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Original Work

Correlation between hyperuricemia and lipid profile in untreated dyslipidemic patients

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ABSTRACT: There are a number of epidemiological studies that suggest the association of cardiovascular diseases and uric acid but very few studies highlight the direct association of deranged lipid profile with uric acid levels. The present study was indented to find out if any association exists between hyperuricemia and dyslipidemia. Blood samples were collected from healthy controls (n=70) and patients with dyslipidemia (n=70) who were not receiving any treatment for dyslipidemia. These samples were processed for estimating lipid profile and uric acid levels. The parameters in the two groups were compared. Correlation between different parameters was calculated by Pearson correlation analysis in both the groups. Uric acid levels (6.40 ± 1.27 vs 4.89 ± 0.21 mg/dl, P<0.001) were significantly higher in patients as compared to those in controls. There was significant increase in the levels of total cholesterol (TC), triglycerides (TAGs), LDL-C, VLDL-C, non-HDL cholesterol (P<0.001 in each case), in patients of dyslipidemia. However, significant decrease in the levels of HDL-C (P<0.001) was seen in patients compared to controls. LDL-C/HDL-C ratio (P<0.001), TC/HDL-C ratio (P<0.001) and TAG/HDL-C ratio (P<0.001) were also significantly increased in dyslipidemic subjects when compared to controls. Uric acid had significant correlations with TC (r=0.334, P<0.001), TAGs (r = 0.288, P<0.001), LDL-C (r = 0.241, P<0.001), VLDL-C (r= 0.158, P<0.001) and HDL-C (r= –0.652, P<0.001) in patients. Results of this study imply that there is higher association of hyperuricemia in dyslipidemic patients than normal subjects. Therefore treatment of underlying hyperuricemia should be an important aspect in planning the treatment strategy for dyslipidemia to reduce the cardiovascular morbidity.

KEY WORDS: ***Cardiovascular disease; Coronary artery disease; Dyslipidemia; Hyperuricemia; Lipid ratio***

INTRODUCTION

Dyslipidemia has been long recognized as a major biochemical event predisposing to atherogenicity and cardiovascular disease (CVD). It is manifested by elevation or attenuation of plasma concentrations of lipoproteins. India is currently experiencing increasing trends in mean cholesterol, LDL cholesterol and triglyceride levels[1]. In India, there has been an alarming increase in the prevalence of CVD over the past two decades so much so that it accounts for 24% of all deaths among adults aged 25–69 years[2]. Inflammatory processes have been increasingly recognized to play a role in pathogenesis of CVD[3]. Various circulating markers of inflammation have been extensively evaluated for their role as risk predictors[4]. Uric acid was once viewed as an inert metabolic product but recently has been shown to be involved in a number of cardio-metabolic disease states including hypertension, metabolic

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syndrome, cardiovascular disease and diabetes[5]. Recently, the question whether it is the cause or effect of these inflammatory conditions has come into the limelight. Experimentally, uric acid (UA) has been shown to generate amino carbonyl radicals, which have pro-inflammatory, and antioxidant effects on vascular smooth muscle cells subsequently leading to cardiovascular disease[6-7]. Thus, it has now been shown to be a contributory causal factor in hypertension, cardiovascular diseases, metabolic syndrome, diabetes, non-alcoholic fatty liver disease and chronic kidney disease.

Uric acid is a weak organic acid, the final enzymatic end product of purine nucleotides degradation[8]. It represents a marker for high levels of damaging oxidative stress associated with the enzymes involved in uric acid production e.g. xanthine oxidase[9]. There are reports, which implicate uric acid as a surrogate marker for oxidative stress[9]. Though there is controversial opinion about pro-oxidative and antioxidant properties of uric acid as it is also a powerful free radical scavenger in humans[10].

Hyperuricemia is a metabolic consequence originating with different etiologies concerned with either increased production or decreased excretion of uric acid or as a combination of both. It is frequently associated with lifestyle related disease factors like gender, diet, obesity, reduced physical activity, increased alcohol consumption, smoking, increased body mass index, etc.[11,12].All these factors are, in themselves, risk factors for Coronary Artery Disease (CAD) and stroke as well[13]. Therefore the definitive role of uric acid is subject to debate, whether it is only a co-existing marker, or a causative risk factor for the pathologic processes occurring in these diseases.

Number of reports supported that hyperuricemia could be seen as an independent predictor of mortality in patients with coronary artery disease (CAD) after adjustment for classic risk factors[14,15]. However some studies did not find a similar relationship between serum UA and cardiovascular outcomes[16]. The relationship between serum uric acid and dyslipidemia is also complex and needs further comprehension. Although some researchers have shown that hyperuricemia is associated with dyslipidemia[17], we did not come across any study specifically assessing the levels of uric acid in untreated patients of dyslipidemia. Therefore the present study was indented to investigate the independent association of serum uric acid and lipid profile including lipid ratios such as LDL-C/HDL-C ratio (LDL-C/HDL-C), total cholesterol/HDL-C ratio (TC/HDL-C) and triglycerides/HDL-C ratio (TAGs/HDL-C) along with non-HDL-C, which can be calculated from the standard lipid profile.

METHODOLOGY

Study design

This study was conducted in the department of Biochemistry, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India, for 10 months (November 2016 to August 2017), after obtaining ethical clearance from the institutional ethical committee for human studies. This was a case-control study in which all dyslipidemic patients coming to the outpatient department of the hospital were recruited to the department. Controls comprised relatives, spouses or friends of the patients and staff members of the institute and were matched for age and sex. Written consent was obtained from all the participants of the study and their detailed medical history recorded. All participants were in the age group of 20-60 years and had no history of any cardiovascular events. Out of 70 patients considered for the study, 33 were recently diagnosed with diabetes but were considered in the study group, as various studies have shown that uric acid is a predictor of diabetes but diabetes does not lead to hyperuricemia[18,19]. Exclusion criteria for this study were: renal dysfunction, liver dysfunction, previous or present history of cardiovascular disease as assessed from history of chest pain, stroke and ECG. Those who had a history of diabetes for more than six months, alcoholics and patients on any kind of anti-hypertensive, hypolipidemic or hypouricemic drug were also excluded from the study.

Anthropometric and blood pressure measurements

Weight was measured using digital scale with sensitivity of 0.1 kg; height was measured to the nearest 0.1 cm using wall-mounted scale. Body Mass Index (BMI) was calculated as weight in kg divided by squared height (m^2). Waist-hip ratio (WHR) was calculated as ratio of waist circumference measured at the level of umbilicus after expiration to hip circumference (measured as maximal horizontal circumference at the level of the buttocks). Blood pressure was measured twice in the right arm of subjects who had been resting for at least 10 min in a seated position using a mercury sphygmomanometer.

Blood collection and biochemical analysis

Four ml of venous blood sample was collected aseptically from all participants, after a 12-14 hour overnight fast, and allowed to clot. Serum was separated by centrifugation at 3000 rpm for 5 min and was subsequently used for estimation of biochemical parameters, *i.e.* for lipid profile parameters (total cholesterol, HDL-C, LDL-C,

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VLDL-C and triglycerides), serum uric acid, renal functions (serum urea and creatinine), liver functions (serum bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) and glucose levels.

Serum cholesterol, serum triglycerides, uric acid, urea, creatinine and glucose were estimated using standard colorimetric enzymatic methods on Advia2400, Germany. Serum cholesterol estimation was carried out by using cholesterol esterase and cholesterol oxidase enzymes[20]. Serum triglycerides were determined after enzymatic hydrolysis with lipase and production of H_2O_2 by glycerol kinase and glycerol phosphate oxidase[21]. Glucose was measured using glucose oxidase enzyme[22]. H_2O_2 produced in all three methods converts 4-aminoantipyrene to red colored quinoneimine dye in presence of peroxidase enzyme. Serum urea was assayed by urease enzyme, creatinine by Jaffe's kinetic method and uric acid by uricase method. HDL-C levels were analyzed by direct method according to standard protocol[23]. Direct LDL-C assay was based on the clearance method.

Statistical Analysis

Results are expressed as mean ± standard deviation (SD). Student's t test has been used for comparison between the continuous variables of the two groups. The relationship between uric acid level and other variables in lipid profile were assessed by Pearson's correlation coefficients.*P*-value less than 0.05 was considered to be statistically significant. All statistical analyses were tabulated in MS Excel and statistically analyzed by using Graphpad online calculator.

RESULT

Table 1 shows anthropometric, physiological and biochemical characteristics of the study population. A total of 140 individuals participated in this study. Considering the cut-off limits of WHR for abdominal obesity as ≥0.85 for females and ≥0.95 for males, 89 per cent of the patients and 18 percent of the controls were found to be obese[24]. However, WHR in the two groups was not significantly different. BMI in the patients was significantly higher (P<0.001) than in controls. Presence of dyslipidemia was diagnosed when a subject had one or more of the following criteria (i) LDL cholesterol of ≥2.58 mmol/l; (ii) non- HDL cholesterol of ≥3.36 mmol/l; (iii) plasma triglycerides of ≥1.69 mmol/l; and (iv) HDL cholesterol of ≤1.03 mmol/l[25]. According to the cut-off values given by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure[26], 55.5 per cent of patients and 10 per cent of controls were categorized as hypertensive. We noted significant difference in the lipid profile parameters and lipid ratios in control and patient group. Levels of Total cholesterol (TC), triglyceride (TAG), HDL-C, LDL-C, VLDL-C are significantly high in dyslipidemic patients (P<0.001 in each case) as compared to controls. We also observed significant increase in LDL-C/HDL-C, TC/HDL-C and TAG/HDL-C ratios (P<0.001 in each case) and levels of non-HDL-C (P<0.001) in dyslipidemic subjects when compared to controls. The increase in serum uric acid levels in dyslipidemic patients is also statistically significant (P<0.001) than the control group.

Table 1:Anthropometric, physiological and biochemical parameters of patients and controls

SN	Parameters	Controls(n=70)	Patients(n=70)	*P*- value
1.	Age (yrs)	39.4±7.96	41.03±6.7*	0.19
2.	Male: Female ratio	33:37	38:32	-
3.	Body mass index (kg/m^2)	25.68±3.32	28.79±4.59**	0.001
4.	SBP (mmHg)	121.2 ± 6.17	140.8 ± 8.47**	0.001
5.	DBP (mmHg)	73.96 ± 9.6	91.9 ± 11.1**	0.001
6.	Waist Hip ratio	0.90±0.08	0.92±0.09*	0.16
7.	Total Cholesterol(mg/dl)	150.07± 5.02	240.56±11.31**	0.001
8.	TAGs(mg/dl)	99.02± 12.72	233.95± 53.74**	0.001
9.	HDL(mg/dl)	42.79± 2.45	37.10± 4.21**	0.001
10.	LDL(mg/dl)	94.82± 0.93	135.40± 0.65**	0.001
11.	VLDL(mg/dl)	18.26± 4.39	68.05±24.86**	0.001
12.	LDL/HDL	2.66± 0.18	3.87± 1.85**	0.001
13.	Total Cholesterol/HDL	4.18± 0.06	6.19± 2.13**	0.001
14.	Triglycerides/HDL	2.73± 0.23	7.068± 4.0**	0.001
15.	Non-HDL(mg/dl)	113.08± 3.46	203.46 ± 25.52**	0.001
16.	Uric acid(mg/dl)	4.89± 0.21	6.40± 1.27**	0.001

TAGs, triglycerides; HDL, high-density lipoprotein; LDL, low density lipoprotein; VLDL, very low density lipoprotein. P*>0.05: Non- significant. P**<0.05: Significant.

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Table 2 shows that there is no significant difference in the levels of urea and creatinine (*P*> 0.05 each) in patients and controls, which depicts normal kidney functions in the two groups. Liver function tests, namely total bilirubin, direct bilirubin. Indirect bilirubin, alanine aminotransferace and alkaline phosphatase (*P* >0.05 in each case) did not show significant difference in the two groups and signify normal liver functions. However levels of blood glucose are statistically different (P<0.05), as we have considered newly diagnosed diabetics (<6 months) in our study.

Figure 1 depicts positive correlations between uric acid and the lipid profile parameters *viz* TC (r=0.334, *P*<0.001), TAGs (r=0.288, *P*<0.001), LDL-C (r=0.241, *P*<0.001) and VLDL-C (r=0.158, *P*<0.001). However, negative correlation was found between uric acid and HDL-C (r= -0.652, *P*<0.001).

Table 2:Fasting blood glucose, hepatic and renal markers in patients and controls

SN	Particulars	Controls(n=70)	Patients(n=70)	*P*- value
1	Glucose(mg/dl)	94.08± 22.63	119.85± 5.65**	0.0001
2	Total Bilirubin(mg/dl)	0.65±0.27	0.63± 0.20*	0.5361
3	Direct Bilirubin(mg/dl)	0.21±0.07	0.20±0.06*	0.3657
4	Indirect Bilirubin(mg/dl)	0.44±0.2	0.46±0.1*	0.421
5	AST	24.75±0.70	25.97±2.48**	0.0001
6	ALT	25.32±7.78	27.69± 8.90*	0.0957
7	ALP	91.08±19.79	90.97±14.84*	0.9704
8	Urea(mg/dl)	22.46± 1.20	22.43± 1.13*	0.8792
9	Creatinine (mg/dl)	0.64 ± 0.17	0.67± 0.08*	0.1838

AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase. P*>0.05: Non-significant. P**<0.05: Significant.

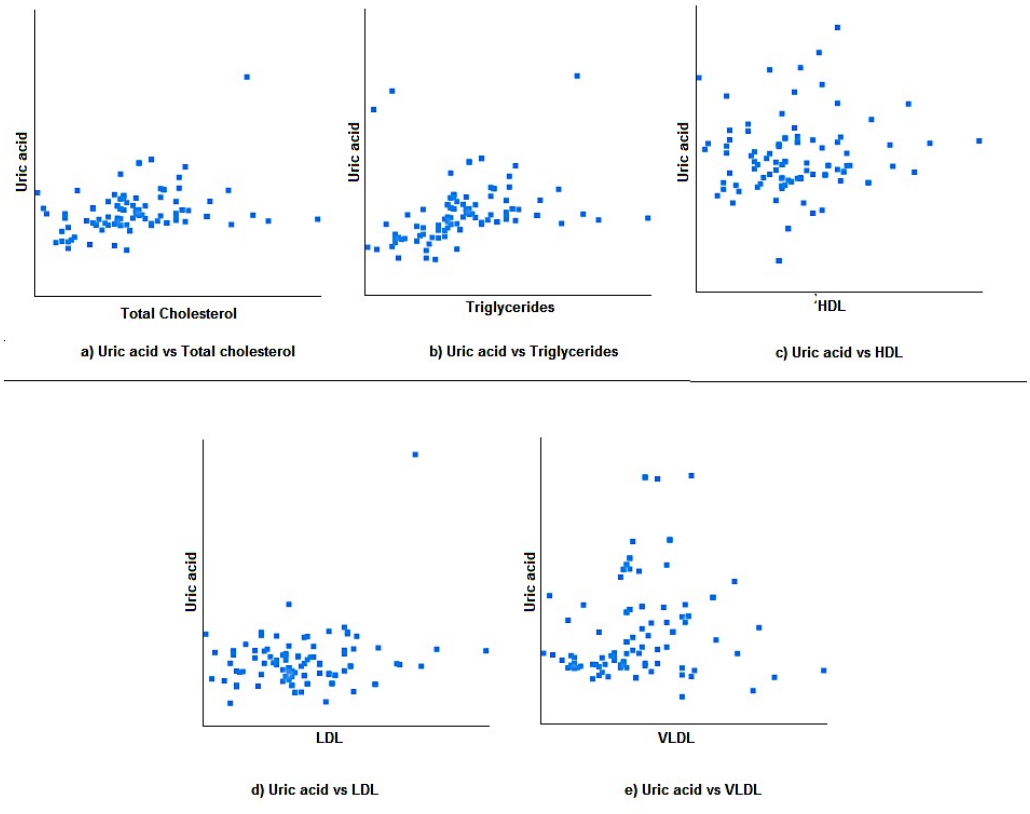

Fig. 1: Relation of Serum uric acid with lipid profile in dyslipidemia patients

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DISCUSSION

Our study illustrated a strong association between serum uric acid levels and lipid profile of dyslipidemic patients after controlling for sex, age and BMI. Several epidemiological studies highlight the contribution of dyslipidemia to cardiovascular risk[27,28]. Moreover, serum uric acid has been observed to be highly associated with the development of cardiovascular disease for more than 50 years. Cardiovascular diseases (CVDs) are consequences of atherosclerosis and are related to oxidative stress[29]. Uric acid represents a marker for high levels of damaging oxidative stress associated with increased xanthine oxidase activity[30]. It is a product of purine nucleotide catabolism, the process catabolized by hepatic enzyme xanthine oxidoreductase (XOR), which enables the oxidation of hypoxanthine to xanthine and its further oxidation to uric acid[31]. It not only catalyzes the production of uric acid but also nitric oxide and reactive oxygen species, which potentially damage nucleic acids and proteins and convert polyunsaturated fatty acids to lipids[32]. Thus in this process of catabolism, reactive oxygen species (ROS) are generated as by-products, having significant role in the increased oxidative stress[31].

Experimental data also suggests the impact of uric acid on oxidative stress per se, via mechanism that NO- labeled 1,3-$^{15}N_2$ uric acid ($^{15}N_2$-UA) under anaerobic conditions in several different media, including human plasma and endothelial cell lysates results with the production of 5-aminouracil (5-AU) and 6-aminouracil (6-AU)[33].

Although in experimental studies it has been shown that rats administered with uric acid exhibited dyslipidemia and glucose intolerance, which were probably mediated by hypothalamic inflammation and hypothalamic neuroendocrine alterations as uric acid produces this inflammatory response through activation of NF-κB in the hypothalamus[34], very few studies in humans link the association of uric acid with dyslipidemia[35].

Several past studies have shown that high levels of plasma TAG are related to hyperuricemia[36,37] and potential mechanism for the same could be explained on the basis that TAG synthesis accelerates the de novo synthesis of ribose-5-phosphate to phosphoribosyl pyrophosphate(PRPP) through the common metabolic pathway of NADP-NADPH, and as a result, uric acid production increases[38].A positive correlation of uric acid and TAG as depicted in our study is in line with these studies. Negative correlation observed between uric acid and HDL-C is also in support from some previous studies[39,40].

Detection of dyslipidemia at a preliminary level and its proper management will be able to prevent the morbidity and complications of CVD. Positive correlation between hyperuricemia and dyslipidemia, as illustrated in our study, may facilitate the claim that serum uric acid could serve as a simple and economically viable biomarker in CAD patients. Moreover, due to strong concurrence of dyslipidemia and hyperuricemia, it is advisable to develop appropriate treatment guidelines, taking into consideration the pharmacologic measures at improving hyperuricemia and holistic approach for treating CVD risk factors including diet and life style modification.

Traditionally, cholesterol measurements were considered most accurate at predicting the risk of atherosclerosis, especially in those at lower or higher ends of the risk spectrum, but these measurements are less helpful in the majority of people whose risk falls somewhere in between the spectrum. Therefore, recently lipid ratios have gained much attention. Changes in these ratios represent a better indicator for risk reduction in CAD patients than the absolute values of individual lipoproteins[41].

In the *Helsinki* Study, a five-year clinical trial of more than 4,000 middle-aged men with elevated lipids, the LDL-C/HDL-C ratio and TC/HDL-C ratio had more prognostic value[28].Moreover, the LDL-C/HDL-C and TC/HDL-C ratios help in initiating lipid-lowering therapy[42]. Results of prospective studies[43] have suggested that a high LDL-C/HDL-C ratio combined with hypertriglyceridemia, together referred to as atherogenic dyslipidemis[44], along with TC/HDL-C ratio may be simpler cumulative markers for Ischemic Heart Disease (IHD). Also current NCEP guidelines recommend non-HDL-C as a secondary target of therapy if triglyceride levels exceed 200mg/dl[45].

Thus in our study, we have taken into consideration the lipid fractions i.e. LDL-C/HDL-C, TC/HDL-C and TAG/HDL along with non-HDL-C as more accurate markers of dyslipidemia and observed significant increase in their values in patients when compared to controls (**Table 1**). Our results are in accordance to the study conducted by Sathiya *et al*[46], who also found altered values of these parameters in CAD patients

The limitations of this study warrant consideration. Firstly, the population size was small and only included patients from southern region of the National Capital Territory of Delhi, as well as the adjoining areas of the neighboring state. Thus, our population was not representative of the entire Indian population. Secondly, we did not analyze our patients gender-wise because of small sample size. It is also possible that unmeasured confounding variables may exist. The strength of the study was that treatment-naïve dyslipidemic subjects were considered for the study. Also, we studied lipid fractions in addition to the standard parameters of lipid profile in patients and controls.

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CONCLUSION

Our study showed significant higher levels of uric acid in dyslipidemic subjects. Since dyslipidemia predicts the risk of CAD, it is important to consider uric acid levels in these patients for more comprehensive strategic management of risk factors. Visa-versa, while establishing the diagnosis of hyperuricemia, clinical suspicion of coexistent dyslipidemia should also be considered.

REFERENCES

1. Gupta R, Guptha S, Gupta VP, Agarwal A, et al. Twenty year trends in cardiovascular risk factors in India and influence of educational status. *Eur J PrevCardiol*.2012;19:1258-71.
2. Sample Registration System. Million Death Study: Preliminary Report on Causes of Death in India 2001–2003. New Delhi: Registrar General of India, 2007.
3. Eckel RH, Wassef M, Chait A, Sobel B, et al. Prevention Conference VI: Diabetes and Cardiovascular Disease: Writing Group II: pathogenesis of atherosclerosis in diabetes. *Circulation*. 2002;105:e138-43.
4. Folsom AR, Chambless LE, Ballantyne CM, Coresh J, et al. An assessment of incremental coronary risk prediction using C-reactive protein and other novel risk markers: the atherosclerosis risk in communities study. *Arch Intern Med*. 2006;166:1368-73.
5. Kanbay M, Jensen T, Solak Y, Le M, Roncal-Jimenez C, et al. Uric acid in metabolic syndrome: from an innocent bystander to a central player. *Eur J Intern Med*. 2016;29:3-8.
6. Santos CX, Anjos EI, Augusto O. Uric acid oxidation by peroxynitrite: multiple reactions, free radical formation, and amplification of lipid oxidation. *Arch Biochem Biophys*.1999;372:285–94.
7. Rao GN, Corson MA, Berk BC. Uric acid stimulates vascular smooth muscle cell proliferation by increasing platelet derived growth factor A-chain expression. *J Biol Chem*. 1991;266:8604-8.
8. George J, Struthers AD. Role of urate, xanthine oxidase and the effects of allopurinol in vascular oxidative stress. *Vasc Health Risk Manag*. 2009;5:265-72.
9. Ferguson LD, Walters MR. Xanthine oxidase inhibition for the treatment of stroke disease: a novel therapeutic approach. *Expert Rev CardiovascTher*.2011;9:399-401.
10. Waring WS. Uric acid: an important antioxidant in acute ischaemic stroke. *QJM*. 2002;95:691-3.
11. Kang DH. Potential role of uric Acid as a risk factor for cardiovascular disease. *Korean J Intern Med*. 2010;25(1):18-20.
12. Rathmann W, Funkhouser E, Dyer AR, Roseman JM. Relations of hyperuricemia with the various components of the insulin resistance syndrome in young black and white adults: the CARDIA study. Coronary Artery Risk Development in young adults. *Annals Epidemiol*. 1998;8(4):250-61.
13. Nagahama K, Iseki K, Inoue T, Touma T, et al. Hyperuricemia and cardiovascular risk factor clustering in a screened cohort in Okinasura, Japan. *Hypertens Res*. 2004;27:227-33.
14. Freedman DS,Williamson DF, Gunter EW, Byers T. Relation of serum uric acid to mortality and ischemic heart disease. The NHANES I Epidemiologic Follow-up Study. *Am J Epidemiol*.1995;14:637-44.
15. Puddu P, Puddu GM, Cravero E, Vizioli L, et al. The relationships among hyperuricemia, endothelial dysfunction, and cardiovascular diseases: molecular mechanisms and clinical implications. *J Cardiol*.2012;59:235-42.
16. Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. *Ann Intern Med*. 1999;131:7-13.
17. Sarmah D, Sharma B. A correlative study of uric acid with lipid profile. *Asian J Medical Sci*. 2013;4(2):8-14.
18. Johnson RJ, Perez-Pozo SE, Sautin YY, et al. Hypothesis: could excessive fructose intake and uric acid cause type 2 diabetes? *Endocr Rev*. 2009;30:96-116.
19. 19. Lin KC, Tsai ST, Lin HY, Chou P. Different progressions of hyperglycemia and diabetes among hyperuricemic men and women in the kinmen study. J Rheumatol.2004;31:1159-65.
20. Allain CC, Poon LS, Chan CS, Richmond W, et al. Enzymatic determination of total serum cholesterol. *ClinChem*.1974;20(4):470-5.
21. Fossati D, Prencipe L. Serum triglycerides determined colorimetrically with an enzyme that produces hydrogen peroxide. *ClinChem*.1982;28:2077-80.
22. Barham D, Trinder P. An improved color regent for the determination of blood glucose by oxidase system. *Analyst*.1972;97:142-5.
23. Burstein M, Scholnick HR, Morgin R. Rapidmethod for isolation of lipoprotein from human serum by precipitation with polyanion. *J Lipid Res*. 1970;11(6):583-95.
24. Rexrode KM, Carey VJ, Hennekens CH, Walters EE, et al. Abdominal adiposity and coronary heart disease in women. *JAMA*.1998;280:1843-8.
25. National Cholesterol Education Program. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in

 DOI: http://dx.doi.org/10.4314/ijmu.v13i1.2

adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486-97.
26. Chobanian AV, Bakris GL, Black HR, Cushman WC, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure.*JAMA*. 2003;289:2560-71.
27. Libby P. Pathophysiology of coronary artery disease. *Circulation*. 2005;111(25):3481-88.
28. Manninen V, Tenkanen L, Koskinen P, Huttunen JK, et al. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study. Implications for treatment. *Circulation*.1992;85(1):37-45.
29. Reunanen A, Takkunen H, Knekt P, Aromaa A. Hyperuricemia as a risk factor for cardiovascular mortality. *Acta Med Scand Suppl*.1982;668:49-59.
30. Ferguson LD, Walters MR. Xanthine oxidase inhibition for the treatment of stroke disease: a novel therapeutic approach. *Expert Rev Cardiovasc Ther*.2011;9:399-401.
31. Schulz E, Gori T, Munzel T. Oxidative stress and endothelial dysfunction in hypertension. *Hypertens Res*.2011;34:665-73.
32. Riegersperger M, Covic A, Goldsmith D. Allopurinol, uric acid and oxidative stress in cardiorenal disease. *IntUrol Nephrol*.2011;43:441-9.
33. Gersch C, Palii SP, Kim KM, Angerhofer A, et al. Inactivation of nitric oxide by uric acid. *Nucleosides Nucleotides Nucleic Acids*.2008;27:967-78.
34. Lu W, Xu Y, Shao X, Gao F, et al. Uric acid produces an inflammatory response through activation of NF-Kb in the hypothalamus: Implications for the pathogenesis of metabolic disorders.*Sci Rep*.2015;5:12144.
35. Peng TC, Wang CC, Kao TW, Chan JH, et al. Relationship between hyperuricemia and lipid profile in US adults. *BioMed Res Inter*.2015;2015:127596
36. Clausen JO, Borch-Johnsen K, Ibsen H, Pedersen O. Analysis of the relationship between fasting serum uric acid and the insulin sensitivity index in a population-based sample of 380 young healthy Caucasians. *Eur J Endocrinol*.1998;138:63-9.
37. Conen D, Wietlisbach V, Bovet P, Shamlaye C, et al. Prevelence of hyperuricemia and relation of serum uric acid with cardiovascular risk factors in a developing country. *BMC Public Health*. 2004;4:9.
38. Matsuura F, Yamashita S, Nakamura T, Nishida M, et al. Effect of visceral fat accumulation on uric acid metabolism in male obese subjects: visceral fat obesity is linked more closely to overproduction of uric acid than subcutaneous fat obesity. *Metaboism*.1998;47:929-33.
39. Silva HA, Carraro JC, Bressan J, Hermsdorff HH. Relation between uric acid and metabolic syndrome in subjects with cardiometabolic risk. *Einstein (Sao Paulo)*. 2015;13:202-8.
40. Rho YH, Choi SJ, Lee YH, Ji JD, et al. The prevalence of metabolic syndrome in patients with gout: a multicenter study.*J Korean Med Sci*.2005;20:1029-33.
41. Lloyd-Jones DM. Cardiovascular risk prediction basic concepts,current status, and future directions. *Circulation*. 2010;121:1768-77.
42. Rana JS, Boekholdt SM, Kastelein JJP, Shah PK. The role of non-HDL cholesterol in risk stratification for coronary artery disease. *CurrAtheroscler*. 2012;14(2):130-4.
43. Asssmann G, Schulte H, Funke H, von-Eckardstein A. The emergence of triglycerides as a significant independent risk factor in coronary artery disease. *Eur Heart J*. 1998;19(suppl M):M8-M14.
44. Grundy SM. Small LDL, atherogenic dyslipidemia, and the metabolic syndrome. *Circulation*.1997;95:1-4.
45. Third Report of the National Cholesterol Education Program (NCEP) Expert panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106-421.
46. Sathiya R, Velu VK, Niranjan G, Srinivasan AR, et al. A comparative study of serum uric acid levels and lipid ratios in coronary artery disease patients. *Int J Biomed Sci*.2014;10(2):124-8.

 DOI: http://dx.doi.org/10.4314/ijmu.v13i1.2