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Original Research Article

SERUM URIC ACID LEVELS AND CARDIOVASCULAR OUTCOMES IN ACUTE CORONARY SYNDROME- 30 DAY FOLLOW UP

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Abstract

Coronary artery disease is a leading cause of morbidity and mortality globally. Various risk factors for the development of cardiovascular disease are known, however, the role of uric acid has been debatable. Patients more than 40 years of age diagnosed as Acute Coronary Syndrome were admitted and observed for in hospital course, in-hospital mortality and then were followed up at 30 days after discharge. The patients were stratified according to uric acid level as normouricemia and hyperuricemia and the observations were made. We found that hyperuricemia was seen more in patients with diabetes, dyslipidemia, obesity and smokers. In-hospital course was more complicated in patients with hyperuricemia.Heart failure, arrhythmias, cardiogenic shock and in-hospital mortality were significantly higher in hyperuricemic patients. Hyperuricemia was also associated with more severe coronary artery disease. 30 day MACE rate was significantly higher in patients with baseline hyperuricemia driven mainly by cardiovascular death and reinfarction.

Keywords: acute coronary syndrome, myocardial infarction, Uric acid, hyperuricemia, heart failure, death, mortality.

Introduction

Cardiovascular disease is the most common cause of death in developing and developed countries. Coronary artery disease and acute coronary syndrome are the leading cause of morbidity and mortality[1]. The dysfunctional endothelium is the fundamental problem of many cardiovascular pathologies. It is induced by genetic, biochemical and hemodynamic defects, which in turn can be influenced by well-known risk factors like age, dyslipidemia, smoking, hypertension, male sex and so on, In recent years, lot of interest has been generated around the role of uric acid as a risk factor for cardiovascular disease. An association between uric acid and cardiovascular disease has been recognized for many years, however, the role of uric acid as an independent risk factor for cardiovascular disease remains debatable[2]. Uric acid is the end product of purine metabolism. It is biologically active and can stimulate oxidative stress, endothelial dysfunction, inflammation and vasoconstriction[3,4]. Elevated uric acid levels are often associated with various other cardiovascular risk factors such as obesity, hypertension,

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lipid disorders, diabetes and renal dysfunction[5-8].

Studies have demonstrated a positive relationship between uric acid levels and incidence of cardiovascular events[9-14] and also severity of coronary artery disease[15]. Some studies have shown that the association is significant only in female patients[16,17] and some on the other hand have reported that uric acid is not a causal risk factor for cardiovascular events[2]. The ESC/ESH 2018 guidelines have introduced uric acid evaluation among the cardiovascular risk factors to stratify patients' risk[18].

In this study, we tried to evaluate the role of serum uric acid in acute coronary syndrome patients and the in-hospital outcome & 30 day major adverse cardiovascular events (MACE) rate.

Materials and Methods

Design:

We conducted a prospective observational study at Sri Jayadeva Institute of Cardiovascular Sciences and Research, Kalaburagi. Patients were recruited from April 1, 2022 to March 31, 2023. The in-hospital course of all the patients was observed. All discharged patients were followed up to know the 30 day MACE (Major adverse cardiovascular events) which included Cardiovascular mortality (CV mortality), Heart Failure hospitalization and reinfarction. Approval was obtained from the ethical committee.

Participants:

Patients more than 40 years of age diagnosed as acute coronary syndrome based on clinical history, ECG, 2D Echocardiography and cardiac biomarkers were admitted and treated as per standard protocol. Out of 5132 patients, 582 patients met exclusion criteria(mentioned below) and hence were excluded from the study. Baseline demographic and clinical characteristics were recorded.

Inclusion criteria:

Patients more than 40 years of age who were diagnosed as acute coronary syndrome.

Exclusion criteria:

Patients with:

- Chronic Kidney Disease
- Prior Atrial fibrillation (AF)
- Gout
- Hematological malignancies
- Chronic alcoholism
- Patients with H/O intake of drugs that increase serum uric acid level

Lab investigations:

CBC, Blood sugar, HbA1c, Lipid profile, Serum uric acid, RFT were analysed on admission and were monitored serially when indicated.

CBC, blood sugar were measured using automated analyser. Lipid profile was analysed by automatizer based on spectrophotometry. HbA1c was analysed using enzyme linked assay. Serum uric acid was measured by uricase method.

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ECG was performed using a 6 channel BPL Cardiart 9108 machine. 2D ECHO was done using Vivid iq, GE Medical systems ultrasound equipment. All standard ECHO views were used. Troponin T was measured using standardized enzyme linked assay (Elecsys Troponin T hs, ROCHE Diagnostics, Germany).

Definitions:

Acute coronary syndrome: comprises unstable angina, non ST elevation MI (NSTEMI) and ST elevation MI (STEMI)

Unstable angina was defined according to Braunwald's criteria[19] - Clinical characteristics +/- ECG changes

NSTEMI and STEMI were defined according to 2018 universal definition of Myocardial Infarction[20].

Hyperuricemia: serum uric acid > 7.0 mg/dl was considered hyperuricemia in our study[21].

Statistical Analysis

The data were coded and entered in MS-excel office 2010. The data were analyzed using Graph Pad Prism version 5. The categorical data were represented as n (%) and numerical data in mean with SD. P value was calculated using two tailed 't' test. P <0.05 was considered statistically significant.

RESULTS

Table 1; Baseline characteristics stratified by uric acid level

	Total (n)	Normal Uric acid < 7.0 mg/dL (n = 2003)	Hyperuricemia > 7.0 mg/dL (n = 2547)	P value
Age, mean(yrs)		53	64	0.02
Male sex	2970 (65.3%)	1298	1672 (56.3%)	
Female sex	1580 (34.7%)	705	875 (55.4%)	
Diabetes mellitus	2478 (54.4%)	812	1666	0.01
Hypertension	2079 (45.7%)	978	1101	0.46
Smoking	2013 (44.2%)	657	1356	0.02
Dyslipidemia	3755 (82.5%)	1689	2066	0.01
Obesity (BMI > 28 kg/m^2)	987 (21.7%)	419	568	0.01

Out of 4550 patients, 2970 were male. Hyperuricemia was seen in 56.3% of males and 55.4% of females in our study. 2003 patients had normal uric acid level whereas hyperuricemia was seen in 2547 patients. Baseline characteristics like older age, prevalence of diabetes, dyslipidemia, obesity and smoking were higher in patients with hyperuricemia. Prevalence of hypertension was not significantly different among the two groups.

Table 2: In-hospital course stratified by uric acid level

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	Normal uric acid (n = 2003)	Hyperuricemia (n = 2547)	P value
Uncomplicated course	1828 (91.2%)	1663 (65.3%)	0.09
Reinfarction	3 (0.1%)	11 (0.4%)	0.63
Heart failure	151 (7.5%)	573 (22.5%)	0.01
Arrhythmias Fatal Non fatal	57 (2.8%) 12 (0.6%) 45 (2.2%)	313 (12.3%) 34 (1.3%) 279 (10.9%)	0.02
Cardiogenic Shock	76 (3.8%)	356 (13.9%)	0.01
Acute Kidney injury	115 (5.7%)	427 (16.7%)	0.01
In hospital mortality	84 (4.2%)	189 (7.4%)	0.03

Uncomplicated course was numerically higher in patients with normal uric acid level which was not statistically significant. But when we looked into complications individually, heart failure, cardiogenic shock, arrhythmias, acute kidney injury and in-hospital mortality were more frequently seen in patients with hyperuricemia. The occurrence of reinfarction was not significantly different among the two groups.

Table 3: Coronary Angiographic findings stratified by uric acid level
217 normouricemic and 693 hyperuricemic patients did not undergo coronary angiography for various reasons. i. Acute kidney injury ii. Heart failure iii. Death before proceeding to coronary angiography iv. Patient/ relatives did not consent for procedure

	Normal uric acid (n = 1786)	Hyperuricemia (n = 1854)	P value
Non-Obstructive CAD	634 (35.5%)	311 (16.7%)	0.02
Single Vessel disease	513 (28.7%)	473 (25.5%)	0.09
Double vessel disease	371 (20.7%)	564 (30.4%)	0.04
Left Main and triple Vessel disease	268 (15%)	506 (27.3%)	0.02

Patients with hyperuricemia had significantly higher number of patients with double and Left main &/or triple vessel disease on coronary angiography. On the other hand, non-obstructive CAD was higher in normouricemic patients. Occurrence of single vessel disease was not significantly different among the two groups.

Table 4: Diabetes with Hyperuricemia patients – Coronary angiography findings

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We also studied effect of diabetes on coronary angiographic findings in patients with hyperuricemia

	Diabetes (n = 1234)	No Diabetes (n = 620)	P value
Non Obstructive CAD	55 (4.5%)	256 (41.3%)	0.005
Single Vessel disease	350 (28.3%)	123 (19.8%)	0.04
Double vessel disease	425 (34.4%)	139 (22.4%)	0.04
Left Main and Triple Vessel disease	404 (32.7%)	102 (16.4%)	0.02

Patients with both diabetes and hyperuricemia had higher prevalence of single, double and triple vessel disease than hyperuricemic patients without diabetes. Patients without diabetes had significantly higher prevalence of non obstructive CAD.
Also, the diabetics had higher number of triple vessel disease which was diffuse in nature and was not suitable for revascularization than patients with hyperuricemia but no diabetes.
Patients who had neither diabetes nor hyperuricemia tend to have less severe disease.

Table 5: 30 day follow-up data stratified by uric acid level

273 patients died in hospital during the index admission. Out of 4277 discharged patients, 26 patients could not be followed up at 1 month.

	Normal uric acid (n = 1913)	Hyperuricemia (n = 2338)	P value
Reinfarction	13 (0.7%)	56 (2.4%)	0.02
HF hospitalization	43 (2.2%)	219 (9.3%)	0.33
CV Death	23 (1.2%)	54 (2.3%)	0.01
Total MACE	79 (4.1%)	329 (14%)	0.01

Out of the 4251 patients who were followed upto 30 days, the 30 day MACE rate was significantly higher in patients with baseline hyperuricemia which was driven by cardiovascular death and reinfarction. Heart failure hospitalization was numerically higher in hyperuricemic patients but was not found to be statistically significant.

Discussion

Uric acid, a final product of purine metabolism, is influenced by dietary factors (meat, sea food, alcohol, fructose), renal function, high cell turnover (cancer), medications. The normal uric acid values are higher in males and increases with age. Uric acid has paradoxical effects, based on its intracellular (antioxidant) or extracellular (prooxidant) localization[22].

Hyperuricemia is associated with many variables that are risk factors for coronary artery disease including hypertension[23,24,25], obesity[23,26-29], dyslipidemia[23,30] and insulin resistance[31,32]. Even if uric acid perse may not represent a direct risk factor for cardiovascular disease, it may be considered as a predictive marker for cardiovascular events that can worsen other established risk factors. Uric acid is a known risk factor for the development of hypertension, probably by activation of renin angiotensin system leading to renal vasoconstriction[33,34].

Uric acid might be involved in the development of diabetes mellitus and metabolic syndrome, a result of alterations in the hepatic and adipose tissue metabolism[35-37].
Elevated plasma insulin concentrations secondary to insulin resistance may enhance renal sodium retention and reduce urinary uric acid clearance, thereby contributing to hyperuricemia

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and hypertension[38]. Renal dysfunction causes hyperuricemia via decreased excretion of uric acid. Moreover, an elevation of uric acid level itself may lead to renal dysfunction by damaging proximal renal tubular cells[39-44]. Many studies and meta-analyses have shown the relationship between hyperuricemia and cardiovascular diseases[13] and also a risk factor for the presence of coronary artery disease[45].

Several possible mechanisms have been suggested for explaining hyperuricemia leading to cardiovascular involvement in the form of diastolic dysfunction, arrhythmias, myocardial infarction and heart failure. One mechanism is the formation of oxygen free radicals, platelet adhesion and aggregation, which are responsible for the formation of thrombi[46,47]. Another mechanism is direct infiltration of vascular endothelial cells by uric acid, leading to endothelial dysfunction, alteration in nitric oxide production, lipid peroxidation and smooth muscle cell proliferation resulting in atherosclerosis, plaque formation and stenosis[12,13, 48-51].

In our study, occurrence of hyperuricemia did not differ by gender. This is in contrast to some of the previous studies[52,53,54]. Concurrent with previous studies, we found that hyperuricemia was seen more in patients with diabetes, dyslipidemia[55], obesity[56] and smokers[5-8]. We, in our study, observed that prevalence of hypertension did not differ among two groups, in contrast to previous studies[8,24].

In-hospital course was more complicated in patients with hyperuricemia in our study. This is consisent with various studies[47,49]. HF occurred in 22.5% of patients with hyperuricemia, which was statistically much higher than HF in normouricemic patients(7.5%). Incidence of arrhythmias was significantly higher in patients with hyperuricemia driven mainly non fatal arrhythmias. This is again consistent with the fact that hyperuricemia has been noted to be associated with atrial fibrillation[57]. We also noted significantly higher incidence of cardiogenic shock and acute kidney injury in hyperuricemic patients. In-hospital mortality was seen in 7.4% in hyperuricemia group, which was significantly higher than that seen in the normouricemic group consistent with previous studies[58,59,60]. The in-hospital course of acute MI that we studied, consisted of parameters that are interrelated.

In our study, we also studied effect of hyperuricemia on coronary artery disease. We compared the occurrence of non-obstructive CAD, single vessel disease, double vessel disease and LMCA &/or triple vessel disease among the groups. More severe disease – double vessel and triple vessel disease were significantly higher in hyperuricemic patients again underlining the role of uric acid in endothelial dysfunction and atherosclerosis. This is consistent with a few previous studies[58,61] although there is a study which did not show positive relationship between hyperuricemia and severity of CAD[62].

We also noted that triple vessel disease which was diffuse in nature and not suitable for any revascularization was significantly higher in hyperuricemia patients with diabetes than hyperuricemic patients without diabetes which suggests that uric acid may play an additive role as risk factor for coronary artery disease and its severity.

At 30 day follow up, in our study, we noted that the MACE rate was higher in patients with baseline hyperuricemia mainly driven by CV death and reinfarctions. This is concurrent with previous study[63].

LIMITATIONS

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Cut-off of uric acid level of 7.0 mg/dl was used. Some studies have used 6.8 mg/dl as cut off. We did not use gender based uric acid cut-offs.
Hence we may have missed hyperuricemia in a few more patients, especially female patients. Also, hyperuricemia group in our study had higher uric acid levels than if the cut-off was 6.8 mg/dl. This may have skewed the result toward more adverse cardiovascular events and complications in the hyperuricemia group.
Follow up uric acid level was not measured. It is difficult to attribute the 30 day follow up events to baseline uric acid level alone without follow up measurements.
Confounding variables like diabetes, hypertension, obesity and smoking were not statistically adjusted in our study to understand the independent effect of hyperuricemia.
In our study, stratification was based on a cut-off value of serum uric acid and two groups were made to compare the observations. So, we did not study the effect of different uric acid levels (as continuous variable) on cardiovascular disease.

Conclusions

Hyperuricemia was observed to be significantly associated with worse in-hospital course after acute coronary syndrome. The group had higher rates of heart failure, arrhythmias, cardiogenic shock and in-hospital mortality. Hyperuricemia was significantly associated with more severe coronary artery disease. Hyperuricemia together with diabetes had significantly higher rates of diffuse triple vessel disease not amenable to any revascularization. 30 day MACE rate after an ACS was significantly higher among hyperuricemic patients driven mainly by reinfarction and CV death.
Hence, uric acid is a very important risk factor for cardiovascular disease manifestations and also cardiovascular death. It needs further well controlled randomized trials to be accepted as an independent risk factor and a therapeutic target in management of cardiovascular disease.

References

1. WHO, Health statistics and information system. Cause specific mortality estimates for 2000-2012; 2012.
2. Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for cardiovascular disease and death: The Framingham Heart Study. Ann Intern Med. 1999; 131:7–13.
3. Master AM. Acute coronary artery diseases; history, incidence, differential diagnosis and occupational significance. Am J Med. 1947 May; 2(5):501–16.
4. Rusnak J, Fastner C, Behnes M, Mashayekhi K, Borggrefe M, Akin I. Biomarkers in Stable Coronary Artery Disease. Curr Pharm Biotechnol. 2017;18(6):456-–71.
5. Vaccarino V, Krumholz HM. Risk factors for cardiovascular disease: one down, many more to evaluate. Ann Intern Med. 1999 Jul 6;131(1):62-3.
6. Alderman MH. Serum uric acid as a cardiovascular risk factor for heart disease. Curr Hypertens Rep. 2001 Jun;3(3):184-9.
7. Choi HK, Ford ES. Prevalence of the metabolic syndrome in individuals with hyperuricemia. Am J Med. 2007 May;120(5):442-7.
8. Takae K, Nagata M, et al. Serum Uric Acid as a Risk Factor for Chronic Kidney Disease in a Japanese Community - The Hisayama Study. Circ J. 2016 Jul 25;80(8):1857-62.
9. 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 May 10;283(18):2404-10.
10. Niskanen LK, Laaksonen DE, et al. Uric acid level as a risk factor for cardiovascular and all-cause mortality in middle-aged men: a prospective cohort study. Arch Intern Med. 2004 Jul 26;164(14):1546-51.

11. Zhao G, Huan L, et al. Baseline uric acid level as a predictor of atherosclerosis 2013;
12. Kanbay M, Segal M, Afsar B, Rodriguez B, Kang DH, Johnson RJ. The role of uric acid in the pathogenesis of human cardiovascu- lar disease. Heart. 2013;99:759-66.
13. Kim S, Guevara J, Kim K, Choi HK, Heitjan DF, Albert DA. Hyperuricemia and coronary heart disease: a systematic review and meta-analysis. Arthritis Care Res (Hoboken). 2010;62: 170-80.
14. Okura T, Higaki J,et al; Japanese Coronary Artery Disease Study Investigators. Elevated serum uric acid is an independent predictor for cardiovascular events in patients with severe coronary artery stenosis: subanalysis of the Japanese Coronary Artery Disease (JCAD) Study. Circ J. 2009 May;73(5):885-91.
15. Yang Y, Lin LH, et al. Association Between the Serum Uric Acid Level and the Severity of Coronary Artery Disease in a Retrospective Study of China Nondialysis CKD Patients. Metab Syndr Relat Disord. 2020 May;18(4):206-211.
16. Freedman DS, Williamson DF, Gunter EW, Byers T. Relation of serum uric acid to mortality and ischemic heart disease. The NHANES I Epidemiologic Follow-up Study. Am J Epidemiol. 1995 Apr 1;141(7):637-44.
17. Moriarity JT, Folsom AR, Iribarren C, Nieto FJ, Rosamond WD. Serum uric acid and risk of coronary heart disease: Atherosclerosis Risk in Communities (ARIC) Study. Ann Epidemiol. 2000 Apr;10(3):136-43.
18. Williams B, Mancia G, et al; ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018 Sep 1;39(33):3021-3104. doi: 10.1093/eurheartj/ehy339. Erratum in: Eur Heart J. 2019 Feb 1;40(5):475. PMID: 30165516.
19. Braunwald E. Unstable angina: a classification.Circulation. 1989; 80:410–414.
20. European Heart Journal (2019) 40, 237–269 Fourth universal definition of myocardial infarction (2018) Kristian Thygesen* et al.
21. Hisatome I, Ichida K, Mineo I, et al. Japanese society of gout and uric and nucleic acid 2019 guideline for management of hyperuricemia and gout 3rd edition. Gout Uric nucleic acids 2020; Vol. 44 Supplement
22. Kang D H, Ha S K e al. Uric acid puzzle: Dual role as anti-oxidant and pro-oxidant. Electrolyte blood press 2014; 12 : 1-6.
23. Iribarren C, Folsom AR, Eckfeldt JH, McGovern PG, Nieto FJ. Corre- lates of uric acid and its association with asymptomatic carotid athero- sclerosis: The Aric Study. Ann Epidemiol. 1996;6:331–340.
24. Jossa F, Farinaro E, Panico S, Krogh V, Celentano E, Galasso R, et al. Serum uric acid and hypertension: The Olivetti Heart Study. J Hum Hyperten. 1994;8:677–681.
25. Facchini F, Chen YD, Hollenbeck CB, Reaven GM. Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. JAMA. 1991; 266:3008–3011.
26. Emmerson BT. Alteration of urate metabolism by weight reduction. Austr NZJ Med. 1973;3:410–412.
27. Bonora E, Targher G, Zenere MB, et al. Relationship of uric acid concentration to cardiovascular risk factors in young men. Role of obesity and central fat distribution: The Verona Young Men Atherosclerosis Risk Factors Study. Intl J Obes Relat Metab Disord. 1996;20:975–980.
28. Rathmann W, Hauner H, Dannehl K, Gries FA. Association of ele- vated serum uric acid with coronary heart disease in diabetes mellitus. Diabetes Metab. 1993;19:159–166.
29. Folsom AR, Burke GL, Ballew C, et al. Relation of body fatness and its distribution to cardiovascular risk factors in young blacks and whites. The role of insulin. Am J Epidemiol.

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1989;130:911–924.
30. Russo C, Olivieri O, Girelli D, Guarini P, Corrocher R. Relationships between serum uric acid and lipids in healthy subjects. Prev Med. 1996;25:611–616.
31. Vuorinen-Markkola H, Yki-Jarvinen H. Hyperuricemia and insulin resistance. J Clin Endocrin Metab. 1994;78:25–29.
32. ModanM, Halkin H, KarasikA, LuskyA. Elevated serum uric acid—a facet of hyperinsulinaemia. Diabetologia. 1987;30:713–718.
33. Kanbay M., Segal M., Afsar B. et al. The role of uric acid in the pathogenesis of human cardiovascular disease. Heart. 2013; 99: 759-766
34. Yu M.-A., Sánchez-Lozada L.G., Johnson R.J. et al. Oxidative stress with an activation of the renin-angiotensin system in human vascular endothelial cells as a novel mechanism of uric acid-induced endothelial dysfunction. J. Hypertens. 2010; 28: 1234-1242.
35. Johnson R.J., Nakagawa T., Sanchez-Lozada L.G et al. Sugar, uric acid, and the etiology of diabetes and obesity. Diabetes. 2013; 62: 3307-3315
36. Matsuura F., Yamashita S., Nakamura T. et al. Effect of visceral fat accumulation on uric acid metabolism in male obese subjects: visceral fat obesity is linked more closely to overproduction of uric acid than subcutaneous fat obesity. Metabolism. 1998; 47: 929-933
37. Lanaspa M.A., Sanchez-Lozada L.G., Choi Y.-J. et al. Uric acid induces hepatic steatosis by generation of mitochondrial oxidative stress: potential role in frucotse-dependent and -independent fatty liver disease. J. Biol. Chem. 2012; 287: 40732-40744
38. Reaven GM. The kidney: An unwilling accomplice in Syndrome X. Am J Kidney Dis. 1997;30:928–931.
39. Joe M, McCord JM. Oxygen-derived free radicals in postischemic tissue injury. N Engl J Med. 1985; 312: 159-163
40. Harrison R. Structure and function of xanthine oxidoreductase: where are we now?. Free Radic Biol Med. Sep 2002; 33: 774-797
41. Kang D.H., Nakagawa T., Feng L. et al.A role for uric acid in the progression of renal disease. J Am Soc Nephrol. 2002; 13: 2888-2897
42. Iseki K., Oshiro S., Tozawa M., Iseki C., Ikemiya Y., Takishita S. Significance of hyperuricemia on the early detection of renal failure in a cohort of screened subjects. Hypertens Res. 2001; 24: 691-697
43. Iseki K., Ikemiya Y., Inoue T., Iseki C., Kinjo K., Takishita S. Significance of hyperuricemia as a risk factor for developing ESRD in a screened cohort.Am J Kidney Dis. 2004; 44: 642-650
44. Lee J.E., Kim Y.G., Choi Y.H., Huh W., Kim D.J., Oh H.Y. Serum uric acid is associated with microalbuminuria in prehypertension. Hypertension. 2006; 47: 962-967.
45. Braga F, Pasqualetti S, Ferraro S, Panteghini M. Hyperuricemia as risk factor for coronary heart disease incidence and mortality in the general population: a systematic review and meta-analysis. Clin Chem Lab Med. 2016 Jan;54(1):7-15.
46. Kivity S, Kopel E, Maor E, Abu-Bachar F, Segev S, et al. Associ- ation of serum uric acid and cardiovascular disease in healthy adults. Am J Cardiol. 2013;111:1146-51.
47. Brodov Y, Chouraqui P, Goldenberg I, Boyko V, Mandelzweig L, Behar S. Serum uric acid for risk stratification of patients with coronary artery disease. Cardiology. 2009;114:300-5.
48. Borghi C, Arrigo F, Cicero G. Serum uric acid and car- diometabolic disease: another brick in the wall? Hypertension. 2017:1-4.
49. Miranda H, Castro P, Verdejo H, Chiong M, Díaz G, Mellado R, et al. Oxidative stress and inflammation in heart failure: mechanism of damage and therapeutic alternatives. Rev Méd Chile. 2007;135:1056-63.
50. Anker S, Doehner W, Rauchhaus M, Sharma R, Francis D, Knosalla C, et al. Uric acid and

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survival in chronic heart failure: valida- tion and application in metabolic, functional and hemodynamic staging. Circulation. 2003;107:1991-7.
51. Kang DH, Park SK, Lee IK, Johnson RJ. Uric acid-induced C-reactive protein expression: implication on cell proliferation and nitric oxide production of human vascular cells. J Am Soc Nephrol. 2005; 16: 3553-3562.
52. Longo-Mbenza B, Luila EL, Mbete P, Vita EK. Is hyperuricemia a risk factor of stroke and coronary heart disease among Africans? Int J Cardiol. 1999 Sep 30;71(1):17-22.
53. Bickel C, Rupprecht HJ, Blankenberg S, Rippin G, Hafner G, et al. Serum uric acid as an independent predictor of mortality in patients with angiographically proven coronary artery disease. Am J Cardiol. 2002 Jan 1;89(1):12-7.
54. Nadkar MY, Jain VI. Serum uric acid in acute myocardial infarction. J Assoc Physicians India. 2008 Oct;56:759-62.
55. Chen S, Yang H, Chen Y, Wang J, Xu L, Miao M, Xu C. Association between serum uric acid levels and dyslipidemia in Chinese adults: A cross-sectional study and further meta-analysis. Medicine (Baltimore). 2020 Mar;99(11):e19088.
56. The Association Between Hyperuricemia and Obesity Metabolic Phenotypes in Chinese General Population: A Retrospective Analysis; Xiaojing Feng et al. Front. Nutr., 18 April 2022, sec. nutrition and metabolism, vol.9 – 2022
57. Maharani N, Kuwabara M, Hisatome I. Hyperuricemia and Atrial Fibrillation. Int Heart J. 2016 Jul 27;57(4):395-9.
58. Deveci OS, Kabakci G, Okutucu S, Tulumen E, Aksoy H, Kaya EB, Evranos B, et al. The association between serum uric acid level and coronary artery disease. Int J Clin Pract 2010; 64:900 907.
59. Liese AD, Hense HW et al. Association of serum uric acid with all-cause and cardiovascular disease mortality and incident myocardial infarction in the MONICA Augsburg cohort. Epidemiology. 1999 Jul;10(4):391-7.
60. Høieggen A, Alderman MH et al. LIFE Study Group. The impact of serum uric acid on cardiovascular outcomes in the LIFE study. Kidney Int. 2004 Mar;65(3):1041-9.
61. Goodarzynejad H, Anvari MS, Boroumand MA, Karimi A, Abbasi SH, Davoodi G. Hyperuricemia and the presence and severity of coronary artery disease. Lab Med 2010; 41:40 45.
62. Gur M, Yilmaz R, Demirbag R et al. Relation of serum uric acid levels with the presence and severity of angiographic coronary artery disease. Angiology 2008; 59:166 171.
63. Kojima S, Sakamoto T, Ishihara M, et al. Prognostic usefulness of serum uric acid after acute myocardial infarction (Japanese Acute Coronary Syndrome Study). Am J Cardiol 2005; 96:489-495