Original Research Article

Serum uric acid as an independent risk factor for carotid atherosclerosis in elderly persons without metabolic syndrome

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Abstract

Background: Metabolic syndrome (MetS) is a group of metabolic abnormalities which include visceral obesity, insulin resistance, raised blood pressure (BP), hypertriglyceridemia, low high-density lipoprotein (HDL), hypercholesterolemia and impaired fasting plasma glucose (FPG).Uric Acid (UA) is the metabolic end product of purine metabolism in humans. Patients with hyperuricemia are at increased risk of renal, cardiovascular disease (CVD) events and vascular damage. Now there is evidence to suggest that urate-lowering treatment may reduce CVD risk. Cardiovascular disease is the leading cause of death in India.CVD related death rate in India is 272 per 1 lakh population which is higher than world incidence which is 235 per 1lakh.Uric acid is an independent risk factor and marker for atherosclerosis. It causes atherosclerosis by increased cytokine release leading to endothelial dysfunction through inactivation of Nitric oxide and suppression of endothelial cell proliferation. **Aim**: To find out the association of the uric acid level in the development of atherosclerosis in elderly subjects with metabolic syndrome and in elderly subjects without metabolic syndrome. **Materials and methods**:100 outpatients in the age group above 60yrs were selected. 5ml of Blood samples were taken for fasting blood sugar, blood cholesterol and serum uric acid. BMI was measured using their height and weight. Carotid artery thickness was measured by ultra-sonogram. Results were statistically analysed by using SPSS software. **Results:** In subjects with metabolic syndrome incidence of atherosclerosis is increased when uric acid level is increased. And it was observed that there was a statistically significant relationship in patients without metabolic syndrome (p value <0.001). **Conclusion:** Uric acid is found to be a risk factor for CVD independent of metabolic syndrome status.

Key words: cardiovascular disease, cholesterolemia, metabolic syndrome, plasma glucose, uric acid

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Introduction

Metabolic syndrome (MetS) consists of aggregation of various established cardiovascular risk factors. Prevalence of obesity and metabolic syndrome is rapidly increasing in India and other South Asian countries, leading to increased mortality and morbidity due to CVD and T2DM[1]. Uric Acid (UA) is the metabolic end product of purine metabolism in humans and also a pro-inflammatory mediator. Excess accumulation can lead to various diseases[2].

Hyperuricemia can be caused by high intake of dietary purine, high-fructose corn syrup, and table sugar can increase levels of uric acid. Serum uric acid can be elevated by reduced excretion via the kidney. Fasting or rapid weight loss can temporarily elevate uric acid level. Certain drugs, such as thiazide diuretics can increase blood uric acid levels by interfering with renal clearance.

Tumour lysis syndrome, a metabolic complications of certain cancer or chemotherapyalso causes increased uric acid level. Increased uric acid level causes decreased Nitric oxide, increased Reactive oxygen species, increased smooth muscle proliferation and inhibition of endothelial growth.

One of the mechanism by which uric acid induces metabolic syndrome is by the insulin-stimulated release of nitric oxide from endothelial cells. Features of the metabolic syndrome develop in mice lacking endothelial nitric oxide synthase [3] This indicates that hyperuricemia can induce endothelial dysfunctions. Treatment with allopurinol can improve endothelial functions in patients with hyperuricemia.

Second mechanism isuricacid causes inflammatory and oxidative changes in adipocytes and also it causes expression of xanthine oxido-reductase (the enzyme which generates uric acid from xanthine) in adipocytes and is critical to the process of adipogenesis. The Global Burden of CVD death rate is 272 per 100 000 population in India and it is higher than the global average of 235 per 100 000 population.

Carotid intima-media thickness (IMT) is an useful marker of cardiovascular disease(CVD)[4, 5, 6].This study was carried out to find out the association of uric acid levels in the development of atherosclerosis in elderly subjects with and without metabolic syndrome.

Materials and Methods

This study was carried out after getting approval from Institutional ethical committee. The procedure was explained to the subjects and study was done after getting informed consent from the subjects in their own language. Sample size was 100. More than 60 years old male and female medical out patients from tertiary care hospital, in South India were included in the study as subjects.

Patients with Rheumatoid arthritis, Gout, patients taking drugs that increase uric acid level, severe cardiac &Renal disease patients were excluded from the study. Carotid Intima media thickness was measured by ultra-sonogram using 7.5 MHz linear type B-mode probe to evaluate sclerotic lesions of the common carotid arteries within 2 days of blood biochemical analysis. Wall thickness >10mm was taken as IMT positive.

5ml of blood sample was taken in a fasting state to measure blood parameters like lipid level, uric acid level and blood sugar level. Serum Uric acid is measured by uricase enzyme based method (Triders method). Subjects were divided into 4 groups according to their uric acid level. Blood glucose was measured by GOD POD (Glucose oxidase peroxidase method).BMI was calculated using Quetlet's formula(weight in kg/height in m^2).

Blood pressure was measured using standard sphygmomanometer after 5 minutes of rest. Relationship between Carotid intima media thickness and uric acid level were compared in persons with and without metabolic syndrome in all 4 groups. Normal Uric acid level is2.5 to 6 mg/dl in female and 3.5to 7 mg/dl in male.

According to **National Cholesterol Education Programme-Adult Treatment Panel III criteria for Metabolic syndrome(MS)**[8.1] the subjects

with BMI ≥ 25kg/m^2 ,BP ≥ 130/85mmHg ,TG ≥ 150mg/dl, HDL≤ 40 for men and ≤ 50 for women and Fasting sugar≥100mg/dl is considered as having metabolic syndrome.

Out of 100 subjects who were grouped depending on uric acid levels group 1 had 35 subjects (22 males 13 females)group 2 had 27 subjects (21 males 8 females) group 3 had 22 subjects (14 males 8 females) and group 4 had 15 subjects (10 males 5 females).in this study. Age group varied from 60 – 76 years.

Results were analysed by SPSS version 23.0 using pearson's correlation to find out the association of uric acid in the development of carotid atherosclerosis.

Groups –By Uric Acid Level

Group	Uric acid range
UA 1	0.8- 4.3mg/dl
UA 2	4.4- 5.5mg/dl
UA 3	5.6- 6.8mg/dl
UA 4	> 6.9mg/dl

Results

Table1 -Descriptive Statistics of all study parameters

PARAMETERS	MEAN	SD
BMI	23.20	3.414
FBS	94.44	11.398
TG	144.80	16.666
HDL	43.74	4.694
URIC ACID	5.055	1.7960
IMT	0.591	0.2031

Table1 shows descriptive statistics of following parameters-BMI –Body mass index, FBS-Fasting blood sugar,TG -Triglycerides, HDL –High density lipoprotein,BP –Blood pressure, Uric acid,and IMT-Intima media thickness in this study.

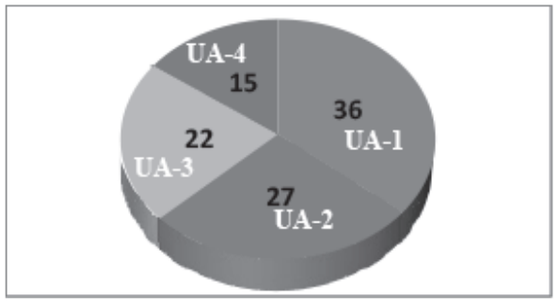
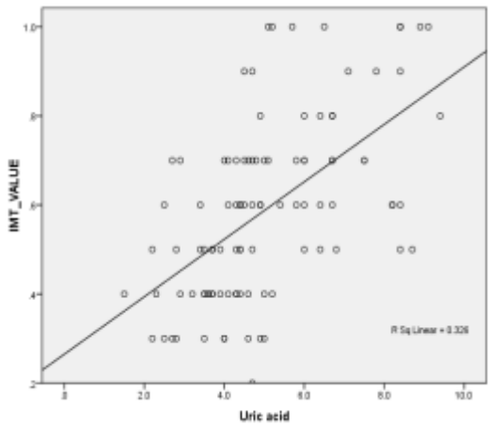


Fig 1. This picture shows number of subjects in each group

Correlation between uric acid and IMT value



This graph shows the correlation between uric acid and IMT. It showed that when the uric acid level increased, carotid artery thickness also increased.

Table 2–Association of uric acid and development of carotid atherosclerosis in elderly subjects with metabolic syndrome

Groups	IMT +ve	IMT –ve	Total	P value
1	0	7	7	<0.001
	0%	100%	100%	
2	5	8	13	
	38.5%	61.5%	100%	
3	6	1	7	
	85.7%	14.3%	100%	
4	5	0	5	
	100%	0%	100%	
Total	16	16	32	
	50%	50%	100%	

Table 2 shows the association between uric acid and metabolic syndrome. In group 1, there was no IMT positive.

When uric acid level was increased as in groups 2,3,4 there were more number of IMT positive (p <0.001). It shows that when uric acid level is increased, the incidence of carotid atherosclerosis also increased.

Table 3 - Association of uric acid and development of carotid atherosclerosis in elderly subjects without metabolic syndrome

Groups	IMT +ve	IMT –ve	Total	P value
1	1	28	29	<0.001
	3.4%	96.6%	100 %	
2	0	14	14	
	0%	100 %	100 %	
3	5	10	15	
	33.3%	66.7%	100 %	
4	6	4	10	
	60 %	40 %	100 %	
Total	12	56	68	
	17.6%	82.4%	100 %	

Table 3 shows the association of uric acid in subjects without metabolic syndrome in the development of atherosclerosis .In group 1, 3.4% of subjects were IMT+ve. In group 2,3,4 there were 0%, 33%,60% IMT positive subjects respectively (P<0.001).Development of atherosclerosis in subjects without metabolic syndrome is not having linear association as in metabolic syndrome subjects, but it also shows statistically significant association in subjects without metabolic syndrome.

Discussion

Hyperuricemia is one of the risk factor for the development of atherosclerosis, especially CVD. Several previous studies have reported possible association between hyperuricemia and the prevalence of MetS[9, 10, 11]. In a prospective study of 8,429 men and 1,260 women aged 20-82 years, 1,120 men and 44 women developed MetS during a mean follow-up of 5.7 years, and men with UA levels ≥6.5 mg/dL had a 1.60-fold increase in risk of MetS as compared with those who had levels < 5.5 mg/dL (P < 0.001), and women with UA levels ≥4.6 mg/dl had a 2.29-fold higher risk of MetS (P = 0.02).

These findings suggest that hyperuricemia may leads to metabolic syndrome. The atherosclerosis risk in Communities (ARIC) study observed that the UA level was significantly associated with carotid intima-media thickness. Subsequently, another study reported that hyperuricemia is an independent predictor of early atherosclerosis in hypertensive subjects with normal renal function. Hypertensive patients with left ventricular hypertrophy (LVH) have higher UA levels, independent of other CV risk factors, and a more strict association between UA and LV mass index was observed in women. These results suggest that UA may have an atherogenic role in the pathophysiology of

CVDs. In the Framingham Offspring cohort study (n=2,169, mean age 57 years, 55 % women) a decrease in systolic function parameters was observed in subjects with UA >6.2 mg/dl compared with those with lower uric acid. In our study UA level was higher in males.It maybe due to alcohol consumption and influence of sex hormones [12]. Effects of alcohol consumption or sex hormone require further investigation in the future. Hyperuricemia might be partially responsible for the proinflammatory endocrine imbalance in the adipose tissue and vascular smooth muscle cells which is an underlying mechanism of the low-grade inflammation and insulin resistance in subjects with the MetS, and causes dysfunction of endothelial cells.[15]

UA also promotes endothelial dysfunction through inactivation of nitric oxide and suppression of proliferation of endothelial cell[13,14] When Uric acid level increased to7mg/dl there is 3-5 fold increased risk of cardiovascular disease than normal uric acid level. Risk of CVD related mortality increased by 15% for every 1mg/dl rise in uric acid levels. Since all participants were patients, we could not eliminate the possible effects of underlying diseases (e.g., hypertension and diabetes), alcohol consumption, medication (e.g. anti-hyperuricemic and anti-lipidemic medications) on the results.Association of uric acid in the development of CVD in elderly metabolic syndrome subjects is well established in many studies.

In our study we have demonstrated association of uric acid in the development of CVD even in elderly subjects without metabolic syndrome. So uric acid is found to be an independent risk factor for cardiovascular diseases. By doing simple biochemical tests, we can prevent the morbidity and mortality caused by CVD. Future study regarding use of drugs that reduce the uric acid in preventing the development of cardiovascular diseases is required.

Conclusion

This study concludes that regardless of presence or absence of metabolic syndrome, carotid artery thickness is increased, with increased uric acid level. So uric acid is found to be a risk factor for CVD independent of MetS status. Thus uric acid can be used as a screening marker for cardiovascular diseases.

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Conflict of interest: Nil

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