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Correlation between Hyperuricemia and Severity of Coronary Artery Disease Detected by Coronary Angiography in Men and Women

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Abstract:

The association between serum uric acid and ischemic heart disease remains controversial and serum uric acid has not yet been established as cardiovascular risk factor. Our objective was to study the association of serum uric acid level with angiographic severity of coronary artery disease in males and females with ischemic heart disease. This observational study was conducted on two hundred patients divided into one hundred male patient, subdivided into fifty patient with elevated SUA and fifty patient with normal SUA and one hundred female patient subdivided into fifty patient with elevated SUA and fifty patient with normal SUA underwent coronary angiography for detection of CAD in cath lab unit of cardiology department of Beni-Suef and Sohag university. The severity of CAD was assessed on the basis of Gensini score and clinical vessel score. For all groups, conventional risk factors, levels of serum uric acid, and other biochemical markers were assessed.

Keywords: Serum uric acid, Coronary artery disease, Gensini score, Coronary angiography.

1. Introduction:

Uric acid is the final breakdown product of purine degradation in humans. Hyperuricemia results from increased production of uric acid, decreased excretion or a combination of both [1].

Since *Klein et al* reported the relationship between serum uric acid (SUA) level and coronary artery disease (CAD) in 1973, the question of whether high SUA is a risk factor for arteriosclerosis has remained controversial [2]. The relation between SUA and CAD is observed not only in frank hyperuricemia (defined by SUA> 7 mg/dl in male and > 6 mg/dl in female), but also in high normal values of SUA (defined by SUA> 5, 5 mg/dl). The significance of this relationship is still unknown and in literature there are controversies concerning the significance of elevated SUA level in cardiovascular disease:

Is it only a marker or is it also a risk factor? [3].

The scientific literature makes widespread reference to the association between chronic non-communicable diseases, especially cardiovascular diseases, rheumatic, and hyperuricemia. Despite all the studies and technological advances, there is still limited evidence to show a direct relationship between hyperuricemia and cardiovascular diseases [4].

Coronary angiography allows a direct evaluation of coronary anatomy. The study of severity of CAD in patients with confirmed disease may be of help in elucidating mechanisms underlying growth of coronary atherosclerosis lesions. This type of evidence may be of use, to be added to evidence on the risk of having the disease. Risk factors for ischemic heart disease include hypertension, age, male sex, high plasma cholesterol, high plasma glucose and excessive weight [5].

Gender might be an important effect modifier in the association between elevated SUA level and coronary artery calcification (CAC) because of differences in the distribution of SUA and the prevalence of CAC [6].

Few studies have assessed the relationship of hyperuricemia with severity of CAD. Some investigators have reported an independent relationship of SUA and CAD in females but not in males [7].

2. Patients and Methods:

This study is a prospective observational comparative study using consecutive patients undergoing diagnostic coronary angiography in cath lab unit of cardiology department of Beni-Suef university hospital and Sohag university hospital from June 2012 to April 2013. The study included 200 patients undergoing elective coronary angiography because of known ischemic heart disease. The selected patients were divided into four groups according to gender and SUA level**:** Group I: 50 male patients with normal SUA ≤ 7 mg /dl. Group II: 50 male patients with elevated SUA >7 mg /dl. Group III: 50 female patients with normal SUA ≤ 6 mg /dl. Group IV: 50 female patients with elevated SUA > 6 mg /dl.

2.1 Inclusion criteria: The study included patients undergoing elective coronary angiography for diagnosis of ischemic heart disease including:

1- Chronic stable angina: Chest pain or discomfort caused by myocardial ischemia that is precipitated by physical or emotional stress and relieved with rest or sublingual nitroglycerin. [8].

2- Unstable angina: Chest pain with at least one of three features: It occurs at rest (or with minimal exertion) and usually lasts >20 minutes (if not interrupted by nitroglycerin). It is severe and of new onset. It occurs in a crescendo pattern (more frequent than previously) [9].

3- Previous myocardial infarction: Any one of the following criteria meets the definition for prior MI: Pathological Q waves with or without symptoms in the absence of non-ischemic causes and imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause [10].

2.2 Exclusion criteria:

1- Recent myocardial infarction: The first 4 weeks of acute myocardial infarction (AMI).

2- Congestive heart failure.

3- Renal impairment.

4- Malignancies.

5- Patients on diuretic therapy.

6- Patients taking medication to lower SUA level.

7- Active gouty arthritis.

8- Active infection.

9- Pregnancy.

2.3 Methods: Each patient was subjected to the following:

1- A full history: taking with analysis for risk factors of CAD which include: age, male gender, smoking, and history of DM, history of hypertension, hyperlipidemia and family history of CAD:

A- Hypertension: patients receiving anti-hypertensive drugs or their Bp ≥ 140/90 mmHg [11].

B- Diabetes Mellitus: patients who receive insulin or oral hypoglycemic drugs or awareness of their past history of DM were defined as: A fasting blood sugar ≥ 126 mg /dl [12].

C- Hyperlipidemia: cholesterol level ≥ 200 mg/dl, LDL cholesterol level ≥ 130 mg/dl, Triglycerides level ≥ 150 mg/dl, HDL-Cholesterol level ≤ 40 mg/dl in male and ≤ 50 mg /dl in female or therapy for a lipid disorder. [13].

D- Smokers*:* patients who currently smoked any kind of tobacco or who had quit smoking less than one month prior.

E- Positive family history of CAD was defined as CAD noted under the age of 55 year for males and 65 year for females in a parent or sibling of the patient.

2- Clinical evaluation:

A- General medical examination includes:

- Weight and height were measured and body mass index [BMI] were calculated using that formula [BMI] (kg/m^2) = weight in kilograms/ height in $meters^2$).

- Vital signs (pulse and blood pressure)

B. Local cardiac examinations.

3- Electrocardiography: 12 lead ECG for detection of manifestations of ischemia.

4- Echocardiography: Transthoracic Echo Doppler study was done to all patients for assessment of systolic wall motion abnormalities (SWMA) and to exclude congenital, valvular heart disease, or dilated cardiomyopathy.

5- Venous blood samples: Tested for:

A- Serum uric acid.

B- Lipid profile.

C- Blood glucose level.

D- Renal functions: Blood urea and serum creatinine.

6- Coronary angiography and Gensini score system [17]:

A- In all patients, selective Left and Right coronary angiography was performed under local anesthesia at right groin via right femoral artery approach using the Judkin's technique on (GE, European community) and (Siemens Axiom Artis, Germany) machines of both cath lab unit of cardiology department of Beni-Suef university hospital and Sohag university hospital respectively.

B- The severity of each lesion was visually assessed by two experienced cardiologists.

C- The Gensini score was computed by assigning severity score to each coronary stenosis according to the degree of luminal narrowing and by its geographic importance.

D- Reduction in lumen diameter and radiological appearance of concentric lesions and eccentric plaques were evaluated (reductions of 25%, 50%, 75%, 90%, 99%, and total occlusion were given Gensini scores of 1, 2, 4, 8, 16, and 32, respectively).

E- This score is then multiplied by a factor that takes into account importance of lesion's position in the coronary arterial tree. For example; 5 for left main coronary artery, 2.5 for proximal left anterior descending coronary artery and proximal left circumflex coronary artery, 1.5 for the mid region of left anterior descending coronary artery, 1 for the distal left anterior descending coronary artery, first diagonal, proximal, mid region, distal regions of right coronary artery, mid region, and distal region of left circumflex coronary artery and 0.5 for second diagonal and postero-lateral branch.

F- The Gensini score was expressed as the sum of scores for all the coronary arteries lesions.

G- The presence of CAD has been defined as Gensini > (0).

H- Reporting of coronary angiogram was done by a consultant of cardiology not aware of clinical or biochemical profile of patients.

Statistical methodology

Analysis of data was done by IBM computer using SPSS (statistical program for social science) as follows:

- Description of quantitative variables as mean, S.D. and range.
- Description of qualitative variables as number and percentage.
- Unpaired t-test used to compare quantitative variables, in parametric data (S.D. < 50 % mean).

• P value > 0.05 insignificant

• P < 0.05 significant

• P < 0.01 highly significant [18].

3. Results:

3.1. Population characteristics:

A- Sex: The study included 200 patients. Group one included 50 male patients with normal SUA ≤ 7mg/dl [14]. Group two included 50 male patients with elevated SUA > 7mg/dl. Group three included 50 female patients with normal SUA ≤ 6 mg/dl. Group four included 50 female patients with elevated SUA > 6 mg/dl.

B- Age: There was a statistically no significant difference between the four groups, P value > 0.05 (0.588).

3.2. Coronary artery disease (CAD)risk factors: (Table 1)

Table 1: Prevalence of risk factors of CAD in study groups:

Risk factor	Group				Total (%)	Chi square	P value
	Group I	Group II	Group III	Group IV			
HTN	27	31	27	30	57%	1.043	0.791
DM	26	30	27	33	58%	2.463	0.482
DL	18	22	21	28	45%	4.371	0.224
Smoking	32	34	3	5	37%	72.5	<0.001
FH	11	13	9	11	23%	0.932	0.818

3.3 Type of coronary artery disease: Figure (1)

There was a statistically no significant difference between the four groups according to type of CAD, P value > 0.05 (0.634).

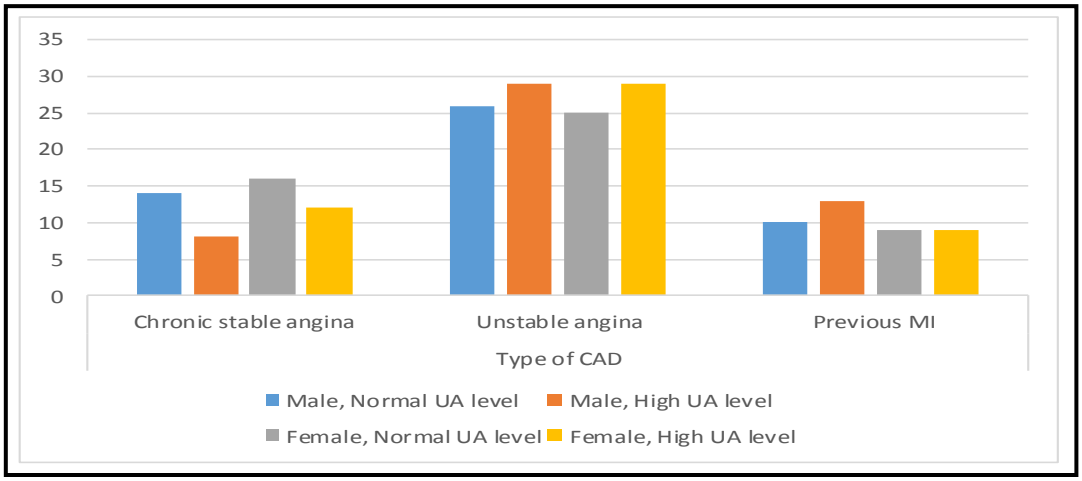

Figure (1): Type of (CAD) among study groups.

3.4 Laboratory Investigations:

A- Renal functions: There was a statistically no significant difference between the four groups according to blood urea. P value > 0.05 (0.431), while serum creatinine showed statistically significant difference between the four groups, P value < 0.01 (0.001), as it was highest among group II then group IV, followed by group I and lastly group III.

B- Lipid profile: There was a statistically no significant difference between the four groups according to TC, TG, LDL and HDL, P value> 0.05 (0.332, 0.814, 0.336, and 0.200 respectively).

C- Blood sugar: There was a statistically no significant difference between the four groups according to (2HPP), P value >0.05 (0.111).

D- Uric acid: (Table 2)

Table 2: Laboratory investigations (Uric acid level):

Group	Group I	Group II	Group III	Group IV	Total	P value
Mean	5.0966	8.2462	4.4096	7.3976	6.2875	0.001
Std. Deviation	1.14889	0.75881	0.81190	1.02986	1.84560	
Minimum	3.06	7.18	3.06	6.15	3.06	
Maximum	7.00	10.62	5.82	10.23	10.62	
Range	3.94	3.44	2.76	4.08	7.56	

3.5 Coronary angiography:

3.5.1 Gensini score (GS): (Table 3)

In study groups: statistically significant difference between the four groups, P value < 0.05 (0.012), as GS was highest among group II, then group IV, with a significant difference from group I and lastly group III.

Table 3: Gensini Score (GS) of study groups:

Group	Group I	Group II	Group III	Group IV	Total	P value
Mean	27.00	44.26	23.02	39.70	33.49	0.012
Std. Deviation	20.879	41.501	22.906	31.540	27.780	
Minimum	0	0	0	0	0	
Maximum	135	190	158	149	190	
Range	135	190	158	149	190	

3.5.2 Coronary angiographic parameters:

- Clinical score: (Number (N.) of CAD): There was a statistically significant difference between the four groups according to N. of coronary arteries diseased, P value <0.05 (0.015), as groups II and IV showed the highest prevalence of multiple vessel disease (2 or 3), compared to group I and group III.

- Left main (L.M) CAD and complete total occlusion (CTO) of coronary arteries:

Both shows statistically no significant difference between the four groups, but there was a tendency to increase incidence of L.M CAD and CTO of coronary arteries in hyperuricemic groups [group II and group IV] in comparison with normal-uricemic groups [group I and group III] was observed.

3.6 Correlations between SUA level and other risk factors of CAD: (Table 4)

Correlations between SUA level and other risk factors of CAD were tested using Pearson correlation test among all study population and among male and female patients separately.

Table 4: Pearson Correlation test between SUA level and other risk factors of CAD.

	All study population [n= 200 patients]		**Male patients [n= 100 patients]**		**Female patients [n= 100 patients]**	
	r	**P- value**	***r***	**P- value**	***r***	**P- value**
Age	0.180	0.011	0.198	0.048	0.184	0.067
BMI	0.235	0.125	0.312	0.763	0.412	0.016
BP	0.139	0.051	0.114	0.258	0.031	0.762
CR	0.146	0.039	0.053	0.604	0.136	0.178
CH	0.130	0.066	0.490	0.026	0.172	0.087
TG	0.077	0.281	0.049	0.625	0.081	0.424
LDL	0.121	0.088	0.172	0.479	0.152	0.013
HDL	-0.047	0.038	-0.078	0.044	-0.264	0.008
FBS	0.171	0.016	0.240	0.016	0.180	0.074
2HP	0.221	0.002	0.219	0.029	0.252	0.011
GS	0.484	0.001	0.468	0.001	0.500	0.001

[r: correlation coefficient, BMI: body mass index, BP: mean blood pressure, CR: creatinine, CH: total cholesterol, TG: triglycerides, LDL: low density lipoprotein, HDL: high density lipoprotein, FBS: fasting blood sugar, 2HPP: 2 hour post-prandial, GS: Gensini score].

3.7. Linear Logistic Regression analysis: (Table 5 a & b)

The effect of the same risk factors on the severity of CAD assessed by the Gensini Score were put into model in univariate linear regression analysis and the factors affecting the angiographic severity of CAD were determined. According to this analysis, increased SUA level was found to be an independent risk factor for severity of CAD in the whole study groups, in male and female population groups. Other independent risk factors found in this analysis were age, DM [16], smoking and lipid profile [15] in all study groups, TC and TG in male patients, and age, DM, BMI and lipid profile in female patients.

The risk factors which had been shown to be significantly associated with the severity of CAD using linear univariate analysis were then introduced into a stepwise linear multivariate analysis. By multivariate analysis, age, DM, high LDL, low HDL and high serum uric acid level only were found to be independent risk factors for severity of CAD determined by GS among all study population; while among male patients, only DM, TC and serum uric acid were found to be independent risk factors for severity of CAD. On the other hand, among female patients, age, DM, low HDL and serum uric acid were found to be independent risk factors for severity of CAD.

Table 5 a: Results of Univariate Linear Logistic Regression analysis for several risk factors effects on severity of CAD assessed by GS in all study groups:

Variable	Un-standardized Coefficients		Standardized Coefficients	t	P value	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
Age	1.012	0.276	0.252	3.663	0.002	0.467	1.557
HTN	4.605	5.408	0.060	0.852	0.395	-6.059	15.269
DM	13.005	5.347	0.170	2.432	0.016	2.460	23.549
Smoking	5.554	2.603	0.033	2.470	0.039	0.833	13.536
Family History	0.764	6.465	0.008	0.118	0.906	-11.985	13.513
BMI	-0.572	0.496	0.082	1.154	0.250	-1.550	0.406
TC	0.226	0.068	0.231	3.343	0.002	0.093	0.360
TG	0.217	0.065	0.232	3.349	0.001	0.089	0.344
LDL	0.221	0.073	0.211	3.044	0.003	0.078	0.364
HDL	-0.442	0.187	-0.166	2.371	0.019	-0.810	-0.075
UA	9.910	1.273	0.484	7.785	0.001	7.399	12.420
CR	17.029	14.827	0.081	1.149	0.252	-12.210	46.269

[DM: diabetes mellitus, HTN: hypertension, BMI: body mass index, TC: total cholesterol, TG: triglyceride, LDL: low density lipoproteins, HDL: high density lipoproteins, UA: uric acid and CR: creatinine].

Table 5 b: Results of Multivariate Linear Logistic Regression analysis for several risk factors effects on severity of CAD assessed by GS in all study groups:

variable	Un-standardized Coefficients		Standardized Coefficients	t	P value	95.0% Confidence Interval for B	
	B	Std. Error	Beta			Lower Bound	Upper Bound
Age	.661	0.244	0.165	2.705	0.007	.179	1.144
DM	6.905	0.670	0.090	1.479	0.041	2.306	16.116
Smoking	-4.096	0.794	0.052	-0.854	0.394	-13.551	5.360
TC	0.198	.230	0.202	.862	0.390	-0.255	.652
TG	0.100	.085	0.107	1.169	0.244	-0.069	.268
LDL	0.433	.230	0.127	2.580	0.046	0.186	0.320
HDL	-0.823	.257	-0.084	3.868	0.038	-0.730	-1.284
UA	8.667	1.312	0.423	6.607	0.001	6.079	11.254

[DM: diabetes mellitus, TC: total cholesterol, TG: triglyceride, LDL: low density lipoproteins, HDL: high density lipoproteins, UA: uric acid and CR: creatinine].

4. Discussion:

The current study was designed to determine the relationship between SUA level in males and females. Severity of CAD assessed by coronary angiography. The study included two hundred patients divided into one hundred male patient, subdivided into fifty patient with elevated SUA and fifty patient with normal SUA and one hundred female patient subdivided into fifty patient with elevated SUA and fifty patient with normal SUA underwent coronary angiography for detection of CAD in cath lab unit of cardiology department of Beni-Suef and Sohag university. The severity of CAD was assessed by using the Gensini score [17] and the clinical vessel score [19]. Main findings of this study were: (A) In comparison between the whole study groups: There was a significant positive correlation between SUA level and severity of CAD assessed by Gensini and clinical score (N. of coronary arteries diseased), P-value: 0.012, P-value: 0.015, respectively.

Correlation between SUA level and other risk factors of CAD: Using Pearson correlation test showed that SUA level was significantly correlated with age (P-value: 0.011), serum cretinine (P-value: 0.039), low HDL (P-value: 0.038), blood sugar FBS (P-value: 0.016) and 2HPP (P-value: 0.002) and finally GS (P-value: 0.001). By logistic regression analysis, increased SUA level was found to be an independent risk factor for CAD severity, p-value: 0.001. (B) In comparison between male groups: There was a significant positive correlation between SUA level and severity of CAD determined by Gensini score and Clinical score, P value: 0.020 and P-value: 0.035, respectively. Correlation between SUA level and other risk factors of CAD: Using Pearson correlation test showed that SUA level was significantly correlated with age (Pvalue: 0.048), serum cholesterol (Pvalue: 0.026), low HDL (P-value: 0.044), blood sugar FBS (Pvalue: 0.016) and 2HPP (P-value: 0.024) and finally GS (P-value: 0.001). By logistic regression analysis, increased SUA level was found to be an independent risk factor for CAD severity p-value: 0.001. (C) In comparison between female groups: There was a significant positive correlation between SUA level and severity of CAD determined by Gensini score and Clinical score, P-value: 0.028, and P-value: 0.030, respectively. Correlation between SUA level and other risk factors of CAD: Using Pearson correlation test showed that SUA level was significantly correlated with BMI (P-value: 0.016), high LDL (P-value: 0.013), low HDL (P-value: 0.008), blood sugar 2HPP (P-value: 0.011) and finally GS (P-value: 0.001). By logistic regression analysis, increased SUA level was found to be an independent risk factor for CAD severity, p-value: 0.001. The findings of our study come in agreement with: Duran, et.al. [20], found that patients with hyperuricemia had higher Gensini score, high number of diseased vessels and critical lesions. So the study suggested that high SUA levels are associated with severity of CAD. Study by Deveci, et.al. [3], revealed that higher SUA level is related to the presence and severity of CAD (assessed by Gensini score and clinical vessel score) in both male and female patients. Moreover, it showed that increased SUA level was found to be an independent risk factor of the severity of CAD in both male and female patients according to linear regression analysis. Qureshi, et.al. [21], reported the relation of SUA level and angiographic severity of coronary artery disease in male patients with acute coronary syndrome, founding an association between serum uric acid level and severity of CAD documented by Gensini score. Also, this study revealed no statistically difference in serum uric acid levels in correlation with severity of CAD of diabetic patients vs. non-diabetics and hypertensive's vs. non-hypertensive's

suggesting the role of SUA as an independent by.Akanda, et.al. [22], evaluated the association between high SUA with presence and severity of CAD, reported a significant association between SUA level and severity of CAD. patients were classified into four groups according to their Gensini score, mean SUA level was found to be significantly increased across the GS groups, and a statistically significant difference was detected between the GS groups (p- value:0.001). Other studies reported disagreement with our study: Tuttle, et.al. [23], found that serum uric acid correlated linearly with CAD severity score in female but not in male. the severity of CAD was evaluated according to number of diseased coronary arteries alone and as known, Gensini score is superior in assessing severity of CAD compared to number of involved coronary artery. Petersen, et.al. [24], found that SUA level was higher in patients with coronary artery disease than patients without, but SUA level and degree of diseased coronary arteries was not significantly correlated. The severity of CAD in this study was evaluated by different method, the degree of coronary arteries narrowing in two groups (patient group and control group).

5. Conclusion and recommendations:

Serum uric acid level is positively correlated with severity of CAD in the whole study groups. When gender –specific values were taken into account, the SUA level was found risk factor for severity of CAD [21]. Study to be positively correlated with the severity of CAD in both male and female groups individually. In this study, linear logistic regression analysis [Univariate and Multivariate analysis] demonstrated that increased SUA level is an independent risk factor for the severity of CAD in the whole study groups, male and female groups.

6. References:

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