 292 patients have taken part in the study. Mean age was 50.79±6.08 years included in this study. There were 184 (63.01%) males and 108 (36.99%) female patients. Mean serum uric acid was 7.54±3.60 mg/dl. There were 129 (44.18%) diagnosed with diabetes mellitus, 152 (52.05%) were hypertensives, 148 (50.68%) has dyslipidemia, 145 (49.66%) patients had positive family history, 122 (41.78%) were smokers and 147 (50.34%) patients were obese. Hyperuricemia was diagnosed in 153 (52.40%). Table 1 shows the demographic characters and risk factors among the case and control groups.

Table 1: Demographic characters in case and control groups

Demographic Character	Control	Case
Age (years)	52.92±5.78	48.54±7.52
Gender		
Male	77 (52.7%)	107 (73.3%)
Females	69 (47.3%)	39 (26.7%)
Mean uric acid (mg/dl)	9.18 ±5.17	5.87±3.42
Co-morbid conditions		
Diabetics	58 (39.7%)	71 (48.6%)
Hypertensives	65 (44.5%)	87 (59.6%)
Obese	69 (47.3%)	78 (53.4%)
Smokers	56 (38.3%)	66 (45.2%)
Dyslipidemias	62 (42.5%)	86 (58.9%)
Positive family history	71 (48.6%)	74 (50.7%)

Table 2 shows the cross tabulation between the hyperuricemia and the case and control group.

Table 2: Cross Tabulation of hyperuricemia with the case and control group

Hyperuricemia	Groups		P-value
	Cases	Controls	
Yes	94 (64.4%)	59 (40.4%)	0.001
No	52 (35.6%)	87 (59.6%)	
OR (95% CI)	2.66 (1.66-7.28)		-

Our study showed that 42 (28.8%) patients had mild (single vessel) disease out of which 22 (52.4%) had hyperuricemia and mean serum uric acid level was 8.77±4.39mg/dl. 56(38.4%) patients had moderate (double vessel) disease out of which 34(60.7%) had hyperuricemia and mean serum uric acid level was 9.05±4.88mg/dl. 48(32.9%) patients had severe (triple vessel) disease out of which 38(79.2%) had hyperuricemia and mean serum uric acid level was 9.78±5.97mg/dl. P-value of proportion of hyperuricemia and the severity of CAD came out to be 0.02. Table 3 shows the stratification of results for different risk factors of CAD.

Table 3: Stratification of hyperuricemia in CAD with different risk factors

Risk Factor	Case	Control	Odds Ratio	P-value
Age below 50 years	75 (51.4%)	11 (7.5%)	3.87 [1.69-8.67]	0.001
Age above 50 years	19 (13.0%)	48 (32.9%)	1.74 [0.80-3.77]	0.157
Males	91 (62.3%)	18 (12.3%)	4.19 [2.12-8.28]	0.001
Females	03 (2.1%)	41 (28.1%)	0.35 [0.09-1.35]	0.115
Diabetics	37 (25.3%)	24 (16.4%)	3.45 [1.67-7.14]	0.001
Non Diabetics	57 (39.0%)	35 (23.9%)	2.1 [1.12-3.95]	0.020
Hypertensive	56 (38.3%)	29 (19.9%)	2.86 [1.45-5.55]	0.002
Non-hypertensive	38 (26.0%)	30 (20.5%)	2.38 [1.20-4.71]	0.012
Obese	52 (35.6%)	27 (18.5%)	2.92 [1.49-5.73]	0.002
Non-obese	42 (28.8%)	32 (21.9%)	2.13 [1.10-4.15]	0.020
Smoker	46 (31.5%)	15 (10.3%)	5.07 [2.32-11.03]	0.001
Non-Smoker	48 (32.9%)	44 (30.1%)	1.84 [1.00-3.41]	0.050
Dyslipidemia	49 (33.6%)	33 (22.6%)	1.78 [0.92-3.43]	0.080
Normal lipid profile	45 (30.8%)	26 (17.8%)	4.01 [2.00-8.04]	0.001
Positive family history	35 (23.9%)	36 (24.6%)	2.15 [1.09-4.24]	0.020
No family history	59 (40.4%)	23 (15.7%)	3.18 [1.60-6.33]	0.001

DISCUSSION

The literature has shown the association between raised levels of serum uric acid and CAD for last 60 years.[14] A number of epidemiologic studies have reported that a relation exists between serum uric acid levels and a wide variety of cardiovascular conditions.[15] But to date this is a topic of discussion whether hyperuricemia is an independent risk factor of CAD or not.

Fang et al in the NHANES I epidemiologic study showed that hyperuricemia is directly related to increased death rate due to cardiovascular diseases.[16] Madsen et al showed that in patients with coronary artery stenosis of ≥70% proven in coronary angiography, hyperuricemia is a strong risk factor.[17] Goodarzynejad et al, also showed that hyperuricemia is independently linked with CAD (OR 1.75 95% CI 1.15-2.68).[13] Niazi et al, showed the

same results with OR 2.06 and 95% CI 1.22-3.49.[18] In a local cross sectional survey at Punjab Institute of Cardiology, critical lesions were more frequent in hyperuricemic group than in normouricemic group (p value on Gensini score in two groups is 0.006 which showed significant difference).[19] Our study showed the similar results to these national and international studies adding further evidence that hyperuricemia has been linked with the coronary artery disease. But our study also showed contradictory results to other studies. De Luca et al pointed that there is no association between raised serum uric acid levels and CAD (Odds Ratio at 95% CI,[0.93 to 1.21], p=0.35).[20] Similar results were reported by Li et al and Braga et al where they reported that hyperuricemia is not an independent factor for causing CAD.[10,12]

Goodarzynejad et al showed that hyperuricemia is not only associated with the presence of CAD but also with the severity.[13] They also labeled severity as mild, moderate and severe on the basis of vessel involvement score as ours and showed that mild, moderate and severe disease had 64.4%, 60.0% and 66.1% prevalence of hyperuricemia and the p-value was 0.001. Qureshi et al; also reported that patients with hyperuricemia has tend to have more severe coronary artery disease on coronary angiogram.[19] A Turkish study by Gur et al., also reported that hyperuricemia has shown association with the severity of CAD although they evaluated severity with the Gensini score.[21] Similar findings were reported by Durran et al.[22] Our study also showed similar results that hyperuricemia is also linked with the severity of disease.

Our study also has limitations. First this is a single centre observational study with a small sample size and single measurement of uric acid levels. We know that serum uric acid has complex relationship with many other well established risk factors of CAD and dietary habits and it tends to change with the changes in lifestyle. To establish hyperuricemia as an independent factor of CAD and its association with the severity, multicenter Cohort study with larger sample size is needed.

CONCLUSION

Our study has showed that the raised levels of serum uric acid is more in patients having coronary artery disease as compare to control group. There is also a strong association of hyperuricemia with the severity of coronary artery disease. Hyperuricemia tend to be more prevalent with severe (3 vessel disease) coronary artery disease.

AUTHORS' CONTRIBUTION

AA: Concept and design, data acquisition, interpretation, drafting, final approval, and agree to be accountable for all aspects of the work. MZZ, RM, HYS, GZKN: Data acquisition, interpretation, drafting, final approval and agree to be accountable for all aspects of the work.

Conflict of interest: Authors declared no conflict of interest.

REFERENCES

1. George C, Minter DA. Hyperuricemia. [Updated 2020 Aug 24]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. (Available from: https://www.ncbi.nlm.nih.gov/books/NBK459218/)
2. Wang H, Zhang H, Sun L, Guo W. Roles of hyperuricemia in metabolic syndrome and cardiac-kidney-vascular system diseases. Am J Transl Res. 2018; 10(9):2749-2763.
3. Li M, Hu X, Fan Y, Li K, Zhang X, Hou W, et al. Hyperuricemia and the risk for coronary heart disease morbidity and mortality a systematic review and dose-response meta-analysis. Sci Rep. 2016;6:19520
4. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation. 2015; 131(4):e29-322.
5. Gertler MM, Garn SM, Levine SA. Serum uric acid in relation to age and physique in health and in coronary heart disease. Ann Intern Med. 1951;34(6):1421–31
6. Kuwabra M. Hyperuricemia, cardiovascular disease and hypertension. Pulse. 2015;3(1)242-52
7. Gagliardi AC, Miname MS, Santos MD. Uric acid: A marker of increased cardiovascular risk. Atherosclerosis. 2009;202:11-7
8. Larsen TR, Gerke O, Diederichsen ACP, Lambrechtsen J Steffensen FH Sand NP, et al. The association between uric acid levels and different clinical manifestations of coronary artery disease. Coron Artery Dis. 2018;29(3):194-203
9. Alderman MH. Uric acid and cardiovascular risk. Curr Opin Pharmacol. 2002;2(2):126-30
10. Braga F, Pasqualetti S, Ferraro S, Panteghini M. Hyperuricemia as a risk factor for coronary heart disease incidence and mortality in the general population: a systematic review and meta-analysis. Clin Chem Lab Med. 2016;54(1):7-15
11. Biscaglia S, Ceconi C, Malagu M, Pavasini R, Ferrari R. Uric acid and coronary artery disease: An elusive link deserving further attention. Int J Cardiol. 2015;213(1):28-32
12. Li M, Hu X, Fan Y, Li K, Zhang X, Hou W, et al. Hyperuricemia and the risk for coronary heart disease morbidity and mortality a systematic review and dose-response meta-analysis. Sci Rep. 2016;6(1):1-11
13. Goodarzynejad H, Anvari MS, Boroumand MA, Karimi A, Abbasi SH, Davoodi G. Hyperuricemia and the presence and severity of coronary artery disease. Lab Medicine. 2010;41(1):40-5
14. Edwards NL. The role of hyperuricemia in vascular disorders. Curr Opin Rheumatol. 2009;21(2):132-7.
15. Wu AH, Gladden JD, Ahmed M, Ahmed A, Filippatos G. Relation of serum uric acid to cardiovascular disease. Int J Cardiol. 2016;213:4-7.
16. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971–1992. National Health and Nutrition Examination Survey. JAMA. 2000;283:2404-10
17. Madsen TE, Muhlestein JB, Carlquist JF. Serum uric acid independently predicts mortality in patients with significant, angiographically defined coronary disease. Am J Nephrol. 2005; 25:45-9.
18. Niazi GZK, Zab J, Adnan F, Ahmed N, Akhtar A, Saleemi S. Association of Hyperuricemia with Critical Coronary Artery Disease. Pak Heart J. 2020;53(02):155-9
19. Qureshi AE, Hameed S, Noeman A. Relationship of serum uric acid level and angiographic severity of coronary artery disease in male patients with acute coronary syndrome. Pak J Med Sci. 2013;29(5):1137-41

20. De Luca G, Secco GG, Santagostino M, Venegoni L, Iorio S, Cassetti E, et al. Uric acid does not affect the prevalence and extent of coronary artery disease. Results from a prospective study. Nutr Metab Cardiovasc Dis. 2012;22(5):426-33.
21. Gur M, Yilmaz R, Demirbag R, Aksoy N. Relation of serum uric acid levels with the presence and severity of angiographic coronary artery disease. Angiology. 2008; 59(2): 166-71
22. Duran M, Kalay N, Akpek M, Orscelik O, Elcik D, Ocak A. High Levels of Serum Uric Acid predict severity of ischemic heart disease in Patients With Acute Coronary Syndrome. Angiology. 2012; 63(6): 448-52.

Address for Correspondence:

Dr. Ammar Akhtar, Chaudhary Pervaiz Elahi Institute of Cardiology, Multan, Pakistan.
Email: ammarakhtar176@gmail.com