Serum Uric Acid As A Predictor Of Short-term Mortality And Heart Failure In Acute Myocardial Infarction

Dr. Ala Hussain Abbase Haider , Dr. Aamir Magtoof Shumran

Abstract

This study aimed to determine the association of SUA levels with short term (in hospital) outcome following acute myocardial infarction .

The study included   100 patients presented with acute ST-elevation myocardial infarction (STEMI), serum uric acid (SUA) levels were measured within the 1st 12 hour of admission to coronary care unit.

13 patients had high serum uric acid(450 µmol/L) and 87 patients had normal SUA.

23% of patients with high serum uric acid died, while 2.3% of patients with normal serum uric acid died. 23% of patients with high serum uric acid developed heart failure (HF), while 6.8% of patients with normal serum uric acid developed heart failure.

40% of male patients with high SUA developed cardiac complications (HF and cardiac death)while 8.3% of male patients with normal SUA developed cardiac complications, 66.6% of female patients with high SUA developed cardiac complications ,while 11.1% of female patients with normal SUA developed cardiac complications .The differences were significant(P value < 0.05)

The predictive value of SUA was significant in patients aged   60 years and in those aged < 60 years, as well as in smokers and non smokers, and in those with high BMI, and in patients with increased serum lipids and those with normal lipid profile .

The predictive value of SUA was not significant in hypertensive patients, while it was significant in normotensive patients.

15.6% of patients not received thrombolytic therapy developed elevation of SUA, while non (0%) of patients received thrombolytic therapy developed elevation of SUA. 18.5% of patients with multiple regions MI (by ECG localization) developed elevation of SUA, while 8.3% of patients with inferior MI developed elevation of SUA, while non (0%) of patients with lateral MI developed elevation of SUA .

   By this study it appeared that high SUA levels was associated with higher risk of death and development of heart failure during the hospitalization period, and it may be considered as a prognostic marker for MI complications.

Key Words : Acute Myocardial Infarction, Serum Uric Acid ,cardiac death, HF.

Introduction

   Coronary heart disease (CHD) is the most common form of heart disease and single most important cause of premature death in Europe , the Baltic states , Russia , north and south America , Australia and new Zealand , by 2020 it is estimated that it will be the major cause of death in all regions of the world. [1]

   In the united states men are more often affected then women by an overall ratio of 4:1 , but before age 40 the ratio is 8:1 and after age 70 it is 1:1 , in men , the peak incidence of clinical manifestation is at age 50-60 ; in women at age 60-70. [2]

   Coronary heart disease remains the most common cause of death regardless of significant advancement in it's prevention and treatment . [3]

   ST-segment elevation MI (STEMI) generally occurs when coronary blood flow decreases abruptly after a thrombotic occlusion of a coronary artery previously affected by atherosclerosis . slowly developing , high – grade coronary artery stenosis do not usually precipitate STEMI because of the development of a rich collateral network over time. Instead , STEMI occurs when coronary artery thrombus develops rapidly at a site of vascular injury .

This injury is produced or facilitated by factors such as cigarette smoking , hypertension , and lipid accumulation.

   In most cases , infarction occurs when an atherosclerotic plague fissures , ruptures , or ulcerates and when conditions (local or systemic) favor thrombogenesis , so that a mural thrombus forms at the site of rupture and leads to coronary artery occlusion. [4]

   A joint European Society of Cardiology (ESC) and American College of Cardiology (ACC) committee proposed the following definition of AMI as typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following   [5]

1- Ischemic symptoms

2- Development of pathological Q waves on the ECG

3- ECG changes indicative of ischemia (ST segment elevation or depression)
4- Coronary artery intervention (e.g. angioplasty)

For the patient who is experiencing chest pain , an ECG should be immediately obtained because it is frequently diagnostic of myocardial ischemia or MI , and is important in determining the appropriate treatment plan .

STEMI refers to an acute coronary syndrome in which ST-segment elevation (e.g. 1 m V in concordant limb leads , 2 m V in concordant precordial leads) is present on the surface ECG . these infarctions are the result of complete thrombotic occlusion of a coronary artery and may 1st be exhibited on the ECG by symmetrically peaked or hyperacute T waves . these peaked T waves resolve after several minutes as the characteristic ST-segment elevation develops[6].

Any injury to the myocardial cells results in the release of intracellular enzymes in to circulating blood , permitting their detection by blood test , these include creatine kinase (CK-MB) iso enzyme [7] , and cardiac troponin I and T , an elevated cardiac troponin level on admission is a predictor of subsequent cardiac events .[5]

The early (30- days) mortality rate from AMI is about 30% , with more than half of these deaths occurring before the stricken individual reach the hospital.

Although the mortality rate after admission for AMI has declined by about 30% over the past two decades , approximately 1 of every 25 patients who survive the initial hospitalization die in the 1st year after AMI , survival is markedly reduced in elderly patients (over age 75). [4]

Pump failure is now the primary cause of in-hospital death from STEMI . The extent of ischemic necrosis correlate well with the degree of pump failure and with mortality both early (within 10 days of infarction) and later. [4]

Myoglobine , CK-MB and cardiac troponins are predictors of subsequent cardiac events [5] as well as SUA.[8]

Serum uric acid (SUA)

Purines arise from metabolism of dietary and endogenous nucleic acids , and are degraded ultimately to uric acid which is catalyzed by the enzyme xanthine oxidase , which is responsible for the production of uric acid and damaging free radicals . There is a central link in the association between SUA and myocardial ischemia / dysfunction . [9]

Uric acid is a weak acid distributed throughout the extracellular fluid compartment as sodium urate , and cleared from plasma by glomerular filtration . [10]

Around 90% of filtered uric acid is reabsorbed from the proximal renal tubules , while active secretion in to the distal tubules by an ATPase-dependent mechanism contributes to overall clearance. [11]

The reference range of SUA is variable , according to geographical distribution , gender and dietary sources. For an individual , urate concentration is determined by a combination of the rate of purine metabolism (both the endogenous and the exogenous) and the efficiency of renal clearance . purine metabolism is influenced by dietary , as well as genetic factors regulating cell turn over. Uric acid is sparingly soluble in aqueous media , and persistent exposure to high serum levels predisposes to urate crystal deposition within the soft tissues. [12]

Observational studies show that SUA concentrations are higher in patients with established CHD compared with healthy controls. [13]

SUA possesses antioxidant properties , and contributes about 60% of free radical scavenging activity in human serum , uric acid interacts with peroxynitrite to form a stable nitric oxide donor , thus promoting vasodilatation and reducing the potential for peroxynitrite-induced oxidative damage. [14]

It is interesting to note that treatment of chronic heart failure patients with allopurinol (xanthine-oxidase inhibitor) restore endothelial function. [15]

Aim of the study

The aim of the study was to determine the possibility of using SUA measured within the first 12 hours of presentation as a predictor of short term adverse cardiac events including cardiac death and development of heart failure .

Patients and methods

The study was conducted in Marjan – Teaching Hospital and Ibn-Al Baytar Hospital over the period from 15th of February to 25th of December 2007 .All patients who full field the planned inclusion criteria was taken as a study population.

100 patients were included in this study(after taken a verbal consent from each one), 70 males and 30 females. A questionnaires was prepared which include demographic informations (age, sex) and inclusion and exclusion criteria .

A full history was taken from each patient including age , smoking, the patients divided to smokers (defined as active current smoker) [8]and non smokers ,hypertension (patients who were treated with antihypertensive drugs or those whose daily blood pressure readings   140/90 mmHg during hospitalization were considered to have hypertension) [1]using random zero sphygmomanometer, and full physical examination was performed .

12 leads ECG was done for each patient and the diagnosis of myocardial infarction depend on the history of ischemic chest complaint and the 12-lead ECG[16] (ECG changes are the development of ST segment elevation followed by abnormally persistent Q wave)[17] as cardiac enzymes were unavailable at the time of the study .

Patients who had history of gout or condition that can result   in increase SUA were excluded from the study likealcohol intake , hypothyroidism ,psoriasis ,polycythaemia vera, myeloproliferative diseases , morbid obesity (BMI   40) , renal impairment, and drugs (thiazide and loop diuretics , low dose aspirin , anti-TB drugs , levodopa , cyclosporine) [18].

Patients who died from non-cardiac causes were excluded from the study.

Body mass index (BMI)   was calculated for all patients according to the equation :-

$$ BMI = \frac{Body\ weight\ (kg)}{(\ Height\ (m)\ )^2} $$

Using physic Kan scales.

Patients with BMI < 25 were considered normal [19].

Blood samples had been taken within the 1st 12 hours of admission for the measurement of SUA.

S.U.A measured using enzymatic colorimetric test (uricase PAP)

Normal SUA values [20] (Male 120-420 µmol/L, Female 120 – 360 µmol/L). Male patients with SUA > 420 µmol/L and females with S.U.A more than 360 µmol/L were considered to have high SUA.

Total serum cholesterol and serum triglycerides were measured to all patients in the study within the 1st 24 hours of the onset of symptoms, using the enzymatic method (CHOD PAP test).

Hyperlipidemia was defined as a total cholesterol level   5.2 mmol/L (220 mg/dl) and/or a triglycerides level   1.7 mmol/L (150 mg/dl) [8,20]

Site of MI :-

Serial ECG records were done for all patients in the study and the patients divided in to 3 groups depending on the ECG localization of MI :-

1- patients with inferior MI

2- patients with lateral MI

3- patients with multiple regions MI(anteroseptal MI, anterolateral MI, inferolateral MI)

The patients were followed for the development heart failure (HF) and cardiac death (due to cardiogenic shock , resistant ventricular arrhythmias, and asystole) during hospitalization period which was 5-10 days .

The diagnosis of HF depended on clinical examination and supported by radiological investigation[21] (including chest X-ray and echocardiography [22] ejection fraction < 40%).

The diagnosis of cardiogenic shock depended on clinical examination [23] like hypotension (systolic blood pressure less than 100 mmHg), cold clammy skin , rapid shallow breathing , drowsiness, irritability , confusion , oliguria (urine output < 30 ml/hr).

17 patients were subjected to thrombolytic therapy and the others (83 patients) were not treated by this therapy due either to late presentation of complaining patients or unavailability of the drug or the presence of contraindication (s) and the effect of thrombolytic therapy on the serum uric acid values were identified.

Statistical analysis were done using Hypothesis Testing(proportional Z test)and the results considered to be significant if P value was <0.05 and highly significant if P value was <0.01.

RESULTS

100 patients were studied (70 males and 30 females) throughout their hospitalization periods , their ages range from 30 years to 80 years (mean 60 ± 10 years) .

The patients were divided into two groups :-

Group 1 :- patients with high SUA account 13 patients , 10 males and 3 females , aged 50-80 (mean 68 ± 6 years), mean SUA (500 ± 50 µmol/L).

Group 2 :- patients with normal S.U.A account 87 patients , 60 males and 27 females , aged 30-80 (mean 60 ± 10 years), mean SUA (250 ± 60 µmol/L).

The incidence of cardiac death was high in group 1 ; 3 patients died out of 13 patients (23%) , while 2 patients died out of 87 patients (2.3%) in group 2.

P value < 0.01, so the incidence of cardiac death was significantly higher in patients who developed high SUA values after AMI , as shown in table -1- .

The incidence of HF was high in group 1; 3 patients developed HF out of 13 patients (23%), while 6 patients developed HF out of 87 patients (6.8%) in group 2.

P value <0.05 , so the incidence of HF was significantly higher in patients who developed high SUA values after AMI as shown in table -2- .

The predictive value of SUA was studied in males and females with the following results :-

The incidence of cardiac complications (cardiac death and HF) was high in males with high SUA values , 4 (2 died , 2 developed HF) out of 10 patients (40%), while 5 patients developed cardiac complication (2 died , 3 developed HF) out of 60 (8.3%) with normal SUA .

P value < 0.01, so the incidence of cardiac complications was significantly higher in males patients with high SUA values than other male patients with normal SUA as shown in table -3- .

The incidence of cardiac complications was higher in females patients with high SUA, 2 (1 died , 1 developed HF) out of 3 patients (66.6%) while 3 developed HF out of 27 patients (11.1%) with normal SUA.

P value < 0.05 , so the incidence of cardiac complications was significantly higher in female patients with high SUA values than other female patients with normal SUA values as shown in table -3-.

The incidence of cardiac complications in male patients with high SUA was 4 out of 10 patients (40%) while 2 out of 3 (66.6 %) in female patients with high SUA developed cardiac complication.

P value was not significant, so there is no difference in the predictive value of SUA with regard to the sex as shown in table -3-.

The predictive value of SUA was studied in the patients with regard to their age .

The incidence of cardiac complications was high in patients aged   60 years with high SUA 4 (2 died , 2 developed HF) out of 10 patients (40%) while it was 5 (1 died , 4 developed HF) out of 37 patients (13.5%) with normal SUA .

P value <0.05 , so the incidence of cardiac complications was significantly higher in patients aged   60 yrs with high SUA than those patients aged   60 years with normal SUA as shown in table -4-.

The incidence of cardiac complications was high in patients aged < 60 years with high SUA , 2 (1 died , 1 developed HF) out of 3 patients (66.6%) while it was 3 (1 died , 2 developed HF) out of 50 patients   (6%) with normal SUA , p value < 0.01 , so the incidence of cardiac complications was significantly higher in patients aged < 60 years with high SUA than those patients of the same age group with normal SUA as shown in table -4-.

The incidence of cardiac complications in patients aged   60 years with high SUA was 4 out of 10 patients (40%) while it was 2 out of 3 patients (66.6%) in patients aged < 60 years with high SUA .

P value > 0.05(not significant), so there is no difference in the predictive value of SUA in AMI with regard to the age as shown in table -4- .

The predictive value of SUA was studied in smokers and non-smokers with the following results :-

The incidence of cardiac complications in smoker patients with high SUA was high , 3 (2 died , 1 developed HF) out of 3 patients(100%) while it was 5 (2 died , 3 developed HF) out of 47 smoker patients with normal SUA (10.6%).

P value < 0.01, so the incidence of cardiac complications was significantly higher in smokers with high SUA than smokers with normal SUA as shown in table -5- .

The incidence of cardiac complications in non-smokers with high S.U.A was high 3 (1 died , 2 developed HF) out of 10 patients (30%) while it was 3 (developed HF) out of 40 patients (1.5 %) with normal SUA .

P value was < 0.05, so the incidence of cardiac complications was significantly higher in non-smoker patients with high SUA than non-smokers with normal SUA as shown in table -5-.

The incidence of cardiac complications in smokers with high SUA was 3 out of 3 patients (100%) while it was 3 out of 10 patients   (30%) in non-smoker patients with high SUA .

P value was < 0.05 , so the predictive value of SUA in AMI was significantly higher in smokers as shown in table -5-.

The predictive value of SUA was studied in patients with high and normal BMI with the following results :-

The incidence of cardiac complications in over weight and obese patients (BMI   25 Kg/m2) with high SUA was 5 (3 died , 2 developed HF) out of 9 patients (55.5 %) while it was 5 (2 died , 3 developed HF) out of 56 patients (8.5%) in those with normal SUA .

 p value was < 0.01 , so the incidence of cardiac complications was significantly higher in overweight and obese patients with high SUA than overweight and obese patients with normal SUA as shown in table -6-.

The incidence of cardiac complications in patients with normal BMI and high SUA was 1 (developed HF) out of 4 patients (25 %) while it was 3 (developed HF) out of 31 patients (9.6 %) with normal SUA , p value > 0.05(not significant), as shown in table -6- .

The incidence of cardiac complications in overweight and obese patients with high SUA was 5 out of 9 patients (55.5%) while it was 1 out of 4 patients (25%) with normal BMI and high S.U.A ,

 p value > 0.05(not significant),   as shown in table -6-.

The predictive value of SUA was studied in all patients according to their lipid profile with the following results :-

The incidence of cardiac complications in patients with increased lipids and high SUA was high 5 (3 died , 2 developed HF) out of 10 patients (50%), while it was 6 (**2** died , 4 developed HF) out of 50 patients (12%) in those with increased serum lipids and normal SUA .

P value was < 0.01 , so the incidence of cardiac complications was significantly higher in hyperlipidemic patients with high SUA than in hyperlipidemic patients with normal SUA as shown in table -7-.

The incidence of cardiac complications in patients with normal lipid profile and high SUA was 1 (developed HF) out of 3 patients (33.3%), while it was 2 (developed HF) out of 37 patients (5.4%) with normal lipid profile and normal SUA .

P value was < 0.05 , so the incidence of cardiac complications was higher in patients with normal lipid profile and high SUA than those with normal lipid profile and normal SUA , as shown in table -7-.

The incidence of cardiac complications in patients with increased serum lipids and high SUA was 5 out of 10 patients (50%) , while it was 1 out of 3 patients (33.3%) in those with normal lipid profile and high SUA .

P value > 0.05(not significant),so there is no significant difference in the predictive value of SUA with regard to lipid profile as shown in table -7-.

The predictive value of SUA was studied in all patients according to their B.P and the patients divided into hypertensive and normotensive patients with the following results :-

The incidence of cardiac complications in hypertensive patients with high SUA was 1 (died) out of 5 patients (20 %) while it was 2 (1 died , 1 developed HF) out of 19 hypertensive patients (10.5%) with normal SUA , p value was not significant as shown in table -8-.

The incidence of cardiac complications in normotensive patients with high SUA was 5 (2 died , 3 developed HF) out of 8 patients (62.5 %), while it was 6 (1 died , 5 developed HF) out of 68 normotensive patients (8.8%) with normal SUA , p value was < 0.01 so the incidence of cardiac complications was higher in normotensive patients with high SUA than normotensive patients with normal SUA as shown in table -8-.

The incidence of cardiac complications in hypertensive patients with high SUA was 1 out of 5 patients (20%) , while it was 5 out of 8 patients (62.5 %) in normotensive with high SUA , p value > 0.05   (not significant) .

The effect of thrombolytic therapy on the cardiac complications and SUA was studied with the following results :-

17 patients received thrombolytic therapy no one developed elevation in SUA (0%) , while 13 out of 83 (15.6%) of those not received thrombolytic therapy had high SUA, as shown in table -9- .

The association of SUA and ECG localization of the myocardial infarction was studied with the following results :-

10 patients out of 54 patients (18.5%) with multiple regions MI (anteroseptal , anterolateral and inferolateral MI) had high SUA, as shown in table -10-.

3 patients out of 36 (8.3%) with inferior MI had a high SUA , as shown in table -10 .

10 patients with lateral MI had no elevation in SUA (0%) , as shown in table -10.

Discussion

The result of this study showed that high S.U.A in patient with AMI is associated with poor short term outcome .

High SUA on admission were strongly associated with adverse cardiovascular events including death and HF which was independent of the gender, age , smoking habit and serum lipid concentrations. these findings are in agreement with the Japanese acute coronary syndrome study . [8]

Also in agreement with the Italian cardiovascular study in the elderly [24]which demonstrated that SUA was an important predictor of overall mortality in 2254 elderly men and women ,and other study by fang and alderman [25]which found that high SUA levels were independently and significantly associated with higher risk of cardiovascular mortality and morbidity.

In this study, the predictive value of S.U.A was significant in both smoker and non-smoker patients , this is in agreement with the JACSS [8] and Fang and Alderman [25] . although the predictive value of S.U.A is strongest in smoker patients possibly due to enhanced inflammatory response in AMI and promoting more platelet aggregation [26] and hence more damage and increase in S.U.A .

This study showed that SUA had a good predictive value of adverse cardiac events in patients with high BMI (25 Kg / m^2) which was in agreement with the Japanese acute coronary syndrome study . [8]

Also the study showed that SUA had a good predictive value of adverse cardiac events in patients with normal and high lipid profile.

The predictive value of SUA in hypertensive patients in this study found to be statistically not significant in contrast to Ji-Gaung W. and Jan A. study [27] in older Chinese patients with isolated systolic hypertension (which demonstrate a significant predictive value of S.U.A in hypertensive patients) probably because the sample of hypertensive patients in this study was small, in addition hypertension per se may be associated with increase in SUA [18] .

Under conditions of hypoxia and tissue ischemia , vascular adenosine synthesis and release are up regulated causing significantly increased circulating concentrations [28] cardiac and visceral ischemia promotes generation of adenosine , which may serve as an important regulatory mechanism for restoring blood flow and limiting the ischemia . [29]

Adenosine synthesized locally by vascular smooth muscle in cardiac tissue is rapidly degraded by endothelium to uric acid , which undergoes rapid efflux to the vascular lumen due to low intracellular PH and negative membrane potential . [30]

Xanthine oxidase activity and uric acid synthesis are increased in vivo under ischemic conditions and therefore elevated S.U.A may act as a marker of underlying tissue ischemia . [31]

Hypoxia in human coronary circulation (caused by transient coronary artery occlusion) leads to an increase in the local circulating concentration of uric acid . In conclusion therefore elevated S.U.A may be a marker of local or systemic tissue ischemia and provides one possible explanation for a non-causal associative link between hyperuricemia and cardiovascular disease . [32]

This explain the result of this study in that patients received thrombolytic therapy neither had increase in S.U.A nor developed complications .

Also patients with more extensive disease as evident by ECG localization had more incidence of complication as well as high S.U.A { 18.5 % in anteroseptal , anterolateral and inferolateral MI in contrast to 8.3% in inferior MI , and 0% in lateral MI } .

A failing heart due to AMI may cause tissue hypoperfusion and hypoxia , which trigger xanthine oxidase activation and oxidative stress production .

Xanthine and oxidative stress are reflected by uric acid may form a vicious cycle that promote severe heart failure . [33,34]

Therefore uric acid may not be only a bystander marker but also a causative marker of mortality in patients who have AMI [35] .

The (LIFE) study demonstrated that lowering S.U.A concentrations by losartan was associated with beneficial effect on cardiovascular outcome . [36]

The uric acid lowering effect of atorvastatin may have contributed to the decrease in cardiovascular mortality in(GREACE study) . [37]

It is interesting to note that treatment of chronic heart failure patients with allopurinol (xanthine-oxidase inhibitor) restore endothelial function. [15]

Conclusions and recommendations

1- SUA levels at the time of presentation can predict mortality and development of HF during hospitalization period among Iraqi patients with AMI.

2- It is advised to estimate the SUA level at the time of presentation of all patients presented with AMI , as it is simple and available , for risk stratification .

3- Patients with high SUA at presentation may need more intensive care regarding in-hospital period and the need for coronary angiography and revascularization .

4- Using medications that have uric acid lowering effect in AMI may have a beneficial effect on the mortality and morbidity . However this should be studied on a larger scale trials0020

References

(1) Nicholas A. Boon , Nicki R. colledge , Brain R. walker , Jon A.A. Hunter . Davidson's principles and practice of medicine 20 ed. Churchil livingstone Elsevier. 2006; 581-609 .

(2) Lawerence M.Tierney , Stephen J. Mcphee , Maxine A.Papdaksi . Current Medical Diagnosis and Treatment 43 ed. Lange Medical Books/Mc Graw-Hill.2004.326-328.

(3) Norrapol Wattanasuwan, Ijaz A.Khan, Ramesh M. Gowda ,Balendu C. Vasavada and Terrence J. Sacchi. Effect Of Acute Myocardial Infarction On Cholesterol Ratios. Chest J.2001;120:1196.

(4) Dennis L.Kasper, Eugene Braunwald, Anthong S.Fauci ,Steph L. Hauser,Dan Longo J., Larry Jameson . Harrison's Principles of internal Medicine 16th ed. Mc Graw – Hill ; 2004 , 228:1449-1459.

(5) Alpert JS; Thygesen K; Antman E ,Bassand JP. Myocardial Infarction Redefined, consensus of the Joint European society of cardiology \ American college of cardiology committee for the redefinition of myocardial infarction .Jam coll. cardiol. 2000 ;36 (3) :959-969.

(6) Charles C.J. Carpnter , Robert C. Griggs ,Ivor J. Benjamin. Cecil Essentials of Medicine 7 th ed . SAVOVDERS.2007;9:108.

(7) Roberts R, Kleinman N, Earliest diagnosis and treatment of acute myocardial infarctions necessitates the need for " new diagnostic mind –set ".circulations. 1994;89:872.

(8) Sunao K, Tomohiro S , Masaharu I. Kazuo Kimura,Shunichi Miyazaki, Masakazu Yamagishi , Chuwa Tei , Hisatoyo Hiraoka ,Masahiro Sonoda, Kazufumi T.,Nobuo S.,Tkashi H.,Yasuhiro Ogata,Kunihiko Matsui,Hisao Ogawa. Prognostic Usefulness of Serum Uric Acid After Acute Myocardial Infarction (The Japanese Acute Coronary Syndrome Study). AMJ cardiol. 2005 ; 96: 489-495-

(9) Dobson A, Is raised serum uric acid a cause of cardiovascular disease or death ? Lancet .1999;354:1578

(10)Calberg MJ., Kjoller E,Uric acid as amarker of pathophysiological mechanism in patient with cardiovascular disease .UgeskrLaeger.2005;167:3771-3774.

(11) Emmerson BT . The management of gout . N Engl J Med .1996 ; 334 : 445 -451.

(12) Steele TH; Hyperuricemic nephropathies . Nephron .1999,81:45-49.

(13) Torun M., Yardim S. Simsek B.,Burgaz : Serum Uric Acid in cardiovascular disease. J.Clin Pharm Ther. 1998; 23:25-29.

(14) Skinner KA., White CR, Patel R., Tan S, Barnes S ,Kirk M ,Darley Usmar V ,Parks DA . Nitrosation of uric acid by peroxynitrite : formation of a vasoactive nitricoxide donor . J Biol chem. .1998;273:2491-2497.

(15) Farquharson CAJ, Butter R, Hill A ,Belch JJ, Struther AD : Allopurinol improve endothelial dysfunction in patient with chronic heart failure . Scott Med J.1999;44:24.

(16) Elliott M. Antman , Eugene B. Text book of cardiovascular medicine W.B saunders company , 1997 ; 1208.

(17) Elliott Rapaport , M.D. nomenclature and criteria for diagnosis of ischemic heart disease . American Heart Association 1997.607-609

(18) Dennis L, Eugene Braunwald , Anthony S Fauci ,Steph L. Hauser,Dan Longo J., Larry Jameson. Harrison's Principles of Internal Medicine 16th ed., Mc Grew-Hill , 2004 , 338 : 2309.

(19) Dennis L. , Eugene Braunwald , Anthony S Fauci ,Steph L. Hauser,Dan Longo J., Larry Jameson. Harrison's Principles of Internal Medicine 16th ed. 2004 , 64:422.

(20) Nicholas A. , Nicki R. Colledge , Brain R. walker , Jon A.A. Hunter . Davidson's principles and practice of medicine 20 ed. Churchil livingstone Elsevier 2006 ; 28:1320-1322.

(21) Dennis L.Kasper, Eugene Braunwald, Anthong S.Fauci ,Steph L. Hauser ,Dan Longo J., Larry Jameson Harrison's Principles of Internal Medicine 2004 ; 16 ed : 1371 .

(22) Murray C , Alpert JS , Diagnosis of acute myocardial infarction . Curropin Cardiol . 1994 ; 9 : 465 .

(23) Nicholas A , Nicki R , John A. Davidson's principles and practice of medicine 20 ed. Churchil livingstone Elsevier 2006 ; 1:173 .

(24) Casiglia E , Spolaore P, Ginocchio G et al . predictos of mortality in very old subjects aged 80 years or over , Eur J Epidemiol. 1993;9:577-586.

(25) Fang J , Alderman MH. Serum uric acid and cardiovascular mortality:the NHANESI Epidemiologic follow-up study.JAMA 2000;2404-2410.

(26) Dennis L, Eugene Braunwald , Anthony S .Harrison's principles of internal medicine 16th ed., Mc Grew-Hill , 2004 , 375 : 2574 .

(27) Bengtsson C,Lapidus L,Stendahl C,Waldenstrom J. Hyperuricemia and risk on cardiovascular disease and overall death . Acta Med scand. 1998;224:549-555.

(28) Raatikainen MJ , Peuhkurinen KJ , Hassinen IE : contribution of endothelium and cardiomyocytes to hypoxia-induced adenosine release . J Mol cell cardiol . 1994; 1069-1080.

(29) Fredholm BB , Sollevi A:Cardiovascular effects of adenosine. Clin physio. 1986;6:1-21.

(30) Kroll K, BukowskiTR , Schwatz LM ,Knoepfler D, Bassingthwaighte JB :capillary endothelial transport of uric acid in guinea pig heart . Am J physiol. 1992 ; 262 : 420-431.

(31) Kogure K, Ishizaki M , Nemote M ,Kuwano H, Tatemoto K, Maruyama Y,Ikarashi Y. :Elevation of serum uric acid changes in different form of hepatic vascular inflow occlusion in human liver surgeries . Life Sci.1999; 64 : 305-313.

(32) De Scheerder I, Van Dekraay AM , Lamers JM ,Koster JF,DeJong JW,Serruys PW : Myocardial malondialdehyde and uric acid release after short-lasting coronary occlusion during coronary angioplasty. Am J cardiol. 1991;68:392-395.

(33) Hare JM , Johnson RJ. Uric acid predicts clinical outcome in heart failure : in sights regarding the role of xanthine oxidase and uric acid in disease pathophysiology . circulation 2003 ; 107:1951-1953.

(34) Anker SD, Doehner W, Ranchhans ,Sharma R, Francis D, Kanosalla C, Davos CH : uric acid and survival in chronic heart failure : validation and application in metabolic , functional and hemodynemic staging . circulation 2003;107:1991-1997.

(35) 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 Natt Acad Sci USA , 1992;80:3362-3366.

(36) Hoieggen A, Alderman MH , Kjeldsen SE ,Julius S,De Faire U, Ibsen H , the LIFE study group . The impact of serum uric acid on the cardiovascular outcomes in the LIFE study . kidney Int 2004 ; 65 : 1041-1049 .

(37) Athyros VG , Elisaf M , Papageorgion ,Symeonidis AN,Bouloukos V.I. ,the GREACE study collaborative group. Effect of statine versus untreated dyslipidemia on serum uric acid levels in patients with coronary – heart disease Evaluation (GREACE) study. Am J kidney Dis 2004 ; 43:589-599.