The association of serum uric acid with total white blood cell count in a healthy Indian adult population

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Abstract

Background: Atherosclerosis is the underlying cause for nearly all cases of Coronary Artery Disease (CAD) which is a major cause of mortality in men and women. Numerous studies state that the basic pathology behind atherosclerosis is inflammation and oxidative stress. Though uric acid is an anti oxidant, recently studies show that it can be transported across the cell membrane and exert harmful intracellular actions such as oxidation and inflammation. These observations led to many epidemiological studies suggesting that uric acid is linked to and may be a risk factor for CAD. The aim of this study was to evaluate whether there is an association between serum uric acid and total white blood cell count, a simple marker of inflammation, in a healthy Indian adult population.

Method: This is a cross sectional study. Samples were collected for assaying serum uric acid, total white blood cell count and plasma glucose, along with the medical history from 203 apparently healthy individuals who attended health examination at Sri Ramachandra Medical Centre in Chennai.

Result: The results obtained were subjected to statistical analysis in SPSS software version 16. There was a strong positive correlation between uric acid and total white cell count and the study revealed no significant difference in mean levels of uric acid in tobacco users and non-users. And there was no statistically significant difference between genders in the mean uric acid level.

Conclusion: A strongly positive correlation was found between serum uric acid and total white cell count, both in men and women. It appears likely that additionally larger well designed prospective studies that adjust for all possible confounding factors may help to strongly establish the correlation between serum uric acid and total white cell count and their role in pro-inflammatory states as in atherosclerosis.

Keywords: Uric acid, White blood cell count, Inflammation, Coronary artery disease, Atherosclerosis

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Introduction

Coronary Artery Disease (CAD) is the leading cause of mortality worldwide. Beside the well known risk factors like obesity, smoking, diabetes, hypertension and hyperlipidemia[1], various newer risk factors like C-reactive protein, uric acid, homocysteine, fibrinogen, leukocyte count, von Willebrand factor antigen, carotid intima media thickness and peripheral arterial disease have been identified [2.] Early detection of individuals at high risk is likely to aid in the prevention of CAD and also to lower mortality.

Uric acid is the end product of the dietary and endogenous purine metabolism in humans. It is formed from xanthine and hypoxanthine by the action of the enzyme xanthine oxidase whose active site contains the metal molybdenum bound to sulphur and oxygen. Although serum uric acid has been found to possess anti-oxidant property, controversial evidence regarding it being an independent risk marker of atherosclerosis have been reported[3,4,5,6,7,8,9,10]. The available literature suggest that serum uric acid is an independent risk factor to the development of hypertension[11], myocardial infarction[12], coronary artery disease[13], stroke[13] and cardiovascular disease[14]. It has been suggested that the higher levels of uric acid may be a mechanism to counter the excessive oxidative stress seen in these subjects[15].

Several lines of evidence suggest the involvement of inflammation in the pathogenesis of atherosclerosis. A significant positive correlation between uric acid and inflammation was also found in a small case series of heart failure patients. An elevated total white blood cell count is a marker of inflammation which has been found to be associated with an increased risk for cardiovascular disease in several epidemiological studies[16]. The aim of this cross sectional study was to evaluate whether there is a correlation between serum uric acid levels and total white blood cell count in an apparently healthy Indian adult population attending a routine health examination.

Methods

Subjects and data collection: Data was collected from a total of 203 adults (122 men and 81 women) who attended a master health check-up during the month of

June 2015 at Sri Ramachandra Medical Centre in Chennai, Tamil Nadu. All the individuals selected for the study were healthy individuals and were not under any medications. The medical history and BMI, along with the laboratory reports of Total white blood cell count, serum uric acid and fasting plasma glucose were collected for these patients. Serum uric acid was assayed based on Uricase method and plasma glucose based on glucose oxidase- peroxidase method on Advia Clinical Chemistry 1800 instrument. Total white blood cell count was assayed on Beckmann Coulter instrument based on electrical impedance.

Statistical analysis & Results

All statistical analyses were performed with the Statistical Package for the Social Sciences statistical software package for Windows, version 16.0 (SPSS Inc., Chicago, IL, USA), and a two-tailed p value of < 0.05 was considered statistically significant. Correlation between total white blood cell count and serum uric acid was analyzed. There were a total of 203 subjects in the study with 81 women and 122 men. There was a significant positive correlation between TC and serum uric acid levels both in men and women (Table 1 and Fig. 1). The average serum level of uric acid in males is 5.3±0.98 mg/dL and in females is 5.5±0.95 mg/dL. The average total white cell count in males is 7611±1653.7 cells/mm^3 and in females is 8041±1585.9 cells/mm^3. This difference in white cell count and uric acid levels was not statistically significant between the genders.

Student t test was performed to ascertain the effect of smoking on uric acid (Table 2). There was no significant difference between smokers and non smokers in the mean values of uric acid. Assessment of Karl Pearson's co-efficient of correlation between serum uric acid levels with TC in tobacco abusers and non smoking/ no tobacco users was also done (Table 3).

The study group was divided into quartiles based on the serum uric acid concentration to see the trend in total white cell count and other variables (Table 4). One way analysis of variance by ANOVA was used to assess the trend for risk factors. There was a significant positive trend for total white cell count and Body Mass Index (BMI).

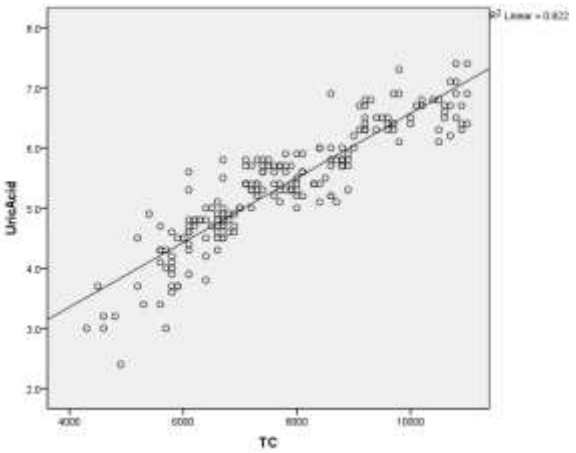

Fig. 1: Scatter plot for correlation of uric acid and total white cell count

Table 1: Correlation between Total white blood cell count and serum uric acid

	n	Correlation
Total	203	0.907
Males	122	0.910
Females	81	0.898

Table 2: Effect of smoking/ tobacco abuse on serum total uric acid levels

	Number	Uric acid (mean±SD)	p Value
Smoker	40	5.8 ± 0.82	0.6
Non smoker	163	5.6 ± 0.77	

Table 3: Correlation between Serum uric acid and total white blood cell count in relation to smoking or tobacco abuse

	Correlation in tobacco abuse	Correlation in non-users of tobacco
Total	0.92	0.90
Males	0.91	0.88
Females	0.86	0.87

Table 4: Characteristics according to the quartiles of serum uric acid

Serum Uric acid level in quartiles	<4.7 n = 50	4.8 – 5.3 n=44	5.4 – 6.0 n=58	>6.0 n=51	p for trend	Linear regression 'p' value
Systolic BP (mmHg)	121.44±17.802	123.77±21.373	134.97±20.479	122.98±24.309	0.003	0.129
Diastolic BP (mmHg)	78.08±8.101	76.18±7.444	81.41±11.492	80.71±10.331	0.028	0.051
Fasting plasma glucose (mg/dl)	113.28±39.226	112.66±54.214	118.41±40.325	121.49±60.157	0.776	0.092
Age (years)	45.88±10.443	46.48±15.716	47.33±12.228	46.75±13.779	0.952	0.099
BMI (kg/m^2)	25.41±4.219	25.76±4.517	26.64±3.928	28.50±4.963	0.003	0.000
TC (cells/ mm^3)	5902±652.621	7190.9±826.823	7915.52±684.618	9984.3±687.713	0.000	0.000

Discussion

The findings in this cross-sectional study of Indian population demonstrate that there is a positive association between uric acid and the simple inflammatory marker, total white cell count. Similar results were found by Kocaman et al in their study[17]. There was no significant difference between tobacco abusers and non-users. Similarly there was no difference in the genders as well. On trend analysis by dividing into quartiles based on uric acid concentration, there was a positive trend in total white blood count, BMI and blood pressure. The positive trend in total white cell count in relation to uric acid was confirmed by multiple linear regression analysis. But the positive trend in BMI was not confirmed by regression analysis. However, uric acid variation with BMI can be further analyzed by choosing individuals with the same BMI in the different uric acid quartiles. There was also a significant positive trend for systolic and diastolic blood pressure except for the last quartile, i.e. persons having > 6.0 mg/dL of uric acid. When this trend was analyzed, a correlation to the mean age was evidenced which could be the confounding factor for this trend. This again, could be further analyzed by including individuals with the same age group in the different uric acid quartiles.

The elevated serum uric acid concentration may be an attempt to compensate for the oxidative stress in CAD. Or, uric acid itself may be involved in the inflammatory process which is an important cause for vascular disease[18]. The essential question of whether uric acid acts as an anti-oxidant or pro-oxidant still remains disturbingly inconclusive. Biscalia et al suggests that this opposing effect of uric acid on oxygen scavenging depends on whether it acts extracellularly or intracellularly[19]. Circulating uric acid has a protective role in vascular endothelial cells. It reacts with different oxidants such as singlet oxygen, hydroxyl and peroxyl radicals producing allantoin, 6-aminouracil and triuret respectively due to its degradation.

This anti-oxidant effect is true only for the uric acid which is in circulation. It becomes a strong pro-oxidant when it penetrates the endothelium or when it is produced within the cell. During the catabolism of hypoxanthine to uric acid, the enzyme xanthine oxidase donates electron to molecular oxygen generating reactive oxygen species (ROS), like superoxide ($O2^-$) and hydrogen peroxide (H2O2). Superoxide exerts a negative effect on numerous membranes thereby playing a causal role in cardiac dysfunction.

The uric acid in circulation was found to enter the cell by a specific renal urate – anion exchange transporter, named URAT-1. Its primary role was found to be reabsorption of uric acid in the proximal convoluted tubule. It was also found to be expressed in the vascular endothelial cells and smooth muscle cells[20]. These observations together suggest that uric acid in circulation can enter the cell and exert harmful effects. It has also been demonstrated in earlier studies in rat models that hyperuricemia causes microvascular changes irrespective of the presence of urate crystals or hypertension[21].

Recent studies also show that uric acid stimulates chemokines such as monocyte chemoattractant protein-1 (MCP-1) and inflammatory markers such as white blood cells, high-sensitivity C reactive protein, interleukins-1,6,10,18, endothelin-1 and tumor necrosis factor-alpha[22], all of which contribute to CAD. Interestingly, allopurinol can block the induction of heat shock protein- 70, a protein related to inflammation[23]. Taken together, these data suggest that uric acid may play a role in the inflammatory process of ischaemia.

Conclusion

There was a strong positive correlation between serum uric acid and total white cell count in this study group. There was no statistically significant difference in mean levels of uric acid in tobacco users and non-users. The difference in white cell count and uric acid levels was not statistically significant between the genders. On trend analysis by dividing into quartiles based on uric acid concentration, there was a positive trend in total white blood count, BMI and blood pressure.

Overall, these findings support the idea that when assessing an individual's risk for atherosclerosis, the concentration of uric acid and the total white blood cell count can be included along with other traditional risk factors like lipid profile.

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References

1. Zhao G, Huang L, Song M, Song Y. Baseline serum uric acid level as a predictor of cardiovascular disease related mortality and all-cause mortality: a meta-analysis of prospective studies. Atherosclerosis. 2013;231(1):61-68. doi:10.1016/j.atherosclerosis.2013.08.023.
2. Evaluation of newer risk markers for coronary heart disease risk classification: a cohort study. Kavousi, Maryam; Elias-Smale, Suzette; Rutten, Joost H W; Leening, Maarten J G; Vliegenthart, Rozemarijn et al. (2012) Annals of internal medicine vol. 156 (6) p. 438-44.
3. Kaya EB, Yorgun H, Canpolat U, et al. Serum uric acid levels predict the severity and morphology of coronary atherosclerosis detected by multidetector computed tomography. Atherosclerosis. 2010;213(1):178-183. doi:10.1016/j.atherosclerosis.2010.08.077.
4. Sinan Deveci O, Kabakci G, Okutucu S, et al. The association between serum uric acid level and coronary artery disease. Int J Clin Pract. 2010;64(7):900-907.

doi:10.1111/j.1742-1241.2009.02263.x.
5. Coutinho T de A, Turner ST, Peyser PA, Bielak LF, Sheedy PF, Kullo IJ. Associations of serum uric acid with markers of inflammation, metabolic syndrome, and subclinical coronary atherosclerosis. Am J Hypertens. 2007;20(1):83-89. doi:10.1016/j.amjhyper.2006.06.015.
6. Gagliardi ACM, Miname MH, Santos RD. Uric acid: A marker of increased cardiovascular risk. Atherosclerosis. 2009;202(1):11-17. doi:10.1016/j.atherosclerosis.2008.05.022.
7. Krishnan E, Pandya BJ, Chung L, Dabbous O. Hyperuricemia and the risk for subclinical coronary atherosclerosis--data from a prospective observational cohort study. Arthritis Res Ther. 2011;13(2):R66. doi:10.1186/ar3322.
8. Neogi T, Ellison RC, Hunt S, Terkeltaub R, Felson DT, Zhang Y. Serum Uric Acid Is Associated with Carotid Plaques: The National Heart, Lung, and Blood Institute Family Heart Study. J Rheumatol. 2008;36(2):378-384. doi:10.3899/jrheum.080646.
9. Riccioni G, D'Orazio N, Palumbo N, et al. Relationship between plasma antioxidant concentrations and carotid intima-media thickness: the Asymptomatic Carotid Atherosclerotic Disease In Manfredonia Study. Eur J Cardiovasc Prev Rehabil. 2009;16(3):351-357. doi:10.1097/HJR.0b013e328325d807.
10. Fazlioğlu M, Sentürk T, Kumbay E, et al. Small arterial elasticity predicts the extent of coronary artery disease: Relationship with serum uric acid. Atherosclerosis. 2009;202(1):200-204. doi:10.1016/j.atherosclerosis.2008.04.014.
11. Grayson PC, Kim SY, LaValley M, Choi HK. Hyperuricemia and incident hypertension: a systematic review and meta-analysis. Arthritis Care Res (Hoboken). 2011;63(1):102-110. doi:10.1002/acr.20344.
12. Trkulja V, Car S. On-admission serum uric acid predicts outcomes after acute myocardial infarction: systematic review and meta-analysis of prognostic studies. Croat Med J. 2012;53(2):162-172.
13. Kim SY, Guevara JP, Kim KM, Choi HK, Heitjan DF, Albert DA. Hyperuricemia and risk of stroke: a systematic review and meta-analysis. Arthritis Rheum. 2009;61(7):885-892. doi:10.1002/art.24612.
14. Kivity S, Kopel E, Maor E, et al. Association of serum uric acid and cardiovascular disease in healthy adults. Am J Cardiol. 2013;111(8):1146-1151. doi:10.1016/j.amjcard.2012.12.034.
15. Nieto FJ, Iribarren C, Gross MD, Comstock GW, Cutler RG. Uric acid and serum antioxidant capacity: a reaction to atherosclerosis? Atherosclerosis. 2000;148(1):131-139. doi:10.1016/S0021-9150(99)00214-2.
16. Wheeler JG, Mussolino ME, Gillum RF, et al. Associations between differential leucocyte count and incident coronary heart disease: 1764 incident cases from seven prospective studies of 30, 374 individuals. Eur Heart J 2004;25:1287–1292.
17. Kocaman SA, Sahinarslan A, Cemri M, Timurkaynak T, Boyaci B, Cengel A. Independent relationship of serum uric acid levels with leukocytes and coronary atherosclerotic burden. Nutr Metab Cardiovasc Dis. 2009;19(10):729-735. doi:10.1016/j.numecd.2008.12.010.
18. Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis J, Watanabe S, Tuttle KR, Rodriguez-Iturbe B, Herrera-Acosta J, Mazzali M. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension 2003;416:1183–1190. [PubMed: 12707287]
19. S. Biscaglia, et al., Uric acid and coronary artery disease: An elusive link deserving further attention, Int J Cardiol (2015), http://dx.doi.org/10.1016/j.ijcard.2015.08.086
20. A. Enomoto, H. Kimura, A. Chairoungdua, Y. Shigeta, P. Jutabha, S.H. Cha, M. Hosoyamada, M. Takeda, T. Sekine, T. Igarashi, H. Matsuo, Y. Kikuchi, T. Oda, K. Ichida, T. Hosoya, K. Shimokata, T. Niwa, Y. Kanai, H. Endou, Molecular identification of a renal urate anion exchanger that regulates blood urate levels, Nature 417 (6887) (2002) 447–452 (May 23).
21. N.L. Edwards, The role of hyperuricemia in vascular disorders, Curr. Opin. Rheumatol. 21 (2) (2009) 132–137 (Mar).
22. C. Ruggiero, A. Cherubini, A. Ble, A.J. Bos, M. Maggio, V.D. Dixit, F. Lauretani, S. Bandinelli, U. Senin, L. Ferrucci, Uric acid and inflammatory markers, Eur. Heart J. 27 (10) (2006) 1174–1181 (May).
23. Y. Shi, J.E. Evans, K.L. Rock, Molecular identification of a danger signal that alerts the immune system to dying cells, Nature 425 (6957) (2003) 516–521 (Oct 2).