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Serum uric acid and albumin as risk predictors of angiographically proven atherosclerosis

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Abstract
Background: Atherosclerosis is a multifactorial disease with various risk factors playing significant role in its pathogenesis. There are various known but underestimated risk factors like uric acid and albumin which are reported to have the potential as risk predictors of atherosclerosis.
Aims and Objectives: To estimate the level of serum uric acid and albumin and study their association with angiographically proven atherosclerosis.
Material and Methods: Study population consisted of angiographically proven 50 cases with atherosclerosis and 50 controls without atherosclerosis. All routine parameters were analysed on SYNCHRON CX-9 using standard kits.
Results: Mean serum uric acid levels of cases were significantly higher than the controls with p=0.007; mean serum albumin levels of controls were significantly higher than the cases p=0.009. No statistically significant difference was found in lipid profiles of two groups.
Conclusion: Increased uric acid and decreased albumin are associated with atherosclerosis risk. But their potential as an independent risk predictor remains inconclusive as their role in atherosclerosis whether it is direct or indirect via promotion of other risk factors is not clear.

Keywords: Atherosclerosis; Uric acid; Albumin; Coronary artery disease.

Introduction

Atherosclerosis is a complex multifactorial disease of medium and large sized vessels resulting from the interactions of various environmental and genetic factors [1-2]. Its manifestation depends upon the vessels involved. Myocardial infarction is one of such common manifestation of atherosclerosis because of involvement of coronary artery. Once, thought to be a disease of developed countries is now rapidly increasing in developing countries as well because of change in lifestyle. Today, it has become one of the major cause of morbidity and mortality worldwide. Atherosclerosis development starts long before it is manifested clinically making its early detection vital. Many researches have been done in the quest of markers which can help in its early detection and management.

Dyslipidaemia, inflammation and hypertension are some of the known risk factors for atherosclerosis [1]. Pharmaceutical agents targeting these risk factors are used along with lifestyle modification by many clinicians as treatment modality to control the disease at its very early stage. Despite of these measures, CAD still remains to be one of the major cause of morbidity and mortality. Therefore, search is still going on for the presence of unknown or known but underestimated biomarkers which can be used as risk predictor of atherosclerosis. In our study we have chosen uric acid and albumin as potential markers to study their role as risk predictors of atherosclerosis.

Albumin is a negative acute phase protein synthesized by liver. During inflammation various cytokines are released which further stimulate the synthesis of acute phase proteins and depressed synthesis of albumin [3]. Recent researches have shown association of albumin with atherosclerosis [4-6].

Uric acid is the end product of purine metabolism and in excess amount it is found to be associated with various diseases [7]. Recent studies have shown its association with Hypertension [8], CVD [9] and metabolic syndrome [8]. Mechanism by which it is involved in above conditions is still not clear; though some studies have shown its involvement via pro-inflammatory pathway. Our aim was to study the role of uric acid and albumin as risk predictors of atherosclerosis.

Materials and Methods

The study was case-control study, carried out jointly in the Department of Biochemistry, Lady Hardinge Medical College and Smt. Sucheta Kriplani Hospital and Department of Cardiology, G.B. Pant Hospital, Delhi. With informed consent 100 non- diabetic subjects undergoing angiography were selected from Cardiology Department of G.B. Pant Hospital. Study population was selected on the basis of angiography; 50 subjects with atherosclerosis as proven by angiography were included in case and 50 subjects without atherosclerosis as proven by angiography were included in control group. Both the groups were age and sex matched. Study groups were subjected to detailed history with special reference to the atherosclerosis followed by clinical examination. Our study was approved by the Ethical Committee of Lady Hardinge Medical College.

The venous blood sample was collected from subjects under sterile conditions after overnight fasting. The blood samples for routine parameters were processed immediately for separation of serum and plasma. Routine parameters and lipid profile were measured by auto analyzer (SYNCHRON CX-9, Beckman Coulter) using standard reagents. Uric acid was estimated by enzymatic method on autoanalyzer. Serum

albumin was measured by Bromo-cresol green method on autoanalyzer.

Statistical Analysis

Statistical analysis was performed with the SPSS version 20.0 software program. Continuous variables were expressed as mean ± S.D. The variables were compared with a normal distribution by unpaired 2-tailed Student's t-test. A value of $p \leq 0.05$ was considered statistically significant.

Results

The study groups were matched for age and sex. Table 1 shows baseline characteristics of our study group. Smoking followed by hypertension were the two most prevalent risk factors in our study population. No statistically significant difference was observed in lipid profile of cases and controls (Table 3). We did find statistically significant difference in serum uric acid and serum albumin levels of cases and controls. (Table 2).

Table 1: General characteristics of study groups:

	CASE (Mean ±S.D)	CONTROL (Mean ±S.D)	p value
Age	51.22 ± 7.6	48 ±7.2	0.105
Sex (M) (F)	35 (70%) 15(30%)	33(66%) 17(34%)	0.668
BMI	22.9 ± 3.4	22.5 ± 2.4	0.544
HYPERTENSION	22 (44%)	9 (18%)	0.005
SMOKING	30 (60%)	11 (22%)	0.000
F/H/O CAD	4 (8%)	3 (6%)	0.695

p value≤0.05 is considered statistically significant.

Table 2: Distribution of routine parameters in study population.

PARAMTERS	CASE	CONTROL	p VALUE
SODIUM (mEq/L)	140.0 ±3.6	139.4±3.7	0.404
POTASSIUM (mEq/L)	3.92± 0.27	3.88 ±0.32	0.298
UREA (mg/dl)	24.3± 8.0	23.3± 7.5	0.533
CREATININE (mg/dl)	0.75± 0.27	0.69± 0.25	0.414
URIC ACID (mg/dl)	5.0±1.26	4.3 ± 1.37	**0.007***
T. BILIRUBIN (mg/dl)	0.60± 0.20	0.62± 0.28	0.684
ALT (IU/L)	31.54± 24.07	30.10 ± 13.44	0.712
AST (IU/L)	24.24 ± 11.67	27.18±10.87	0.196
ALP(IU/L)	106.5±33.51	98.7 ± 27.69	0.211
TOTAL PROTEIN (g/dl)	7.06 ± 0.47	6.98±0.49	0.352
ALBUMIN (g/dl)	3.70±0.45	3.94±0.52	**0.009***
CALCIUM (mg/dl)	9.14±0.56	8.96 ± 0.56	0.219
PHOSPHORUS (mg/dl)	3.54±0.49	3.46 ±0.56	0.519
GLUCOSE (mg/dl)	93.36±6.18	93.32±5.23	0.972

p value≤0.05 is considered statistically significant

Table 3: Distribution of lipid parameters in study groups:

PARAMETERS	CASE (Mean ± S.D)	CONTROL (Mean ± SD)	p value
T.CHOL (mg/dl)	143.4 ± 42.30	142.14 ± 37.30	0.875
TG (mg/dl)	146.08 ± 67.67	134.36 ± 63.89	0.375
HDL (mg/dl)	41.700 ± 8.83	43.580 ± 12.55	0.389
LDL (mg/dl)	81.580 ± 37.57	77.940 ± 34.64	0.616
VLDL (mg/dl)	29.22 ± 13.51	26.84 ± 12.52	0.375
LDL/HDL	1.97 ± 0.80	1.82 ± 0.67	0.308
T CHOL/ HDL	3.58 ± 1.31	3.38 ± 0.89	0.382

p value≤0.05 is considered statistically significant

Discussion

We included 100 subjects in our study population and divided them into two groups on the basis of angiography; angiographically positive subjects were enrolled as cases and angiographically negative subjects as controls. Serum from the both the groups were analysed for lipid profile, uric acid, albumin and other routine parameters. We found statistically significant difference in serum uric level of two groups with p =0.007. We also found statistically significant difference in serum albumin level of two study groups with p=0.009. We didn't find any statistically significantly difference in lipid profile and other routine parameters of cases and controls probably because both groups were on statins.

Albumin is a negative acute phase protein synthesized by liver. During inflammation various cytokines are released which further stimulate the synthesis of acute phase proteins. This leads to an acute-phase reaction in which the synthesis of albumin is depressed and the synthesis of other acute reactant proteins is increased [3]. Researches have shown association of albumin with atherosclerosis. ARIC cohort study[4] found inverse association between serum albumin and incident coronary heart disease. Similar results were observed by Phillip *et al.* [5] in population based middle aged cohort of British men. Another study by Khullar *et al.* [6] reported that risk of coronary heart disease is more in men with lower albumin levels. One of the probable mechanisms by which it is related to CHD is via its role as an anti-oxidant [10]. Albumin has binding site for ions which can accelerate free radical reactions. Albumin acts as anti-oxidant by binding with these free radical ions. In our study population, mean serum albumin level of controls was significantly higher than that of cases indicating increased oxidative stress in cases. In contrast, Folsom *et al.* [11] didn't find any association between albumin and atherosclerosis. Stenvinkel [12] and colleagues also demonstrated the similar findings. Because of this inconsistency, it has been suggested that low albumin might not be an independent risk factor of atherosclerosis but rather mere reflection of the inflammation.

In our study population we also found significantly higher UA in cases than controls. Uric acid is a metabolic end product of purine metabolism and its excess amount has been seen to be associated with various diseases [7]. Recently many studies have found its potential as atherosclerosis risk factor. Sinan *et al.* [13] found an association between hyperuricemia and CAD; also this association was more in women than men. Ishizaka *et al.* [14] reported association of hyperuricemia with carotid atherosclerosis in men without metabolic syndrome. Some studies have demonstrated UA as independent risk factor for CAD while according to others UA cannot be considered an independent risk factor for

CAD. One of the mechanism by which uric acid is thought to be involved in pathogenesis of atherosclerosis is by its pro-inflammatory role. It is thought to promote vascular dysfunction by activating intracellular signalling molecules involved in inflammation and proliferation in vascular smooth muscle cells [15-16]. Uric acid is reported to inactivate NO and supress endothelial cell proliferation [17]. It is also shown to be involved in local activation of renin-angiotensin system [18]. These mechanisms could explain its association with hypertension, metabolic syndrome and atherosclerosis. However, Nieto *et al*. [19] have reported that UA is a powerful free radical scavenger and increased UA in subjects with carotid atherosclerosis may be because of the increased antioxidant capacity. This property of UA could be beneficial in atherosclerosis. Therefore, its role in atherosclerosis is not completely understood. In our study, mean serum UA levels of cases were significantly higher than that of controls, suggestive of its potential role as a risk predictor of atherosclerosis. As most of our cases were hypertensive, indicating that increased UA in atherosclerosis could be secondary to its association with hypertension mediated by above mentioned pathway.

Increase in uric acid and decrease in albumin are associated with atherosclerosis risk, although their potential as an independent risk predictor remains inconclusive as their role in atherosclerosis whether it is direct or indirect via promotion of other risk factors is not clear.

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