

The relationship between coronary artery disease and uric acid levels in young patients with acute myocardial infarction

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Abstract

Background: Serum uric acid concentrations are higher in patients with established coronary artery disease than in healthy controls. This study aimed to determine the role of uric acid in predetermining coronary artery disease in young patients with acute myocardial infarction (AMI).

Methods: This study included 80 of 1612 patients who applied our hospital between January 2000 and December 2005. All of the patients were under 35 years old, diagnosed with AMI by clinical and laboratory findings, and had coronary angiography. The study population was divided into two groups, the first having critical coronary artery disease (group I) and the second having normal coronary arteries (group II). Then we compared these groups with age, body mass index, risk factors, serum protein C, protein S, antithrombin III, creatinine and uric acid levels.

Results: Myocardial infarction was located in 65% anterior, 15% inferior, 15% inferolateral and 5% high lateral, respectively. Forty five % of patients had critical coronary artery disease (group I, $n = 36$) and 55% had normal coronary arteries (group II, $n = 44$). There were no differences in the two groups with regard to body mass index, family history, hypertension, smoking, cholesterol level, triglyceride level and creatinine level, lack of protein C, lack of protein S or lack of antithrombin III. Serum uric acid levels were found to be higher in group I (7.0 ± 1.4 mg/dL) than in group II (4.9 ± 1.1 mg/dL; $p = 0.003$).

Conclusions: This study showed that high serum uric acid levels were associated with critical coronary artery disease in young patients (< 35 years) with AMI (Cardiol J 2008; 15: 21–25)

Key words: acute myocardial infarction, young patients, uric acid, coronary artery disease

Introduction

Acute myocardial infarction (AMI) is an irreversible myocardial injury and necrosis caused by serious and long-term ischemia. AMI is generally

seen in middle-aged people with high risk factors for coronary artery disease. It is difficult to determine the real rate in the younger age population but it is known that it is less common and only 5% of AMI patients are less than 40 years old [1].

Coronary anatomy is normal in 30% of young AMI patients [2]. The presence of normal coronary anatomy is related to coronary vasospasm, embolism from endocardium or heart vessels, platelet aggregation or spontaneous lysis of thrombus [3]. Due to the high rate of normal coronary angiography

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in young patients, it is necessary to evaluate some parameters for the early prediction of coronary artery disease. Therefore, we aimed to evaluate the relationship between coronary anatomy and risk factors, clinical properties, serum uric acid (UA), protein C, protein S and antithrombin III (AT III) levels to determine coronary artery disease predictors in AMI patients less than 35 years of age.

Methods

Patient population

This study included 80 of 1612 patients who applied our hospital between January 2000 and December 2005. These 80 patients were less than 35 years old, diagnosed as AMI with clinical and laboratory findings, and had coronary angiography. Oral informed consent was obtained from all subjects. All patients were admitted within 12 h after the onset of AMI. Diagnosis of AMI was established by ST segment elevation, defined subsequently in more than two leads, associated with typical chest pain and confirmed by an elevation of serum creatine kinase MB isoenzyme greater than two times the normal upper limit during the patient's clinical course. Thrombolytic treatment was applied to all patients. Cardiac catheterization was performed after the patient's clinical status was stabilized on the fifth or sixth day of hospitalization. Coronary angiograms were evaluated by two experienced angiographers (E.T., M.A.) blinded to the characteristics of the patients.

The study protocol was approved by the local ethical committee and informed consent was obtained from each patient.

Cardiac catheterization

Coronary angiography is performed with a Philips Multidiagnosis C2 (Philips, Eindhoven, Netherlands) device by using 'Sones' or 'Jutkins' techniques. Obstruction greater than 50% in coronary vessels was accepted as critical coronary artery disease. Left ventriculography was performed using standard techniques. The study patients were divided into two groups, the first having critical coronary artery disease (group I) and the second having normal coronary arteries (group II), according to their coronary angiographies.

Analysis of hematological profile

Blood samples were taken as soon as patients were admitted to hospital, and the samples were immediately analyzed. Quantitative measurements of protein C and AT III were performed by colorimetric assay using coamatic protein C from Chromogenix (Mölnådal, Sweden), Stachrom AT III automated, and Stachrom PLG (Diagnostica Stoga, Asnieres, France), respectively. Quantitative determination of functional protein S, based on the inhibition of factor Va, was established using a clotting assay of protein S (Stacloot protein S, Diagnostica Stage).

Analysis of serum uric acid levels and other laboratory data

Serum UA levels of patients were measured with a Technicon SMA 12/60 autoanalyser (Technicon Instruments, Tarrytown, New York, USA) device by spectrophotometric method.

Standard clinical chemistry techniques were used to measure creatinine, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglyceride levels. We evaluated the presence of hypertension (systolic blood pressure; 140 mm Hg and/or diastolic blood pressure; 95 mm Hg and/or receiving antihypertensive agents).

Groups were compared in terms of hypertension, cholesterol level, triglyceride level, creatinine level, smoking, family history, age, body mass index, serum UA, protein C, protein S and AT III levels.

Statistical analysis

Quantitative values are expressed as mean \pm SD and were compared using Mann Whitney U test. The χ^2 test, Fisher's exact test and logistic regression analysis were used for analysis of categorical data. For all tests, $p > 0.05$ was designated non-significant, and a value of $p < 0.05$ was considered statistically significant. The SPSS statistical software package (version 10.0) was used to perform all statistical calculations.

Results

All of the patients were male with an average age of 30.2 ± 4.8 years. Smoking, family history, hypertension were in 95%, 20%, 15% of patients, respectively. None of the patients had diabetes mellitus. AMI was localized in 65% anterior, 15% inferior, 15% inferolateral and 5% high lateral. According to the coronary angiography, 55% had normal coronary arteries (group II, $n = 44$) and 45% had critical coronary artery disease (group I, $n = 36$). In group I, 20 patients had one, 12 had two and 4 had three vessel diseases. There were no differences in the two groups regarding body mass index, family history, hypertension, smoking, total cholesterol, HDL and LDL levels, triglyceride level, creatinine level, lack of protein C, lack of protein S

Table 1. Parameters of study groups (mean \pm SD).

| Clinical characteristics | Group I (n = 36) | Group II (n = 44) | p |
|--------------------------------------|------------------|-------------------|-------|
| Age (years) | 32.7 \pm 1.7 | 28.1 \pm 5.6 | 0.120 |
| Body mass index [kg/m ²] | 28.01 \pm 4.1 | 28.34 \pm 4.0 | 0.650 |
| Family history | 8 (22%) | 8 (18%) | 0.320 |
| Smoking | 36 (100%) | 40 (90%) | 0.200 |
| Hypertension | 8 (22%) | 4 (9%) | 0.300 |
| Total cholesterol [mg/dL] | 196 \pm 48 | 180 \pm 32 | 0.780 |
| LDL cholesterol [mg/dL] | 133 \pm 42 | 142 \pm 43 | 0.220 |
| HDL cholesterol [mg/dL] | 39 \pm 12 | 38 \pm 18 | 0.235 |
| Triglycerides [mg/dL] | 117 \pm 62 | 108 \pm 59 | 0.440 |
| Creatinine [mg/dL] | 1.0 \pm 0.2 | 1.0 \pm 0.1 | 0.700 |

HDL — high-density lipoprotein, LDL — low-density lipoprotein

Table 2. Hematological parameters and uric acid levels of study groups (mean \pm SD).

| Variables | Group I (n = 36) | Group II (n = 44) | p |
|--------------------------|------------------|-------------------|-------|
| Uric acid [mg/dL] | 7.0 \pm 1.4 | 4.9 \pm 1.1 | 0.003 |
| Lack of protein C | 8 (22%) | 4 (9%) | 0.300 |
| Lack of protein S | 4 (11%) | 4 (9%) | 0.600 |
| Lack of antithrombin III | 2 (6%) | 4 (9%) | 0.220 |

and lack of AT III ($p > 0.05$). Serum UA levels were found to be higher in group I (7.0 \pm 1.4 mg/dL) than in group II (4.9 \pm 1.1 mg/dL; $p = 0.003$). The groups were compared regarding hematological parameters and clinical properties as shown in Tables 1 and 2.

Discussion

This study showed that high serum UA levels were related to critical coronary artery disease in young patients with AMI. Roskamm et al. [3] showed that the presence of normal coronary anatomy in young AMI patients is 17–30%. Normal coronary arteries, after AMI, are related to coronary vasospasm, embolus arising from endocardium or heart vessels, platelet aggregation or spontaneous lysis of thrombus [2]. Smoking is the most common risk factor in AMI patients with normal coronary anatomy. It impairs endothelium derived vasodilation mechanisms and vasospasm in coronary arteries [4, 5]. Vasospasm is supposed to be the most important physiopathological mechanism in these patients [6, 7]. Hypercoagulopathy and fibrinolytic system defects are also in the etiology. A lack of protein S is responsible these effects [8]. Protein S

is an endothelial derived protein C co-factor, and these two proteins are coagulation inhibitors. Lack of AT III and high levels of plasminogen activator inhibitor-1 may sometimes also be a reason [9]. In a study comparing young AMI patients and normal healthy patients, there were no significant differences in protein C, protein S and AT III levels between coronary artery lesion group, normal coronary artery group and a normal healthy group [10]. We studied these hematological risk factors in our study, but we could not find any significant difference in protein C, S and AT III levels between two groups either.

In men, serum UA concentrations rise during puberty from childhood mean values of 3.5 mg/dL to adult levels of 4.0 \pm 2.0 mg/dL. Hyperuricemia is defined as a serum UA level greater than 7.0 mg/dL, as measured by the automated enzymatic (uricase) method [11, 12].

Over recent years there has been renewed debate concerning the nature of the association between raised serum UA concentrations and cardiovascular disease (CVD). Several large studies have identified the value of serum UA concentrations in young populations in predicting the risk of CVD, such as AMI [13, 14]. Torun et al. [15] showed that serum UA concentrations were higher in patients with established coronary artery disease compared with healthy controls. We were also shown that serum UA levels are higher in young patients (< 35 years) with established critical coronary artery disease. Multivariate analysis of data from the MONICA cohort of 1044 males showed a significant association between raised serum UA and cardiovascular mortality, independent of body mass index, serum cholesterol concentration, hypertension, diuretic use, alcohol intake and smoking

habit [16]. A retrospective analysis of the NHANES data [17] followed 5 926 patients for an average of 16.4 years and found that increased serum UA levels were independently and significantly associated with cardiovascular mortality in both men and women. These findings suggest a relationship between high serum UA levels and coronary artery disease, although the underlying mechanisms remain unclear.

Nitric oxide, which is known to be a potent vasodilator, is important for maintaining vascular tone. Synthesis of nitric oxide is disrupted and its degradation is accelerated by excessive free radical activity. This condition disrupts functions of endothelium dependent vasodilatation; a condition known as endothelial dysfunction. Endothelial dysfunction is the first step for the beginning of atherosclerosis [18]. Thus, increased oxidative stress appears to play an important role in the development and progression of atherosclerosis [19]. Serum UA has antioxidant properties and contributes to free radical scavenging activity in human serum. When uric acid interacts with peroxynitrite to form a stable nitric oxide donor, vasodilatation increases and the potential for peroxynitrite-induced oxidative damage decreases [20]. Thus, UA can be protective against oxidative stresses, but it can also lead directly or indirectly to vascular injury.

Ishizaka et al. [21] showed that the association between serum UA and high brachial-ankle pulse wave velocity was at least in part independent of conventional risk factors for atherosclerosis. What is the possible underlying mechanism that links hyperuricemia and arterial stiffening? It has been reported that UA promotes vascular smooth muscle proliferation and upregulates the expression of platelet-derived growth factor and monocyte chemoattractant protein-1 [22]. Hypoxanthine is converted to uric acid via xanthine. This reaction can be catalyzed by xanthine hydrogenase and xanthine oxidase, the latter of which produces uric acid and superoxide.

Thus, it is possible that, in certain diseased conditions, hyperuricemia is accompanied by the increased production of reactive oxygen species, which may result in the modulation of vascular contractility [23]. Consistent with this is the notion that allopurinol, a xanthine oxidase inhibitor, not only reduces the serum UA levels but also improves vascular endothelial function in patients with chronic heart failure [24]. Another possible explanation is that hyperuricemia may induce endothelial dysfunction by decreasing the production of nitric oxide in the vascular endothelial cells [25].

Adenosine synthesized locally by vascular smooth muscle in cardiac tissue is rapidly degraded by the endothelium to UA, which undergoes rapid efflux to the vascular lumen due to low intracellular PH and negative membrane potential [26]. Uric acid synthesis is increased *in vivo* under ischemic conditions, and therefore elevated serum UA may act as a marker of underlying tissue ischemia. In human coronary circulation, hypoxia, caused by transient coronary artery occlusion, leads to an increase in the local circulating concentration of UA [27]. In conclusion, elevated serum UA may be a marker of local and systemic tissue ischemia and provides one possible explanation for a non-causal associative link between hyperuricemia and cardiovascular disease.

Conclusions

In conclusion, high serum UA levels are associated with critical coronary artery disease in young patients (< 35 years) with AMI. Nevertheless, this finding should be supported by research that is more extensive in order to put it into practice.

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