Impact of sex on uric acid levels and its relationship with the extent of coronary artery disease: A single-centre study

Lucia Barbieri [a], Monica Verdoia [a], Alon Schaffer [a], Paolo Marino [a], Harry Suryapranata [b], Giuseppe De Luca [a, *], on behalf of the Novara Atherosclerosis Study Group (NAS)

[a] Division of Cardiology, Eastern Piedmont University, Novara, Italy
[b] Department of Cardiology, UMC St Radboud, Nijmegen, HS, The Netherlands

A B S T R A C T

Background: Serum uric acid (SUA) elevation has been largely addressed in the past as a possible risk factor for cardiovascular disease. However, uric acid has not clearly emerged as independent risk factor for coronary artery disease. Several studies in literature have assessed sex-related differences in the association between elevated SUA levels and cardiovascular events with conflicting results. Therefore, aim of the current study was to evaluate the relationship between uric acid levels and the extent of coronary artery disease in male and female patients undergoing coronary angiography.

Methods: Our population is represented by 3520 consecutive patients undergoing coronary angiography from March 2007 to October 2012. Patients were divided according to Tertiles of SUA (Males, Group 1, $\leq$5.5 mg/dL—0.33 mmol/mol, n = 762, Group 2, 5.5—6.8 mg/dL—0.33—0.40 mmol/mol, n = 829 and Group 3 $\geq$6.8 mg/dL—0.40 mmol/mol, n = 851), (Females, Group 1, $\leq$4.8 mg/dL—0.28 mmol/mol, n = 349, Group 2, 4.8—6.3 mg/dL—0.28—0.37 mmol/mol, n = 359 and Group 3 $\geq$ 6.3 mg/dL—0.37 mmol/mol, n = 370). Fasting samples were collected for uric acid levels assessment. Coronary disease was defined for at least 1 vessel stenosis >50% as evaluated by QCA. Severe coronary disease was defined as three-vessel disease and/or left main disease.

Results: Among 3520 patients, we identified 2442 men (69.4%) and 1078 women (30.6%). Males had higher levels of uric acid than women (6.33 ± 1.7 vs 5.8 ± 1.9 − p < 0.001). The association between elevated uric acid ($\geq$7 mg/dl or 0.42 mmol/l) and male gender was confirmed after correction for baseline confounding factors (Adjusted OR = 1.28 [1.01—1.62], p = 0.004). Males displayed a significantly higher prevalence and extent of CAD (p < 0.001) and more complex coronary lesions (p < 0.001). However, no significant relationship was observed between uric acid and CAD (Adjusted OR [95% CI] = 0.90 [0.76—1.06], p = 0.22) or severe CAD (Adjusted OR [95%CI] = 0.89 [0.79—1.01], p = 0.08). Among females, higher SUA levels were significantly associated with higher prevalence of severe CAD (p < 0.001) (Adjusted OR [95% CI] = 1.29 [1.03—1.62], p = 0.03).

Conclusion: Our study showed that uric acid levels are significantly higher in men. However, high uric acid levels are associated with severe CAD only in women. Future large studies are certainly needed to confirm our findings and to evaluate the effects of SUA lowering therapies on cardiovascular prevention and outcome, especially in women.

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1. Introduction

Coronary artery disease (CAD) still represents the leading cause of death in developed countries [1,2]. The improvement in pharmacological therapies and percutaneous revascularization procedures have greatly contributed to the relevant reduction in mortality observed in the last decades for coronary artery disease, particularly in the setting of acute myocardial infarction [3—5], however, the results are still unsatisfactory in high-risk subgroups such as patients with diabetes or with impaired renal function [6,7]. Therefore, large interests have been focused on the identification of new risk factors for CAD and its prevention.

Serum uric acid (SUA), a degradation metabolite of purines, has been addressed in the past as a possible risk factor for cardiovascular disease [8,9] on the basis that hyperuricemia could induce atherosclerosis progression increasing oxidative stress and endothelial dysfunction [10,11]. However, in the last decades several studies have assessed the role of SUA as a risk factor for CAD with conflicting results. We previously found no association between uric acid and the extent of CAD [12]. However, even though it is well known that SUA levels are lower in women than in men [13], some, but not all studies, have reported an association between SUA, cardiovascular events and CAD related mortality only in women. Plausible explanation for such a mechanism is still lacking [14,15].

Therefore, aim of the current study was to evaluate the relationship between uric acid levels and the extent of coronary artery disease in male and female patients undergoing coronary angiography.

2. Methods

Our population is represented by 3520 consecutive patients undergoing coronary angiography at Catheterization Laboratory of AOU "Maggiore della Carità", Novara, from March 2007 to October 2012.

All demographic and clinical data were collected after obtaining written informed consent from the patient and included in a dedicated database, in adherence to rules for protection of human subjects. No exclusion criteria were applied. Hypertension was defined as systolic pressure >140 mmHg and/or diastolic pressure >90 mmHg or if the individual was taking an antihypertensive medication. The diagnosis of diabetes was based on previous history of diabetes treated with or without drug therapies, fasting glycaemia >126 mg/dL, random glycaemia >200 mg/dL or HbA1c > 6.5%. ACS was defined as an elevation of cardiac biomarkers beyond the upper limit of normal (ULN) (respectively 0.04 μg/l for Troponin I and 5.00 μg/l for CK-MB) due to angiographically documented critical coronary stenosis (>70%). Hyperuricemia was defined as SUA levels >7 mg/dL or 0.42 mmol/mol.

2.1. Biochemical measurements

Blood samples were drawn at admission in patients undergoing elective (following a fasting period of 12 h) or urgent coronary angiography. Glucose, creatinine, uric acid, blood cells count and lipid profile were determined by standard methods. Cardiac biomerakers (Troponin I and CK-MB) were assessed by sandwich immunoassay with direct chemiluminescence.

2.2. Coronary angiography

Coronary angiography was routinely performed, preferring a radial approach, using 6-French right and left heart catheters. Quantitative coronary angiography was performed by experienced interventional cardiologists by automatic edge-detection systems (Siemens Acom Quantcor QCA, Erlangen, Germany) as previously described [16]. After the visual inspection of the coronary artery, the frame of optimal clarity was selected, showing lesion at maximal narrowing and arterial silhouette in sharpest focus. After the calibration of guiding catheter, analysed arterial segment with coronary lesion was defined by moving the cursor from the proximal to the distal part of coronary artery to ensure adequate determination of reference diameter. We have measured minimal luminal diameter, reference diameter, percent diameter stenosis, and length of the lesion.

Significant coronary artery disease was defined as at least 1 coronary stenosis more than 50%. Severe coronary disease was

defined as three-vessel disease and/or left main disease. For patients who had previously undergone a percutaneous coronary intervention, even though no restenosis was observed, the treated vessel was considered as significantly diseased. In previously bypassed patients, native arteries and grafts were taken into account in the evaluation of extension of artery disease (number of diseased vessels).

2.3. Statistical analysis

Continuous data were expressed as mean ± SD and categorical data as percentage. Analysis of variance and chi-square test were used for continuous and categorical variables, respectively. A trend analysis was performed across tertiles of SUA according to sex [17]. The relationship between uric acid and coronary artery disease was evaluated at multivariate analysis separately in males and females after correction for baseline confounding factors that were entered in the model in block for each analysis. Results were considered statistically significant at two-sided $p < 0.05$. Statistical analysis was performed using the SPSS 17.0 statistical package.

3. Results

Among 3520 patients undergoing coronary angiography, we

Table 1
Clinical and demographical characteristics according to sex.

Baseline clinical characteristics	Female (n = 1078)	Male (n = 2442)	P Value
Arterial hypertension (%)	75.3	69.7	0.001
Age (mean ± -SD)	70.8 ± 10.6	66.2 ± 11.3	<0.001
Smokers (%)			<0.001
Active smokers	15.8	31.7	
Previous smokers	8.0	24.1	
Dyslipidemia (%)	55.3	55.9	0.73
Diabetes (%)	37.3	36.8	0.77
Family history of CAD (%)	27.8	28.9	0.51
History of MI (%)	15.7	28.5	<0.001
Previous PCI (%)	16.1	27.3	<0.001
Previous CABG (%)	6.4	14.3	<0.001
Previous stroke (%)	4	7.9	<0.001
Renal failure (%)	39.2	23.4	<0.001
Indication for angiography			<0.001
Stable angina or silent ischemia (%)	19.2	25.7	
Acute coronary syndrome (%)	60.4	57.4	
DCM or valvular disease (%)	20.4	17	
Biochemistry			
White blood cells (10^3/μl)	7.64 ± 2.5	8.01 ± 3.1	0.001
Platelets count (10^5/ml)	237.3 ± 72.4	206.9 ± 60.3	<0.001
Haemoglobin (g/dl)	12.4 ± 1.5	13.8 ± 1.6	<0.001
Creatinine (mg/dl)	0.98 ± 0.4	1.01 ± 0.36	<0.001
Glycaemia (mg/dl)	126.3 ± 54.7	124.6 ± 48.8	0.35
Glycosylated haemoglobin (%)	6.3 ± 1.3	6.2 ± 1.3	0.08
Total cholesterol (mg/dL)	170.1 ± 43.5	160.7 ± 40.5	<0.001
Tryglicerides (mg/dL)	125.9 ± 67.7	137.7 ± 85	<0.001
HDL cholesterol	44.7 ± 13.6	39.4 ± 11.6	<0.001
LDL cholesterol	104.5 ± 41.6	100.5 ± 46	0.01
Reactive protein C (mg/dl)	1.53 ± 3.1	1.25 ± 2.6	0.009
Uric acid (mg/dl)	5.8 ± 1.9	6.3 ± 1.7	<0.001
Fibrinogen (mg/dL)	464.4 ± 143.1	429 ± 152.6	<0.001
Therapy at admission			
ACE inhibitors (%)	35.5	39.1	0.04
ARB (%)	24.5	18.5	<0.001
Nitrate (%)	35.6	35.7	0.94
Beta blockers (%)	50.8	51	0.95
Calcium antagonists (%)	20.1	20.2	0.93
Diuretics (%)	36.3	27.7	<0.001
Statins (%)	41.8	50.9	<0.001
ASA (%)	52.9	59.8	<0.001
Clopidogrel (%)	21.6	23.7	0.17