Serum Uric Acid / Creatinine Ratio in Patients with Acute Myocardial Infarction

نسبة حامض اليوريك / الكرياتينين في مصل الدم عند المرضى المصابين باحتشاء العضلة القلبية

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Abstract

Several studies reported that serum creatinine and serum uric acid significantly and independently associated with excess mortality of cardiovascular diseases and stroke.

The present study was done to express the relation of serum creatinine and uric acid to mortality and cardiovascular diseases in Iraqi people.Forty one patients (25 males, 16 females) with AMI admitted to Merjan Teaching Hospital in Hilla city (200٥) clinically diagnosed and fifty two (25 males ,27 females) apparently healthy persons as controls subject to present study Serum creatinine was determined calorimetrically according to the reaction with basic picrate solution, whereas uric acid was determined enzymatically using uricase method. Results of present study show significant increase in the levels of serum creatinine and uric acid of patients with AMI when compared with healthy controls($P<0.05$). Whereas serum uric acid/ creatinine (UA/Cr) ratio of patients with AMI found to be significantly decreased when compared with healthy controls($P<0.05$). The relationship between serum uric acid and creatinine was negative correlation in patients, whereas this relationship found to be positive in healthy controls.In conclusion, serum UA/Cr ratio, serum creatinine and serum uric acid in Iraqi people patients with acute myocardial infarction AMI, may aid in the prediction of mortality of cardiovascular diseases.

الخلاصة

بينت العديد من الدراسات بأن كرياتينين المصل، وحامض اليوريك في المصل مرتبط بشكل معنوي وبشكل مستقل بالموت من جراء الإصابة بإمراض الأوعية القلبية والجلطات. صممت هذه الدراسة للتقصي عن علاقة كرياتينين المصل وحامض اليوريك في المصل بالإصابة بإمراض الأوعية القلبية.أجريت الدراسة عام٢٠٠٥ على المرضى الداخلين لمستشفى مرجان التخصصي في مدينة الحلة والمشخّصين سريريا بأنهم يعانون من احتشاء العضلة القلبية وشملت الدراسة واحد وأربعون مريضا (٢٥ ذكر، ١٦ أنثى) واثنان وخمسون (٢٥ ذكر، ٢٧ أنثى) شخصا سليما ظاهريا كمجموعة سيطرة .تم تقدير كرياتينين مصل الدم لونيا اعتمادا على التفاعل مع محلول البكرات ، بينما قدر حامض اليوريك في مصل الدم إنزيميا باستخدام طريقة إنزيم اليوريكيز.بينت نتائج هذه الدراسة وجود زيادة معنوية($P<0.05$) في مستويات كرياتينين المصل وحامض اليوريك عند المرضى المصابون باحتشاء العضلة القلبية عند المقارنة بمجاميع السيطرة . بينما انخفضت نسبة وحامض اليوريك /الكرياتينين معنويا($P<0.05$) عندما قورنت بمجاميع السيطرة. وكان الارتباط بين حامض اليوريك والكرياتينين سلبيا في المرضى، بينما كان هذا الارتباط إيجابيا في مجاميع السيطرة. نستنتج من نتائج الدراسة بان نسبة حامض اليوريك في مصل الدم/ كرياتينين مصل الدم ، وان حامض اليوريك و كرياتينين مصل الدم من الممكن إن تساعد كأداة تكهنية عند المرضى العراقيين المصابين باحتشاء العضلة القلبية .

Introduction

Coronary artery disease remains the most common cause of death regardless of significant advancements in its prevention and treatment.[1] Each year 900 000 individuals in the United States experience acute myocardial infarction (AMI). Of these, roughly 225000 die, including 125 000 who die ‘‘in the field’’ before obtaining medical care.[2]

Myocardial infarction (MI) can be defined from a number of different perspectives related to clinical, electrocardiographic ,biochemical and pathologic characteristics.[3] It is accepted that the term MI reflects death of cardiac myocytes caused by prolonged ischemia.[4]

An acute coronary syndrome is nearly always caused by a sudden reduction in coronary blood flow caused by atherosclerosis with thrombosis superimposed, with or without concomitant vasoconstriction .[5] MI occurs when an atherosclerotic plaque slowly builds up in the inner lining of a coronary artery and then suddenly ruptures, totally occluding the artery and preventing blood flow downstream.[6]

Aggressive management of the risk factors is one of the crucial elements in the treatment of patients with coronary artery disease. [7]

Several serum markers are used to aid in the diagnosis and prediction of AMI such as creatine kinase-MB (CK-MB), cardiac specific troponin T (cTnT) and I (cTnI), lactate dehydrogenase (LDH), glutamate oxaloacetate transaminase (GOT) and myoglobin. [2,4]

Serum creatinine is the most widely used and commonly accepted measure of renal function in clinical medicine.[8] The concentration of creatinine in serum is associated with all-cause mortality or stroke in middle-aged and elderly people and in patients with insulin-dependent diabetes or previous cardiovascular disorders.[9-11] Similarly, several studies have shown that the serum concentration of uric acid predicts mortality, cardiovascular events, or stroke. [9,12-14]

The positive association between serum uric acid and cardiovascular diseases such as stroke or ischemic heart disease has been recognized since the 1950s and has been confirmed by numerous epidemiological studies since then. [12]Although serum uric acid levels were significantly correlated with the risk for cardiovascular events and mortality in women, this relationship became insignificant after allowing for additional variables, including hypertension, body mass index, and diuretic use.[14]

Although the overnight increase in urinary uric acid/creatinine ratio (UA/Cr) is considered by some to be a marker of tissue hypoxia in patients with obstructive sleep apnea-hypopnea syndrome (OSAS), this index is not universally accepted.[15]

The purpose of this study was to confirm the validity of UA/Cr ratio as a risk factor of AMI by measuring the serum level of creatinine and uric acid.

The hypothesis that serum creatinine and uric acid may be predictors of mortality for cardiovascular disease has, to the best of our knowledge, never been tested in the Iraqi population.

Patients and Methods

Forty one patients (25 males, 16 females) with AMI admitted to Merjan Teaching Hospital in Hilla city (200°) clinically diagnosed and fifty two (25 males ,27 females) apparently healthy persons as controls subject to present study. The mean age of patient

males were (51.35 ± 21.45 years) and (52 ± 9.91 years) for patients females, whereas those of healthy persons were (52 ± 12.3 years) for males and (50.32 ± 12.1 years) for females.

Twenty of male patients and nine of female patients subject to present study suffering of hypertension. Also, twelve male patients and five of female patients are smokers.

Uric acid was determined enzymatically using Biomaghreb kit (Morocco). In which uric acid is oxidized by uricase to allantoine and H_2O_2 ,the later react with 4-aminophenazone in presence of peroxydase to form colored quinoneimine.

Creatinine was determined using Spinreact kit (Spain),depending upon Jaffe's method .According to Jaffe's method, creatinine in basic picrate solution forms a colored complex, which were measured colorimetrically.

Statistical Analysis

All values were expressed as mean ± standard deviation (SD) . Student's t-test was used to estimate differences between the groups and differences were considered significant when the probability was ($p < 0.05$).

Results

Serum creatinine and serum uric acid of patients with AMI in the present study found to be significantly ($P<0.05$) increased when compared with healthy controls as shown in Table 1.

Table 1 Serum creatinine, uric acid and UA/Cr ratio of patients with AMI and healthy controls

	Control		AMI	
	Male	Female	Male	Female
Creatinine (mg/dL)	0.736	0.674	4.86	3.966
±SD	0.125	0.08	3.98	1.98
Uric acid (mg/dL)	5.28	5.11	6.59	6.36
±SD	0.55	0.507	1.57	1.17
UA / Cr ratio	7.17	7.587	2.09	1.6
±SD	4.42	5.9	0.39	0.589

As shown in Table 1, there is an increase in creatinine levels in male patients with AMI nearly six folds than healthy controls, while female patients had expressed an increase in creatinine levels in 5.8 folds than healthy controls. On the other hands uric acid levels in male patients, there was increase of 1.13 mg/dL than controls ,while female patients had an increase of 1.25 mg/dL than controls.

UA/Cr ratio in male patients with AMI was less than UA/Cr ratio in female patients due to excessive increase of creatinine levels in male patients more than female patients. Whereas serum UA/Cr ratio of patients with AMI found to be significantly ($P<0.05$) decreased when compared with healthy controls.

The correlation between serum uric acid and serum creatinine was studied by plotting one against other and shows negative correlation in patients with AMI, whereas this correlation found to be positive in healthy controls, as shown in Figures 1,2,3, and4.

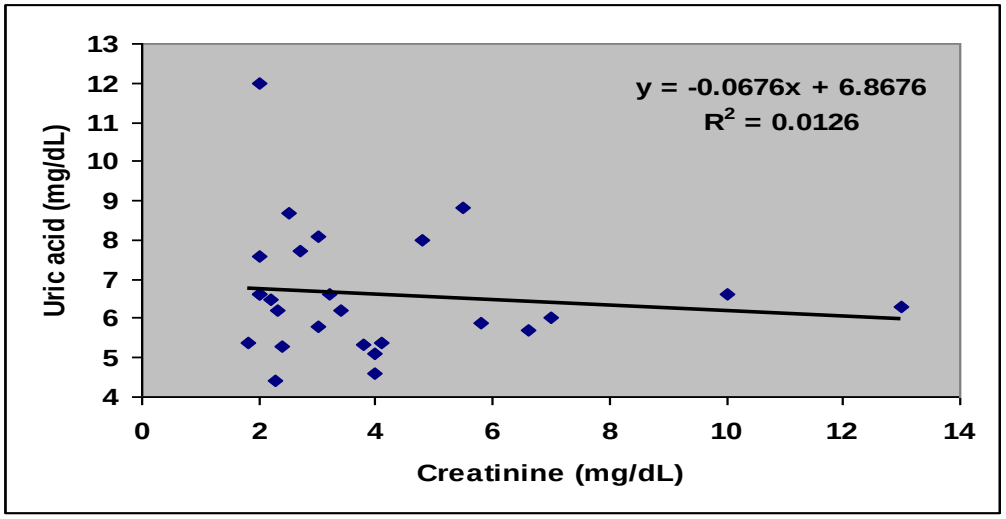

Figure 1 The correlation between serum uric acid and creatinine in male patients with AMI

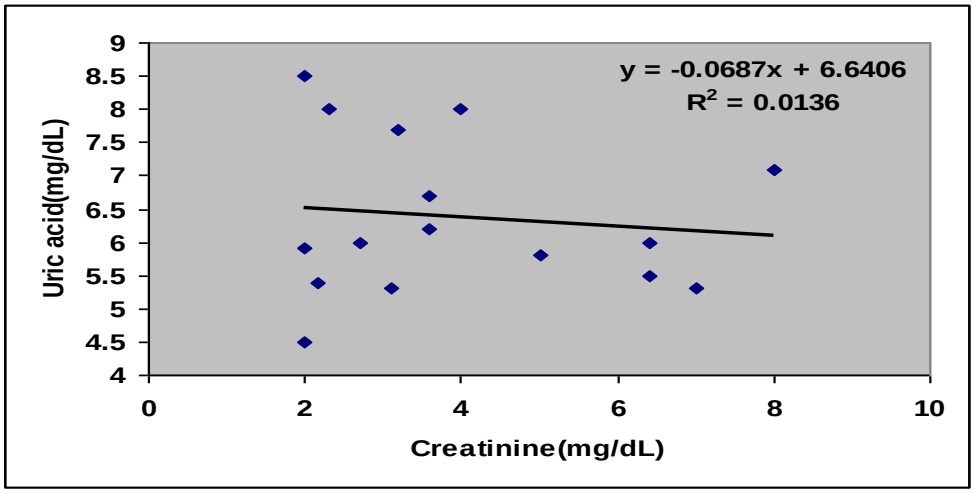

Figure 2 The correlation between serum uric acid and creatinine in female patients with AMI

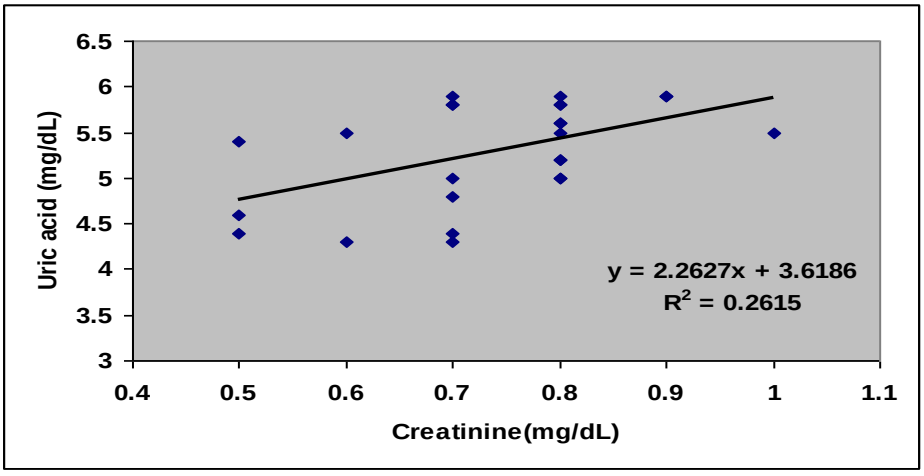

Figure 3 The correlation between serum uric acid and creatinine in healthy males

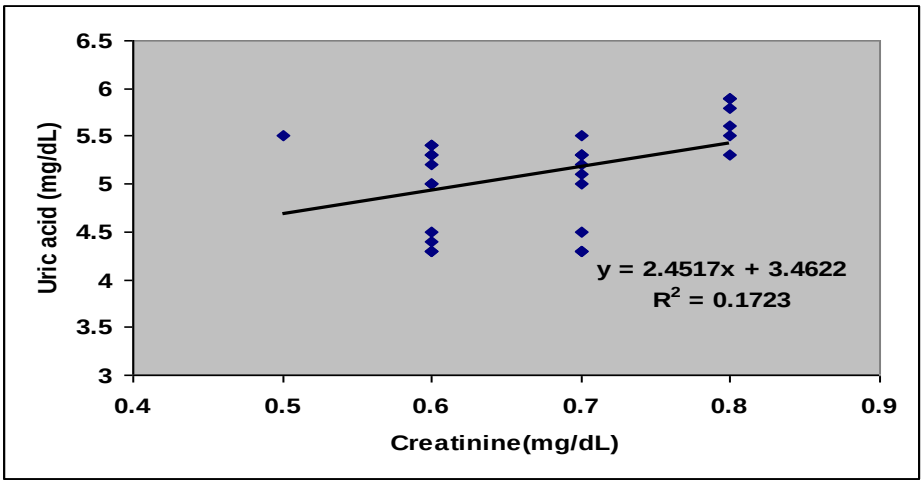

Figure 4 The correlation between serum uric acid and creatinine in healthy females

Usually the results of males found to be higher than those of females, except those of serum UA/Cr ratio.

Discussion

Numerous studies have demonstrated that the prognosis of a variety of diseases is worsened by the concomitant existence of renal dysfunction[16-18]. generally, multivariate analyses of groups of patients with diabetes, congestive heart failure, MI and hypertension will nearly always include renal function as an independent predictor of mortality and morbidity[19,20].

Such analyses are complicated by the fact that a number of diseases are also predictors of reduced renal function. Therefore, it is unclear whether renal dysfunction is a risk factor per se, or whether it is merely a marker of diseases associated with renal dysfunction. If the association between renal dysfunction and mortality were direct, it could indicate that measures of renal function were a sensitive estimator of cardiovascular risk.[21]

Because of the potential importance, current study have analyzed some marker of diseases associated with renal dysfunction in patients with MI.

Usually, UA/Cr ratios were calculated to adjust for kidney function. [22-24] A study carry out on patients after acute stroke had reveals that patients with reduced admission calculated creatinine clearance, raised serum creatinine and urea concentrations ,and raised ratio of urea to creatinine had a higher mortality risk. This finding may be used to stratify risk and target interventions.[25]

A study have been done in UK and shown that a high serum creatinine concentration within the normal range is a marker for increased risk of cerebrovascular disease in both normotensive and hypertensive subjects. These findings support the evidence indicating that subtle impairment of renal function is a factor for increased risk of stroke and suggest mechanisms in the pathogenesis of stroke that warrant further investigation.[11]

Another study was carry out in Nigeria on lead workers shown that serum creatinine level did not differ significantly between lead workers and controls in Nigerians lead workers, and serum uric acid level was significantly higher in lead workers than in controls [26]

In population-based study carry out in Finland, in which the cardiovascular risk factors were determined in patients with non insulin dependant diabetes mellitus (NIDDM), In

this study, men with high uric acid level had higher levels of serum creatinine and total triglycerides and lower levels of HDL cholesterol, and plasma glucose than men with low levels. Whereas, women with high uric acid levels had higher serum creatinine and total triglyceride levels as well as lower LDL cholesterol, and plasma glucose levels than those with low uric acid levels[27]

Numerous studies have been reported that UA/Cr ratio can be used in the diagnosis of perinatal asphyxia, staging of Hypoxic-ischemic encephalopathy (HIE), and determination of the prognosis. Due to the lack of adequate oxygen supply during asphyxia, the formation of ATP is impaired and this leads to an accumulation of ADP and AMP, which are then catabolized to adenosine, inosine, and hypoxanthine.In cases of continuing tissue hypoxia, hypoxanthine is oxidized to xanthine and uric acid in the presence of xanthine oxidase; this leads to an increase in the urinary excretion of uric acid. In the reoxygenation period, radicals are produced parallel to uric acid formation, which may be linked to the severity of perinatal asphyxia[28]

The results of present study agreed with those of previous studies in the case of uric acid [22,26] and creatinine [25,27], in which the levels of uric acid and creatinine were increase. While the disagreement was with those studies that found high ratio of UA/Cr.[28]

In the present study, serum creatinine of patients with AMI found to be highly and significantly ($P<0.05$) increased when compared with healthy controls (Table 1). Also, serum uric acid of patients with AMI found to be significantly ($P<0.05$) increased when compared with healthy controls, resulting a decrement in the ratio of UA/Cr. In other studies, uric acid was increased but creatinine was not elevated enough to reflect the UA/Cr ratio like present study.

The relationship between serum uric acid and serum creatinine shows negative correlation in patients with AMI, whereas this relationship found to be positive in healthy controls.

Uric acid, a product of purine metabolism, is degraded in most mammals by the hepatic enzyme, urate oxidase (uricase), to allantoin, which is freely excreted in the urine.[29] However, during the Miocene epoch (20 to 5 million years ago), two parallel but distinct mutations occurred in early hominoids that rendered the uricase gene nonfunctional. As a consequence, humans and the great apes have higher uric acid levels compared with most mammals.[30]

Uric acid levels also vary significantly within humans as the result of factors that increase generation (such as high purine or protein diets, alcohol consumption, conditions with high cell turnover, or enzymatic defects in purine metabolism) or decrease excretion. A reduction in glomerular filtration rate (GFR) increases serum uric acid, although a significant compensatory increase in gastrointestinal excretion occurs.[31] Hyperuricemia also may result from increased net tubular absorption. After filtration, uric acid undergoes both reabsorption and secretion in the proximal tubule, and this process is mediated by a urate/anion exchanger and a voltagesensitive urate channel.[32,33]

Uric acid is also commonly associated with hypertension. The increase in serum uric acid in hypertension may be due to the decrease in renal blood flow that accompanies the hypertensive state, since a low renal blood flow will stimulate urate (the soluble form of uric acid in the blood) reabsorption.[34]

Hypertension also results in microvascular disease, and this can lead to local tissue ischemia.[35] In addition to the release of lactate that blocks urate secretion in the proximal tubule, ischemia also results in increased uric acid synthesis.[36] With ischemia, ATP is degraded to adenine and xanthine, and there is also increased generation of xanthine oxidase. The increased availability of substrate (xanthine) and enzyme (xanthine oxidase) results in increased uric acid generation as well as oxidant (O_2^-) formation. The finding that ischemia results in an increase in uric acid levels may also account for why uric acid is increased in preeclampsia and congestive heart failure. Other factors may also contribute to why uric acid is associated with hypertension, including alcohol abuse, lead intoxication, obesity and insulin resistance, and diuretic use.[29]

An important observation was that uric acid may function as an antioxidant, and possibly one of the most important antioxidants in plasma. Urate can scavenge superoxide, hydroxyl radical, and singlet oxygen and can chelate transition metals.[37]

Peroxynitrite is a particularly toxic product formed by the reaction of superoxide anion with nitric oxide that can injure cells by nitrosylating the tyrosine residues (nitrotyrosine formation) of proteins. Uric acid can also block this reaction.[38]

As mentioned before, uric acid is one of the major endogenous water-soluble antioxidants of the body.[39] There is accumulating evidence that increased oxidative stress is closely related to diabetes and its vascular complications.[40] Thus, high circulating uric acid levels may be an indicator that the body is trying to protect itself from the deleterious effects of free radicals by increasing the products of endogenous antioxidants. Interestingly, uric acid prevents oxidative modification of endothelial enzymes and preserves the ability of endothelium to mediate vascular dilatation in the face of oxidative stress.[39] There is also some evidence that uric acid may have a direct role in the atherosclerotic process, because human atherosclerotic plaque contains more uric acid than do control arteries.[41]

In this study, significant elevation in serum creatinine concentration was noted when compared with healthy subjects. This finding is similar to those of the Hypertension Detection and Follow-up Program, in which a significantly increased risk of all cause, cardiovascular, cerebrovascular, and noncardiovascular mortality was observed in the top 3% of the creatinine distribution; no association was seen with cancer mortality.[42] The authors suggested that the "elevated creatinine represents the influence of generalized vascular disease in the kidney." This was also suggested in a prospective study in New Zealand, which found serum creatinine to be a strong and independent predictor of survival after stroke in the elderly.[43] In a study of survivors of myocardial infarction, serum creatinine was independently associated with all-cause and coronary heart disease mortality.[44] No significant association was found between serum creatinine and the severity of coronary heart disease or peripheral vascular disease, suggesting that a higher creatinine level was not simply a manifestation of generalized atherosclerosis.[11]

Creatinine is a breakdown product of creatine phosphate (substrate of CK) in muscle, and is usually produced at a fairly constant rate by the body (depending on muscle mass).[45]

This may explain why elevation in serum creatinine occured in patients with AMI in the presence of high levels of CK (one of most known serum markers of AMI) due to infarct cardiac muscle.[2,4]

In conclusion, serum UA/Cr ratio, serum creatinine and serum uric acid in Iraqi people patients with AMI, may aid in the prediction of mortality of cardiovascular diseases.

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