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COMPARISON OF URIC ACID LEVELS IN FIRST DEGREE RELATIVES OF ISCHAEMIC HEART DISEASE PATIENTS AND NORMAL POPULATION

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ABSTRACT

Introduction: Worldwide ischaemic heart disease (IHD) is increasing as a major cause of morbidity and mortality. There is an increasing list of established and evolving risk factors associated with the development of IHD. Uric acid is one of the modifiable risk factor which can be controlled by dietary modification. Better control of uric acid levels can delay the development of IHD in first degree relatives (FDRs) of IHD patients. Aim of this study was to assess serum uric acid levels independent of other established risk factors in FDRs of IHD patients and in normal subjects. It was a cross sectional study conducted in Department of Chemical Pathology, Sheikh Zayed Hospital (SZH), Lahore from January 2008 to January 2009.

Materials and Methods: Seventy five first degree relatives of IHD patients were selected. These were the attendants of the patients coming to the cardiology OPD and patients admitted to Coro-nary Care Unit (CCU), SZH Lahore. An equal number of subjects were selected as a control group who had no family history of IHD. After a detailed clinical history and physical examination, fast-ing blood samples were collected. Blood glucose, lipid profile and serum uric acid levels were estimated.

Results and Conclusion: Uric acid levels were found to be higher in FDRs as compared to normal subjects. Further the values were higher in those with an increase in incidence of IHD in the family.

Key Words: Ischaemic heart disease (IHD), First Degree Relatives (FDRs), Coronary Care Unit (CCU), Sheikh Zayed Hospital (SZH).

INTRODUCTION

Arteriosclerosis is a process in which fatty deposits accumulate in the walls of arteries. These fatty deposits build up gradually and irregularly leading to narrowing / hardening of blood vessels. Arteriosclerosis in the coronary arteries leads to their narrowing or occlusion causing ischaemia of heart muscles and can cause angina pectoris or myocardial infarction (MI). From 1990 to 2020, deaths due to cardiovascular diseases (CVD) are expected to rise from 28.4% to 33.4%.[1] People of South Asian descent living in United Kingdom were found to have higher risk of cardiovascular disease as compared to Europeans. With changing habits and life styles, it is likely that the escalation of global cardiovascular disease epidemic will be most marked in India and Pakistan region.[2]

A number of risk factors have been described in the aetiology of IHD. These risk factors can be classified into modifiable and non-modifiable factors. It is now certain that reducing the modifiable risk factors, we can both prevent coronary artery disease and delay its progressions and complications after it has become manifest. The main aim of this study was to compare the uric acid levels (modifiable risk factor) in FDRs (non modifiable risk factor) of IHD patients and in normal subjects. Family history of IHD is an independent predictor[3] and a positive family history identifies the small subsets of families in the population at highest risk for IHD. These are the people who may benefit most from targeted screening and intensive intervention.[4,5]

Uric acid, a product of purine metabolism, is degraded in most mammals by hepatic enzyme, Uricase to allantoin. Serum uric acid in the early stages of atherosclerotic process is known to act as antioxidant. It may be one of the strongest determinants of plasma antioxidant capacity.[6,7] Thus, it may become prooxidant in atherosclerotic vessels due to certain conditions (timing ; acidity and surrounding oxidant milieu) which are different from the normal vessels. Therefore, it is proposed that there is an existence of antioxidant–pro–oxidant redox shuttle in the atherosclerotic micro vascular intima.[8] Serum uric acid is a graded marker of risk for the development of cardiovascular disease and stroke compared to patients with normal serum uric acid levels. It is specially observed in those with serum uric acid in the upper half of its normal physiological range.[9] Hence, elevation of serum uric acid to more than 4

mg/dl should be considered as "red flag" in those patients at risk of developing IHD. This increase in serum uric acid should alert the clinicians to strive to utilize the global risk reduction programme to reduce the morbidity and mortality associated with IHD.[10,11]

MATERIALS AND METHODS

This cross sectional study was conducted in Sheikh Zayed-Federal Postgraduate Medical Institute Lahore. Seventy five apparently healthy subjects in age group 20 – 50 years, comprising equal number of males and females, who were first degree relatives of ischaemic heart disease patients, were included in the study. Seventy five healthy people with no history of ischaemic heart disease in family, matching age and gender as in first degree relatives were also studied as a control group.

Subjects came willingly with prior consent to undergo tests and examination. Criterion for inclusion of subjects was that they had one or more first degree relatives who were known cases of IHD. Exclusion criteria were the same for both first degree relatives and controls i.e. who were known diabetics, known hypertensive, smokers, obese and had abnormal lipid profiles. They were called with overnight 12 hours fast for sample collection.

Fasting blood samples (6 ml) were collected from individuals of all groups under study. It was allowed to clot for 20 – 30 minutes, centrifuged at 3000 RPM for 3 minu-tes and serum separated and estimation for serum uric acid, lipid profile and blood glucose were performed. Dade Behring kit – the urca flex (R) reagent cartridge, Cat No. DF77 was used on Dimension RXL Clinical Chem. System. The data was analysed on SPSS15 (Statistical package for Social Sciences).

Table 1: *Serum uric acid levels (mg/dl) in first degree relatives of ischaemic heart disease patients and control group.*

Serum uric acid levels (mg/dl)	First degree relatives of ischemic heart disease patients		Control Group	
	No. of Cases	Per-centage	No. of Cases	Per-centage
< 5.2	49	65.3	58	77.3
> 5.2	26	34.7	17	22.7
Mean ± SD	4.94±1.41		4.72±1.06	

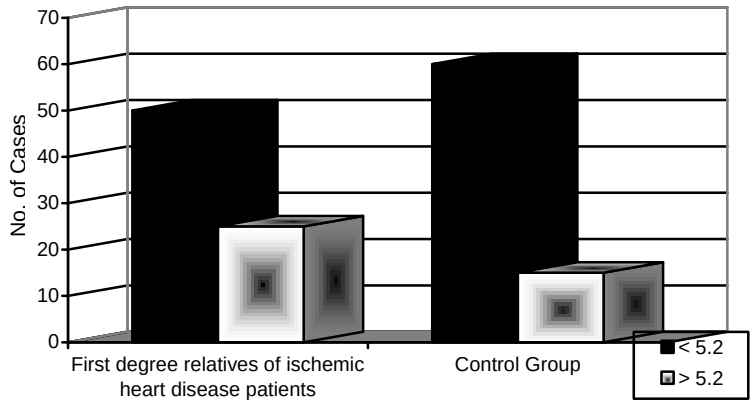

Fig. 1: *Serum uric acid levels (mg/dl) in first degree relatives of ischaemic heart disease patients and control group.*

Table 2: *Descriptive analysis of serum uric acid with the incidence of family history of ischaemic heart disease. Pearson's coefficient of correlation, Mean and S.E.M are given.*

	I Family Member	2 Family Members	>2 Family Members
No. of Cases	37	32	7
Serum Uric Acid	4.573 ± 1.003*	5.212 ± 1.436	05.80 ± 2.492

- P = 0.033 significantly low as compared to those with more than two family members affected.
- Pearson's coefficient of correlation for family history of IHD with serum uric acid = 0.289*

RESULTS

Normal range for serum uric acid is from 3.5 – 7.0 mg/dl. The level of serum uric acid was analysed in the first degree relatives and control group as shown in table 1. Serum uric acid levels were divided in the upper and lower halves i.e. greater than 5.2 mg/dl and less than 5.2 mg/dl.[9,11-13] There were 49 first degree relatives with the levels less than 5.2 mg/dl whereas 26 had more than 5.2 mg/dl. There were 58 cases in control group with values less than 5.2 mg/dl while 17 cases had more than 5.2 mg/dl. Mean ± SD of serum uric acid was higher in the first degree relatives (4.94 ± 1.41) as compared to controls (4.72 ± 1.06). As there is a strong evidence from a number of studies that with the increasing incidence of ischaemic heart disease (IHD) in a family, the relative risk of developing the IHD increases two to three folds in the first degree relatives.[14] Therefore, we analysed the association of serum uric acid with the incidence of ischaemic heart disease in the family (table 2). Serum uric acid when correlated with family history of ischaemic heart disease showed a positive correlation ($P < 0.05$).

First degree relatives were divided into 3 groups. Group A with history of 1 family member affected from IHD. Group B with history of 2 family members affected and group C with history of more than 2 members in family suffering from IHD. The results showed that as the incidence of family history of IHD increased so did the values of serum uric acid in FDRs of IHD patients.

DISCUSSION

Ischaemic heart disease (IHD) is becoming a major health problem worldwide. This disease seems to follow an accelerated course with ischaemic events occurring a decade earlier in Pakistani population as compared to those reported from developed countries.[15] One in four middle aged adults in Pakistan has coronary artery disease and the risk is uniformly increased in young and females.[16] Conventional risk factors do not account for all cases of IHD but still occurs in people with no known risk factor. Amongst the growing list of risk factors for IHD, serum uric acid is a potentially modifiable risk factor. This study was specifically designed to determine the serum uric acid in the high risk group in order to evaluate their future risk of developing ischaemic heart disease. The aim of the present study was to determine the levels of serum uric acid in first degree relatives of IHD patients, as independent predictors to develop IHD, irrespective of known conventional risk factors i.e. (diabetes mellitus, hypertension, hyperlipidaemia and smoking).[17-21] In the present study, serum uric acid was found to be higher in FDR's of IHD patients as compared to normal subjects. This association of uric acid with IHD has been observed in a number of studies.[22] Further, it has been observed that association of SUA with IHD is seen not only with frank hyperuricemia but also in subjects with serum uric acid in the normal to high range (> 5.2 to 5.5 mg/dl).[9,11,12] Similar results were found in the present study with serum uric acid levels less than 5.2 mg/dl in 65% of first degree relatives and 77% of control group, whereas the values were higher than 5.2 mg/dl in 35% of first degree relatives and 23% of control group. Mean ± SD of serum uric acid was higher in the first degree relatives (4.94 ± 1.41) as compared to controls (4.72 ± 1.06). According to Bonora et al, this elevation of serum uric acid is also observed in healthy offspring of parents with coronary artery disease, indicating a possible causal relationship.[22] Another objective of this study was to determine correlation between family history of IHD and serum uric acid level. Serum uric acid increased significantly with an increase in incidence of IHD in the family. Pearson's correlation formula was used that showed a significant positive correlation of serum uric acid with family history.

Main limitation of this study is that these FDR's should have been followed up as it has been observed that if these people are followed up regularly they are likely to develop IHD earlier than those with normal levels. In a meta – analysis of 15 previous relevant studies — Involving a total of more than 9,000 incident cases and more than 150,000 controls, the overall findings suggest that individuals with baseline serum uric acid values in the top third of the population have about a 10% greater risk of developing IHD over the subsequent decade than those in the bottom third of normal range.[18]

Based on this study it is **recommended** that serum uric acid be analysed on a larger scale. Detailed studies should be carried out to define genetics, mechanism of uric acid pathogenicity in development of atherosclerosis in first degree relatives of IHD in our population. These results suggest a positive association of high uric acid and family history of ischaemic heart disease. It indicates that higher serum uric acid may have a significant impact upon early development of atherosclerosis in FDRs as compared to normal population.

It is **concluded** that uric acid can be reduced by simple dietary modification and healthy eating habits. Based on this study it is recommended that all high risk people should be evaluated for serum uric acid along with other established risk factors.

REFERENCES

1. Yusuf S, Dunpuu S, Anand S. Global burden of cardiovascular disease. Circulation 2001; 104: 2855-2864.
2. Raj Bhoopal, Nigel Unwin, Martin White. Heterogeneity of coronary heart disease risk factors in Indian, Pakistan, Bangladeshi, and European origin population. Cross sectional study. BMJ 1999; 319: 215-220.
3. Scheuner MI, Whitworth WC, Mc Gruder H, Yoon PW, Khoury MJ. Expanding the definition of a positive family history for early onset coronary heart disease. Genet Med 2006; 8 (8): 491-501.
4. Leander K, Hallquist J, Reuterwall C. Family history of coronary heart disease, a strong risk factor for MI interacting with other cardiovascular risk factors; results from Stockholm heart epidemiology program (SHEEP). Epidemiology 2001; 12: 215-221.
5. Hunt SC, Williams RR, Barlow GK. Usefulness of cardiovascular family data for population based preventive medicine and medical research (the health family tree study and the NHLBI family heart study. Am J Cardiol 2001; 13: 320-325.
6. Nyyssonen K, Porkkala SE, Salonen JT et al. Ascorbate and urate are the strongest determinants of plasma antioxidantive capacity and serum lipid resistance to oxidation in Finish men. Atherosclerosis 1997; 130: 223-233.
7. Ishizaka N, Ishizaka Y, Ei-Ichi T, Nagai R, Yamakado M. Association between serum uric acid, metabolic syndrome, and carotid atherosclerosis in Japanese individuals. Arterioscler Thromb Vasc Biol. 2005; 25: 1038–1044.

8. Nieto FJ, Iribarren C, Gross MD, Cosmotock GW, Cutler RG. Uric acid and serum antioxidant capacity: a reaction to atherosclerosis? Atherosclerosis. 2000; 148: 131–139.
9. Niskanen LK, Laaksonen DE, Salonen JT et al. Uric acid level as a risk factor for cardiovascular and all cause mortality in middle aged men: a prospective cohort study. Arch Intern Med 2004; 164: 1546-51.
10. Tyagi SC. Intimal redox stress : acclerated atherosclerosis in metabolic syndrome and type 2 diabetes mellitus. Atheroscleropathy Cardiovas Diabetol 2002; 1: 3. doi: 10.1186/1475/-2840-1-3. http://www.cardiab.com
11. Hayden MR, Tyagi SC. Uric acid: A new look at an old risk marker for cardiovascular disease, metabolic syndrome and type 2 diabetes mellitus. The urate redox shuttle. Nutrition and Metabolism 2004; 1: 10. www.nutritionandmetabolism.com/
12. Feig DI, Johson RJ. Hyperuricemia in childhood primary hypertension. Hypertension. 2003; 42: 247–252.
13. Nakagawa T, Tuttle KR, Short RA, Johnson RJ. Fructose - induced hyperuricemia as a casual mechanism for the epidemic of the metabolic syndrome. Nat Clin Pract Nephrol. 2005; 1: 80–86.
14. Maren T. Scheuner, MD, MPH. Clinical application of genetic risk assessment strategies for coronary artery disease: genotypes, phenotypes, and family history. Prim Care Clin Office Pract. 2004; 31: 711–737.
15. Ayub M, Tariq W, Nadeem MA et al. Risk stratification of patients with first acute myocardial infarction with cardiac troponin T. Pak. J. Cardiol. 1996; 10: 54-62.
16. Jaffar T, Jafary F, Jessani S. Heart disease epidemic in Pakistan: Females and males are at an equal risk. Am Heart J 2005; 150: 221-226.
17. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality: the NHANES I epidemiologic follow-up study, 1971–1992. JAMA. 2000; 283: 2404–2410.
18. Wheeler JG, Juzwishin KD, Eiriksdottir G, Gudnason V, Danesh J. Serum uric acid and coronary heart disease in 9,458 incident cases and 155,084 controls : prospective study and meta – analysis. PLOS Med. 2005; 2 (3): e76.
19. W.S. Waring, D.J. Webb and S.R.J. Maxwell. Uric acid as a risk factor for cardiovascular disease. Q J Med 2000; 93: 707-713.
20. Liese AD, Hense HW, Lowel H, Doring A, Tietze M. Association of SUA with all – cause and CVD mortality and incident MI in the MONICA Augsburg cohort. WHO Monitoring Trends and Determinants in CVD's. Epidemiology1999; 10: 391–397.
21. Bengtsson C, Lapidus L, Stendahl C, Waldenstrom J. Hyperuricaemia and risk of cardiovascular disease and overall death. A 12 – year follow-up of participants in the population study of women in Gothenburg, Sweden. Acta Med Scand 1988; 224: 549–555.
22. Bonora E, Targher G, Zenere MB, Saggiani F, Cacciatori V, Tosi F, Travia D, Zenti MG, Branzi P, Santi L, Muggeo M. Relationship of uric acid concentration to cardiovascular risk factors in young men. The Verona Young Men Atherosclerosis Risk Factors Study. Int J Obes Relat Metab Disord1996; 20: 975–980.