Serum Uricacid Estimation in Acute Myocardial Infarction - A Prognostic Indicator

Gandiah P.[1], Venkateshwarlu N.[2], Naveen Kumar M.[3], Indira G.[4], Sivarajappa P.[5]

[1]Professor and H.O.D., [2,4,5]Professor, [3]Ex-Post Graduate Student

Department of General Medicine, SVS Medical College and Hospital, Mahabubnagar, Andhra Pradesh, INDIA.

Corresponding Addresses:

[1]kg_gandiah@yahoo.com, [2]venkatatreya@gmail.com

Research Article

Abstract: **Background**: Elevated serum uric acid is highly predictive of mortality in patients with heart failure or coronary artery disease and of cardiovascular events in patients. Large cohort studies have shown that uric acid is an important independent risk factor for cardiovascular mortality. The role of uric acid in coronary heart disease is less clear. Some studies reported an independent association between uric acid and coronary heart disease. **Material and Methods**: 100 cases of AMI were studied in this study. 50 age and sex matched individuals without any ailments served as control group. Serum uric acid levels were estimated on days 0 and 7 apart from various relevant investigations. The study group was classified into one of the four Killip class. The study was approved by the college ethics committee. **Observations**: There was a statistically significant higher level of serum uric acid concentration in patients of AMI on day of admission as compared to controls ($P< 0.05$). There was no significant difference in serum uric acid levels as regards hypertension and diabetes mellitus in patients with AMI, but there is a statistically significant($p=0.0001$) difference in serum uric acid levels in patients with past history of IHD or stroke. On all the days serum uric acid levels were higher in patients who were in higher Killip class ($P< 0.05$). All the patients who died were in Killip class IV and all had serum uric acid concentration $\geq$ 7mg/dl. It had been concluded that alone serum uric acid may not be the negative prognostic factor in AMI, but with the past history of IHD or stroke and in the presence of heart failure the serum uric acid may be of some significance.

Key words: Serum uric acid, AMI, Killip classification.

Introduction

Uric acid is a powerful antioxidant and has been proposed to protect against cardiovascular disease and some cancers.[1]. Despite the expectation that the antioxidant properties of uric acid might have a protective effect against cardiovascular disease, studies have reported associations with a greater risk of ischemic heart disease, higher blood pressure, and an adverse cardiovascular risk profile[2-6]. These adverse effects have been confirmed in meta-analyses of prospective studies,[3,4,5] which concluded that hyperuricaemia was associated with increases in risk for cardiovascular outcomes and blood pressure, independently of established risk factors. Nearly 120 years have elapsed since uric acid was first described as a risk factor. Hyperuricemia (usually defined as serum uric acid levels 6.5 mg/dL in men and 6.0mg/dL in women) is frequently encountered in hypertensive patients and is often due to a defect in renal urate clearance. Elevated serum uric acid is highly predictive of mortality in patients with heart failure or coronary artery disease and of cardiovascular events in patients[7].

Material and Methods

This study was done at department of General Medicine, S.V.S Medical College, Mahabubnagar A.P. 100 patients presenting to Emergency department of SVS HOSPITAL during the period June 2009 to May 2012 have been selected for the study. All patients who were of age greater than 18yr and diagnosed as ST segment elevation acute myocardial infarction (STEMI) or non – ST segment elevation acute myocardial infarction (NSTEMI) were considered for study. Selection of patients was based on new criteria for the diagnosis of acute evolving or recent MI published by the American College of Cardiology and European Society of Cardiology[8]. 50 patients of acute myocardial infarction who fulfilled inclusion/exclusion criteria were enrolled for the study. A detailed history and physical examination with special reference to KILLIP class was carried out. All patients underwent routine investigations including Haemogram, renal function tests, liver function tests, ECG and Chest X ray. Patients were treated as decided by attending physician. Patients were followed up till hospital stay i.e., 7th day initially and up to one year later on. Serum uric acid level was measured on day 0 and 7 of AMI. All the details of history, physical examination, routine investigation reports and serum uric acid levels were entered in a proforma. Fifty age and sex matched healthy controls were also evaluated for baseline serum uric acid level. A detailed statistical analysis was carried out. Basal serum uric acid levels were compared with controls with unpaired‘t’ test. The levels of serum uric acid on day 0 and 7 were compared by paired‘t’ test. Uric acid levels and KILLIP class was compared with coefficient of

correlation. The study was approved by the Ethics committee of the hospital.

Selection of patients for the study group was subject to the following mentioned inclusion and exclusion criteria -

Inclusion Criteria

Age >18yr

Patient diagnosed as AMI according to the new criteria for the diagnosis of acute evolving or recent MI published by the American College of Cardiology and European Society of Cardiology.[8]

Patients satisfying exclusion criteria

Exclusion Criteria

Any patient with a condition known to elevate uric acid levels – Chronic kidney disease, Gout, Hematological malignancy, Hypothyroidism

Patients on drugs which increase serum uric acid – Salicylates(>2gm/d),Diuretics, Ethambutol, Pyrazinamide and Chronic alcoholics

Observations

We have studied 100 patients with acute myocardial infarction and 50 age and sex matched healthy controls. The comparison of two groups and the profile of patients, their comparative uric acid levels are given in the tables below

Table1: Comparison of Patients and Controls

Parameter	Patients (n=100)	Controls (n= 50)	'p' Value
Age	52.94 ± 13.42	50.22 ± 15.90	0.23(ns)
Sex M:F	74 : 26	33 : 17	not applicable
Mean Serum uric acid on day 0	5.07 ± 1.48	3.38 ± 0.50	0.0012

Table 2: Patient Profile and Serum Uric Acid Levels on Day 0

Parameter			'p' Value
Sex	Male – 74	Female – 26	
Mean Serum Uric Acid	5.07 ± 1.48	3.38 ± 1.44	NS
Hypertension	38 – YES	62 - NO	
Mean Serum Uric Acid	5.00 ± 1.36	4.81 ± 1.56	NS
Diabetes Mellitus	18 – YES	82 – NO	
Mean Serum Uric Acid	5.38 ± 2.18	4.81 ± 1.35	NS
H/O IHD or Stroke	14 – YES	86 – NO	
Mean Serum Uric Acid	7.32 ± 2.06	5.08 ± 1.58	0.001

There was a statistically significant higher level of serum uric acid concentration in patients of AMI on day of admission as compared to controls (P< 0.05). There was no significant difference in serum uric acid levels as regards hypertension and diabetes mellitus in patients with AMI, but there is a statistically significant(p=0.0001) difference in serum uric acid levels in patients with past history of IHD or stroke. Patients included into the study were categorized into 4 quartiles according to their serum uric acid levels and compared against their Killip class indicative of left heart failure on day 0 and day 7. The following 3 tables show the data of the patients on day 0 and day 7, differences in frequencies were analyzed by the chi – square method. On all the days serum uric acid levels were higher in patients who were in higher Killip class (P< 0.05). All the patients who died were in Killip class IV and all had serum uric acid concentration ≥ 7mg/dl.

Table 3: Number of cases – Serum Uric Acid levels (mg/dL) and Killip class

Killip class	< 4	4.1 – 6.5	6.5 – 7.0	> 7.1	Total
I	22	16	06	0	44
II	7	7	0	0	14
III	0	08	11	10	29
IV	0	0	1	12	13
Total	29	31	18	22	100

Table 4: Number of Cases – Serum Uric Acid Levels (Mg/Dl) and Killip Class On Day 7

Killip class	< 4	4.1 – 6.5	6.5 – 7.0	> 7.1	Total
I	19	20	06	0	45
II	9	9	0	0	18
III	0	05	15	10	30
IV	0	0	0	1	1
Total	28	34	21	11	94

Follow up: Six patients died within the first week. Three patients had previous history of IHD, one had ischemic stroke and two were diabetic patients. All of these cases had a serum uric acid level greater than 7 mg/dl and were in Killip

class III or IV. Remaining patients were followed up to a minimum one year. Eight more patients succumbed before the end of one year. Of these 8, 7 were of Killip III or IV class and had a uric acid level above 7mg/dl while only one case had uric acid level at 5.68mg/dl. Twenty two were subjected to CABG (Coronary artery bypass graft), 32 were treated with percutaneous intervention while the remaining 32 were on the medical treatment.

Table 5: Cases Expired Within 7 Days

Total patients	100
Died within first week	6
H/O IHD	3
H/O stroke	1
Diabetes mellitus	2

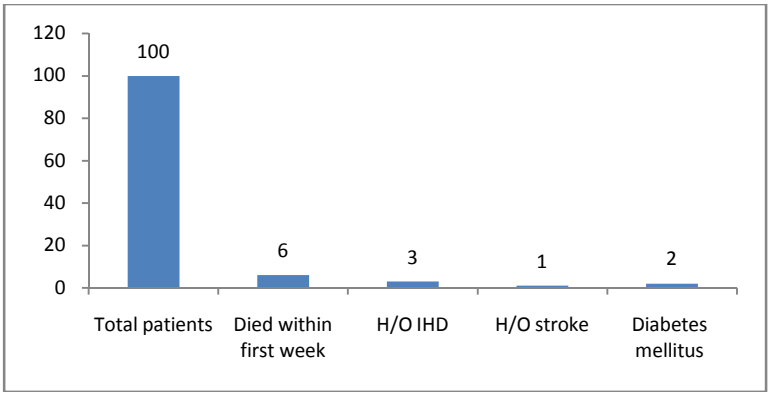

Figure 1: Cases Expired Within 7 Days

Table 6: Cases Expired Between 8 Days And One Year

Total patients	94
Died within first year	8
H/O IHD	5
H/O stroke	1
Diabetes mellitus	2

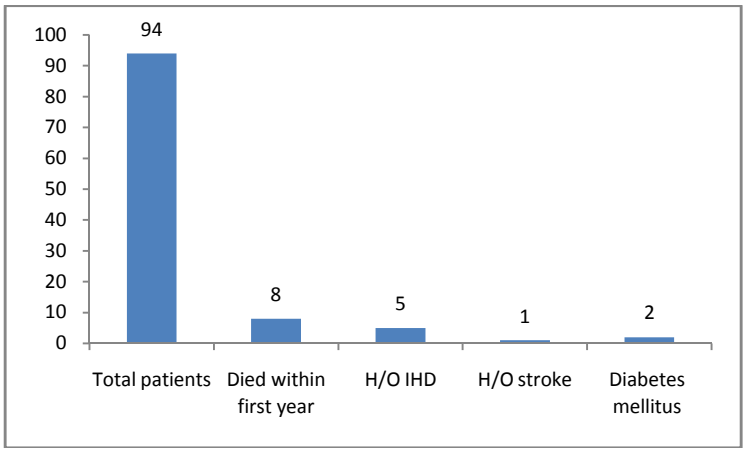

Figure 2: Cases Expired Between 8 Days and One Year

Table 7: Showing the Details of Death with Level of Serum Uric Acid and Killip Class

	Number of deaths < 7 days	**Number of deaths between 8 days and one year**
Serum uric acid < 7 mg/dl	0	1
Serum uric acid > 7 mg/dl	6	7
Killip class III	2	6
Killip class IV	4	2

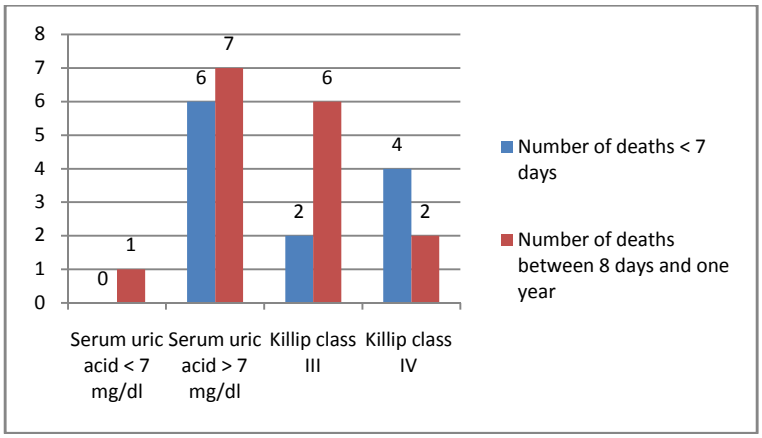

***Figure 3*:** Showing the Details of Death with Level of Serum Uric Acid and Killip Class

Discussion

Elevated SUA levels have been associated with an increased risk for Cardio-vascular disease. The potential mechanisms by which SUA may directly cause cardiovascular risk include enhanced platelet aggregation and inflammatory activation of the endothelium[9]. In few studies, the association of SUA with cardiovascular disease was uncertain after multivariate adjustment as in the Framingham Heart Study (1985)[10] and the ARIC study (1996), but in others the association remained certain and significant. Two of the previous studies have reported that a high concentration of uric acid (UA) is a strong marker of an unfavorable prognosis of moderate to severe heart failure and cardiovascular disease[11, 12]. Large cohort studies have shown that uric acid is an important independent risk factor for cardiovascular mortality[13, 14]. The role of uric acid in coronary heart disease is less clear. Some studies reported an independent association between uric acid and coronary heart disease[12, 13, 14] but others only found an association in women,[15, 16,17] and in yet others, the associations disappeared after adjustment for confounders[15, 17, 18, 19]. Because elevated serum uric acid is correlated with several risk factors including renal dysfunction, hypertension, insulin resistance, hyper-homocystinemia and hyper-lipidemia, it is debated whether SUA is an independent cardiovascular risk factor. The results of epidemiologic studies have been contradictory, although most conclude that serum uric acid is a risk factor for CAD[20-33]. We have studied 100 patients of acute myocardial infarction (AMI) who were admitted to our hospital during the period JUNE 2009 to MAY 2013; 50 age and sex matched healthy individuals were taken as controls. There was a statistically significant higher level of serum uric acid concentration in patients of AMI on day of admission as compared to controls (P<0.05). There was no significant difference in serum uric acid levels as regards hypertension and diabetes mellitus in patients with AMI as shown in the table 18 above. This is in concordance with the study by Nadkar *et al*[34] whereas in the Japanese acute coronary syndrome study[35] patients with hypertension were found to be having higher levels of serum uric acid. Non-diabetic and diabetic patients had comparable serum uric acid levels on Day0 (Table 2). This finding is consistent with study by Tuomilheto *et al*[36] in which there was no significant association between serum uric acid level and diabetic status. However, this finding is in contrast to other study by Safi *et al*[37] which showed that hyperuricaemia is significantly associated with type 2 diabetes mellitus. Serum uric acid levels were comparable on day 0 and day 7 in AMI group, 4.89±1.48, 4.58±1.38, 4.74±1.46 respectively (p=N.S.). Tables 3 and 4 above show the levels of uric acid in relation to Killip class on day 0 and 7 of admission. On the occasions serum uric acid levels were higher in patients who were in higher Killip class (p<0.05). Six patients expired during the 7day hospital stay, among who all were in Killip class IV and having serum uric acid levels ≥7mg/dl, of these three patients were in Killip's class III and two patients were in Killip's class IV on the day of admission. Those two patients who were in Killip's class IV on the day of admission were having serum uric acid levels in 3rd and 4th quartiles and died on the day of admission. Among the three patients in Killip's class one patient deteriorated to Killip's class IV on day 3 with corresponding raise in serum uric acid and died after 3rd day whereas the other two patients shifted to Killip's class IV on day 5 also with raise in serum uric acid concentration and died on day 7. Thus all patients who expired were in Killip's class IV and serum uric acid concentration ≥7mg/dl. Therefore it shows that serum uric acid concentration is significantly correlated with Killip's class and mortality. Results of present study show that serum uric acid concentrations correlate significantly with male gender and correlates positively with Killip's class. A failing heart due to AMI may cause tissue hypoperfusion and hypoxia, which trigger xanthine oxidase activation and oxidative stress

production[38, 39]. Xanthine oxidase and oxidative stress as reflected by UA may form a vicious cycle that promotes severe heart failure[38, 40]. Therefore, UA may not be only a bystander marker but also a causative marker of mortality in patients who have AMI. In this regard, improvement of coronary reperfusion alone may be less effective in ameliorating heart failure and decreasing mortality rate in patients who have AMI and high UA level and are in a high Killip's class. Adjunctive therapy designed to decrease xanthine oxidase activity and inhibit oxidative stress production is expected to sever the vicious cycle. The Losartan Intervention for Endpoint reduction in hypertension (LIFE) study[41] demonstrated that lowering serum UA concentrations by losartan was associated with a beneficial effect on cardiovascular outcome. The UA-lowering effect of atorvastatin may have contributed to the decrease in cardiovascular mortality in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study[42]. Therefore, any drug interventions, such as therapy to decrease serum UA level in addition to coronary reperfusion, may have a favorable effect on mortality in patients who have AMI.

Limitations of the Study

This study has some limitations. We believed that a greater cohort would be desirable to improve the power of the study. We also relied on clinical data to rule out infection and other inflammatory diseases before sampling, but we cannot exclude that some patients had unrecognized conditions responsible for the elevated serum uric acid levels observed. We suppose to mean that these limitations might not have a significant influence on study data interpretation.

Conflict of Interests

The authors declare that they have no conflict of interests.

Disclosure

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Ames BN, Cathcart R, Schwiers E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. Proc Natl Acad Sci U S A 1981;78:6858-62.
2. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality: the NHANES I epidemiologic follow-up study, 1971-1992. JAMA 2000; 283: 2404-10.
3. Kim SY, Guevara JP, Kim KM, Choi HK, Heitjan DF, Albert DA. Hyperuricemia and risk of stroke: a systematic review and meta-analysis. Arthritis Care Res 2009;61:885-92.
4. Meisinger C, Koenig W, Baumert J, Doring A. Uric acid levels are associated with all-cause and cardiovascular disease mortality independent of systemic inflammation in men from the general population: the MONICA/KORA cohort study. Arterioscler Thromb Vasc Biol 2008;28:1186-92.
5. Kim SY, Guevara JP, Kim KM, Choi HK, Heitjan DF, Albert DA. Hyperuricemia and coronary heart disease: a systematic review and meta-analysis. Arthritis Care Res 2010;62:170-80.
6. Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis J, Watanabe S, et al. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension 2003;41:1183-90.
7. Alderman M, Aiyer KJ. Uric acid: role in cardiovascular disease and effects of losartan. Curr Med Res Opin 2004; 20:369-79.
8. Alpert JS, Thygeson K, Antman E. Myocardial infarction redefined: A consensus document of The Joint European Society of Cardiology /American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol 2000; 36: 959.
9. "Systemic Hypertension: Mechanism and Diagnosis." Elsevier Saunders 37:962.
10. Serum Uric Acid and Risk for Cardiovascular Disease and Death: The Framingham Heart Study-Bruce F. Culleton, MD; Martin G. Larson, ScD; William B. Kannel, MD; and Daniel Levy, MD., Ann Intern Med. 1999; 131: 7-13. From the National Heart, Lung, and Blood Institute's Framingham Heart Study, Framingham, Massachusetts; and Boston University School of Medicine, Boston, Massachusetts.
11. Leyva F, Anker S, Swan JW, Godsland IF, Wingrove CS, Chua TP, Stevenson JC, Coats AJ. Serum uric acid as an index of impaired oxidative metabolism in chronic heart failure. Eur Heart J 1997;18: 858–865.
12. Anker SD, Doehner W, Rauchhaus M, Sharma R, Francis D, Knosalla C, Davos CH, Cicoira M, Shamim W, Kemp M, et al. Uric acid and survival in chronic heart failure: validation and application in metabolic, functional, and hemodynamic staging. Circulation 2003;107: 1991–1997.
13. Niskanen LK, Laaksonen DE, Nyyssonen K, Alfthan G, Lakka HM, Lakka TA, Salonen JT. 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;164:1546 –1551.
14. 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. J Am Med Assoc. 2000;283: 2404–2410.
15. 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.
16. Freedman DS, Williamson DF, Gunter EW, Byers T. Relation of serum uric acid to mortality and ischemic heart disease. Am J Epidemiol. 1995;141:637– 644.
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;10:136 –143.
18. Brand FN, McGee DL, Kannel WB, Stokes J III, Castelli WP. Hyperuricemia as a risk factor of coronary heart disease: The Framingham Study. Am J Epidemiol. 1985;121:11–18.

19. Wannamethee SG, Shaper AG, Whincup PH. Serum urate and the risk of major coronary heart disease events. Heart. 1997;78:147–153.
20. Gertler MM, Garn SM, Levine SM. Serum uric acid in relation to age and physique in health and in coronary heart disease. Ann Intern Med 1951;34:1421– 1431.
21. Klein R, Klein BE, Cornoni JC, Maready J, Cassel JC, Tyroler HA. Serum uric acid: its relationship to coronary heart disease risk factors and cardiovascular disease, Evans County, Georgia. Arch Intern Med 1973;132:401–410.
22. The Coronary Drug Project Research Group. Serum uric acid: its association with other risk factors and with mortality in coronary heart disease. J Chronic Dis 1976;29:557–569.
23. Persky VW, Dyer AR, Idris-Soven E, Stamler J, Shekelle RB, Schoenberger JA, Berkson DM, Lindberg HA. Uric acid: a risk factor for coronary heart disease? Circulation 1979;59:969–977.
24. Fessel WJ. High uric acid as an indicator of cardiovascular disease: independence from obesity. Am J Med 1980;68:401–404.
25. Beard JTD. Serum uric acid and coronary heart disease. Am Heart J 1983; 106:397–400.
26. Brand FN, McGee DL, Kannel WB, Stokes JD, Castelli WP. Hyperuricemia as a risk factor of coronary heart disease: The Framingham Study. Am J Epidemiol 1985;121:11–18.
27. Bengtsson C, Lapidus L, Stendahl C, Waldenstrom J. Hyperuricaemia and risk of cardiovascular disease and overall death: a 12-year follow-up of participants in the population study of women in Gothenburg, Sweden. Acta Med Scand 1988; 224:549–555.
28. Levine W, Dyer AR, Shekelle RB, Schoenberger JA, Stamler J. Serum uric acid and 11.5-year mortality of middle-aged women: findings of the Chicago Heart Association Detection Project in Industry. J Clin Epidemiol 1989;42:257– 267.
29. 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;141:637–644.
30. Iribarren C, Folsom AR, Eckfeldt JH, McGovern PG, Nieto FJ. Correlates of uric acid and its association with asymptomatic carotid atherosclerosis: the ARIC Study: Atherosclerosis Risk in Communities. Ann Epidemiol 1996;6:331–340.
31. Wannamethee SG, Shaper AG, Whincup PH. Serum urate and the risk of major coronary heart disease events. Heart 1997;78:147–153.
32. 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.
33. 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;283:2404–2410.
34. MY Nadkar, VI Jain, et al. Serum Uric Acid in Acute Myocardial Infarction : JAPI • VOL. 56 • OCTOBER 2008,pg 759-762
35. Sunao Kojima, MDa, Tomohiro Sakamoto, MD, Masaharu Ishihara, MD, Kazuo Kimura, MD, Shunichi Miyazaki, MD, Masakazu Yamagishi, MD, Chuwa Tei, MD, Hisatoyo Hiraoka, MD, Masahiro Sonoda, MD, Kazufumi Tsuchihashi, MD, Nobuo Shimoyama, MD, Takashi Honda, MD, Yasuhiro Ogata, MD, Kunihiko Matsui, MD, and Hisao Ogawa, MD; Prognostic Usefulness of Serum Uric Acid After Acute Myocardial Infarction (The Japanese Acute Coronary Syndrome Study): The American Journal of Cardiology2005;96:489 – 495
36. Tuomilheto J, Zimmet P, Evawolf. Plasma Uric acid level and its association with Diabetes Mellitus and some Biologic Parameters in a Biracial Population of FIJI Am J Epidemiol 1988;127:32136.
37. Safi AJ, Mahmood R, Khan MA, Haq A. Association of serum Uric Acid with type II diabetes mellitus. J Postgrad Med Inst 2004;18:59-63.
38. Hare JM, Johnson RJ. Uric acid predicts clinical outcomes in heart failure: insights regarding the role of xanthine oxidase and uric acid in disease pathophysiology. Circulation 2003;107:1951–1953.
39. Terada LS, Guidot DM, Leff JA, Willingham IR, Hanley ME, Piermattei D, Repine JE. Hypoxia injures endothelial cells by increasing endogenous xanthine oxidase activity. Proc Natl Acad Sci USA 1992;89:3362–3366.
40. Anker SD, Doehner W, Rauchhaus M, Sharma R, Francis D, Knosalla C, Davos CH, Cicoira M, Shamim W, Kemp M, et al. Uric acid and survival in chronic heart failure: validation and application in metabolic, functional, and hemodynamic staging. Circulation 2003;107: 1991–1997.
41. Hoieggen A, Alderman MH, Kjeldsen SE, Julius S, Devereux RB, De Faire U, Fyhrquist F, Ibsen H, Kristianson K, Lederballe-Pedersen O, et al, for the LIFE Study Group. The impact of serum uric acid on cardiovascular outcomes in the LIFE study. Kidney Int 2004;65: 1041–1049.
42. Athyros VG, Elisaf M, Papageorgiou AA, Symeonidis AN, Pehlivanidis AN, Bouloukos VI, Milionis HJ, Mikhailidis DP, for the GREACE Study Collaborative Group. Effect of statins versus untreated dyslipidemia on serum uric acid levels in patients with coronary heart disease: a subgroup analysis of the GR Eek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. Am J Kidney Dis 2004;43:589–599.