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Evaluation Of Uric Acid Level, A New Biomarker In Patients With Metabolic Syndrome.

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ABSTRACT

The metabolic syndrome, which is characterized by obesity, serum lipid profile alterations, hypertension, and fasting hyperglycemia, is very common in developed countries, and its prevalence is likely to increase. Uric acid, the end product of purine catabolism has been identified as one of the risk factors in the development of metabolic syndrome, coronary artery disease and diabetes mellitus. To study the evaluation of uric acid level a new biomarker in patients with metabolic syndrome. The Present study was carried out in the department of Biochemistry, SLIMS, Puducherry. The present study was conducted on 200 patients with diabetes mellitus, 200 patients with metabolic syndrome, and 200 patients with controls as per International Diabetic Fedaration criteria and waist circumference, The analysis of plasma glucose was done by the glucose oxidase method, while the serum uric acid, LDL, Urea, Creatinine, Ghb and triglycerides were evaluated by enzymatic methods, Lpa -estimated through the turbidometic method. In this method, the presence of cut off value for the consideration as elevated Lp(a) levels was>30mg/dl Serum uric acid levels are elevated when compare to other parameters (FBS, Ghb, LDL, Urea, Creatinine, TGL, Lpa,). This facilitates the claim that serum uric acid in association with the lipid ratios could serve as simple and economically viable biochemical marker.

Keywords: Metabolic syndrome, Uric acid, Hypertension

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INTRODUCTION

Metabolic Syndrome has been an increased prevalence of the disease in the last several years, with almost a quarter of the total population being affected in the United States (Ford et al., 2004), and prevalence has also increased in Europe (Hu et al., 2004), Africa (Longo- Mbenza et al., 2010) and China (Gu et al., 2005), and even in specific aboriginal populations around the world (O'Dea et al., 1999).In a developing country like India, increasing urbanization and lifestyle changes have led to an increased incidence of Metabolic syndrome. Though a limited amount of data exists on the prevalence of metabolic syndrome in India, prevalence data from the diabetic population is lacking. We explored the prevalence of metabolic syndrome in an urban Indian diabetic population using the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines.[1]

Metabolic syndrome is a cluster of metabolic abnormalities which confers upon an individual a substantial increase in cardiovascular disease (CVD) risk - approximately twice as high as those without the syndrome. Compared to those without metabolic syndrome, those with it are at an increased risk of mortality from cardiovascular disease (CVD), coronary heart disease, stroke, vascular dysfunction, and all-cause mortality [2]. While the pathogenesis of metabolic syndrome and its components is not well understood, central obesityand insulin resistance are recognized as causative factors. Several different organizations have outlined diagnostic criteria for metabolic syndrome, which designates values for obesity (waist circumference or BMI), triglyceride levels, HDL (High Density Lipo-protein) levels, hypertension, hyperglycemia, and sometimes urine albumin or albumin: creatinine ratio. Based on AHA criteria, nearly 35% of US adults, and 50% of those older than 60 years old, have metabolic syndrome [3]. Regardless of which criteria are used, the primary concern is early detection of potential CVD complications and early intervention [4,5].

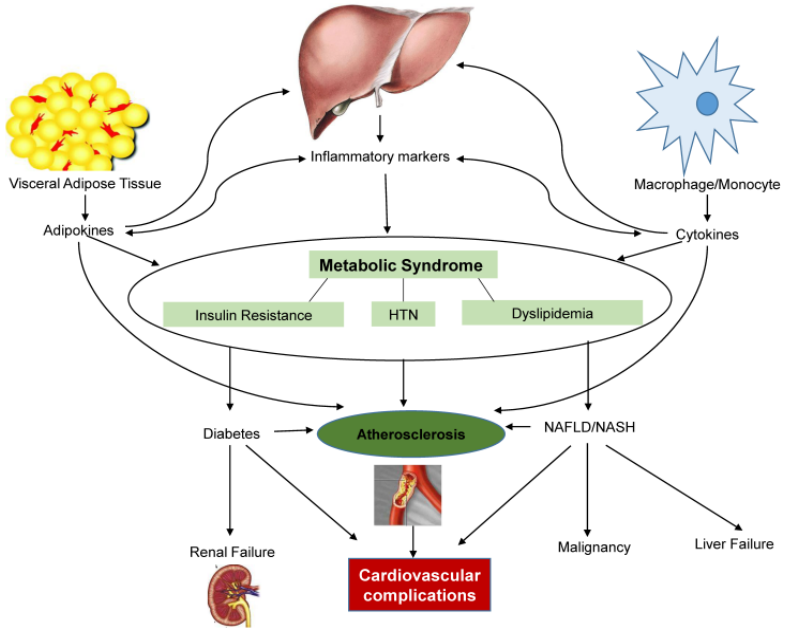

Figure 1: Interaction of adipokines, cytokines, and inflammatory markers that contribute to the development of metabolic syndrome and its complications. HTN-Hypertension, NAFLD/NASH- [Nonalcoholic fatty liver disease/nonalcoholic steatohepatitis].

Though the National Cholesterol Education Program (NCEP) ATP III report and WHO have both identified CVD as the primary clinical outcome of metabolic syndrome, most people with metabolic syndrome will have insulin resistance, which results in increased risk for type 2 diabetes (Figure 1). Once diabetes becomes clinically apparent, CVD risk rises sharply. In addition to CVD and type 2 diabetes, individuals with metabolic syndrome are seem increasingly more susceptible to other conditions, including polycystic ovary syndrome, fatty liver, cholesterol gallstones, asthma, sleep disturbances, and some forms of cancer, such as breast, pancreatic, colorectal, and prostate [6, 7].

Uric acid at normal plasma levels has been known to exert a neuro protective effect, by acting as a free-radical scavenger; however, several observational studies have indicated that high levels of serum uric acid are associated with the risk of cardiovascular disease and may be useful in the assessment of individual cardiovascular risk. Further- more, high uric acid levels have also been associated with insulin resistance (IR), diabetes mellitus type 2 (DM2), and metabolic syndrome (MetS).[8,9]

Elevated serum uric acid (SUA) levels are commonly seen in patients with the metabolic syndrome (MetS). Several mechanisms, both direct and indirect, connect the increased SUA levels with the established diagnostic criteria of MetS. It is possible that the increased cardiovascular disease risk associated with the MetS is partially attributed to elevated circulating SUA concentration. Several drugs used in the treatment of MetS may alter SUA levels. Thus, lifestyle measures together with the judicious selection of drugs for the treatment of hypertension, dyslipidemia, and insulin resistance associated with MetS may result in a reduction of SUA levels and possibly cardiovascular disease risk. If uric acid plays a pivotal role in the development of metabolic syndrome, then it is critical to understand what stimuli are involved in augmenting serum uric acid levels. This is important since these processes themselves might play an active role in contributing to the development/progression of metabolic syndrome. For example, excessive alcohol intake or thiazide diuretics have been shown to result in all components of metabolic syndrome [10,11].

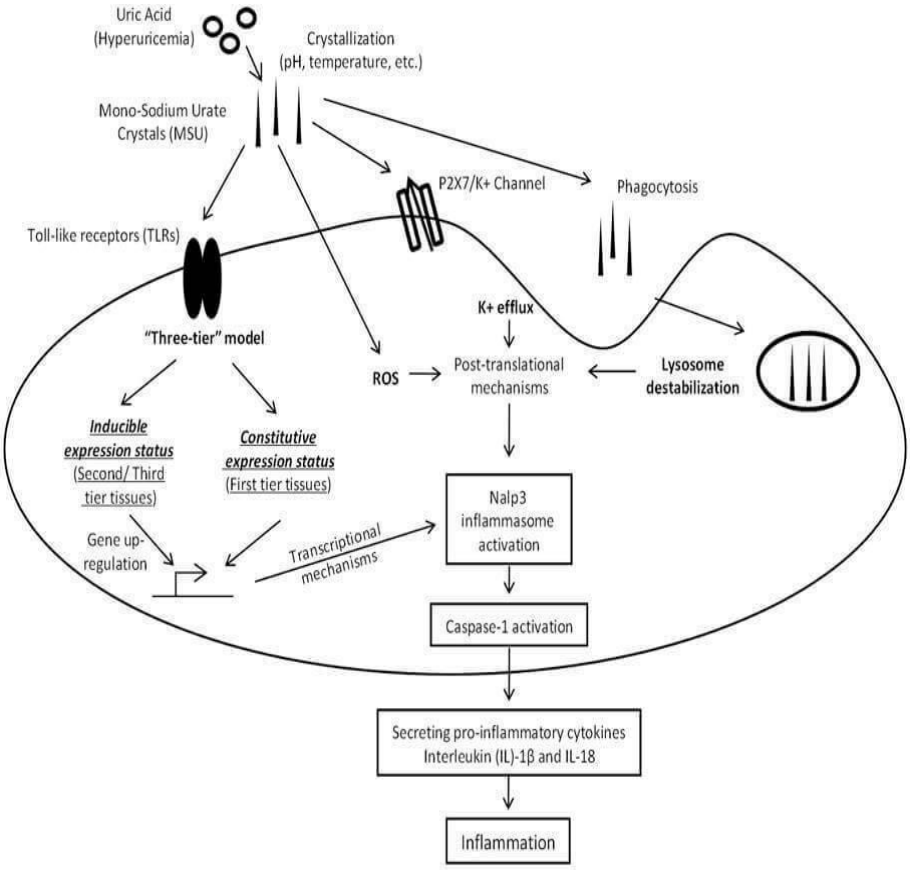

Figure 2: This figure shows the role of uric acid in inflammation conditions.

Hyperuricemia can be an accompaniment disorder with syndrome X (characterized by abdominal obesity, impaired glucose tolerance, increased LDL Cholesterol & decreased HDL Cholesterol). Several studies show that hyperuricemia is one of the risk factors of metabolic syndrome and it clearly has a strong correlation between various components of diabetic dyslipidemia including raised LDL, reduced HDL, raised triglycerides.

Several epidemiologic studies have reported that high serum levels of uric acid are strongly associated with prevalent health conditions such as obesity, insulin resistance, metabolic syndrome, diabetes, essential [12] hypertension, and renal disease. Population- based studies have shown that hyperuricemia is an independent risk factor for cardiovascular disease (CVD). This association has been found to be particularly

robust among individuals at high risk for CVD, including those with [12]obesity, hypertension, diabetes and renal disease. In this background the present study was done to evaluate the relationship between serum uric acid levels and metabolic syndrome.

Objective of the Study

Our aim of the study is to evaluation of uric acid level a new biomarker in patients with metabolic syndrome.

MATERIALS AND METHODS

The Present study was carried out in the department of Biochemistry, SLIMS, Puducherry. This study was conducted over a period of 18 months during which 400 subjects were recruited for the study. 200 subjects were taken as cases of metabolic syndrome and 200 subjects as controls. The controls were age and sex matched with the cases.

Diagnosis of metabolic syndrome was based on the criteria of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP-III). The 5 risk factors mentioned were: (1) triglyceride levels >150 mg/dl; (2) HDL-C levels <40 mg/dl in men or <50 mg/dl in women; (3) fasting plasma glucose levels >110 mg/dl or taking antidiabetic medication; (4) systolic blood pressure>130 mm Hg or diastolic blood pressure >85 mm Hg or taking an antihypertensive medication; and (5) BMI >25 kg/m2. A diagnosis of metabolic syndrome can be made if any three of the above mentioned three characteristics are present in a patient. For the present study, known diabetics and hypertensives were tested for dyslipidemia and blood uric acid levels. Those diabetics and hypertensives who had dyslipidemia were considered to be having Metabolic Syndrome and therefore included for the study.

Inclusion criteria for cases

Age group: 40 – 80 years (males and females) History of type II diabetes mellitus for a minimum of 5 years, History of hypertension for a minimum of 5 years.

Exclusion criteria for cases

Hepatic disorders Renal disorders Alcoholics, smokers Subjects on drugs which may increase serum uric acid level such as Diuretics, Ascorbic acid, Aspirin, Caffeine, Cisplatin, Diazoxide, Epinephrine, Ethambutol, Levodopa, Methyldopa, Nicotinic acid, Phenothiazines, Theophylline were excluded. Subjects on drugs which may decrease serum uric acid level such as Allopurinol, Azathioprine, Clofibrate, Corticosteroids, Estrogen, Guaifenesin, Mannitol, Probenecid, and Warfarin were excluded.

Controls: 200 age and sex matched healthy controls were included in the study.

Methods of analysis

After a 12-hour fasting period, venous blood samples were collected from all the cases and controls. Blood samples were centrifuged and serum was separated. The analysis of plasma glucose was done by the glucose oxidase method, while the serum Uric acid was measured by uricase method. LDL, Urea, Creatinine, Ghb and triglycerides were done by using enzymatic kits on siemens TM autoanalzyer. Lpa-estimated through the turbidometic method. In this method, the presence of cut off value for the consideration as elevated Lp(a) levels was>30mg/dl. Results were tabulated and statistical analysis was done by using Windows SPSS program 15.0.

RESULTS OF THE STUDY

Increased Serum uric acid ($P<0.001$) levels were found in MetS and controls.The p-value <0.001 is comparatively highly significant.Fasting blood glucose($P<0.001$)levels, Ghb ($P<0.002$) were significantly increased inMets patients when compared withcontrols.The p-value <0.001 is comparatively highly significant.

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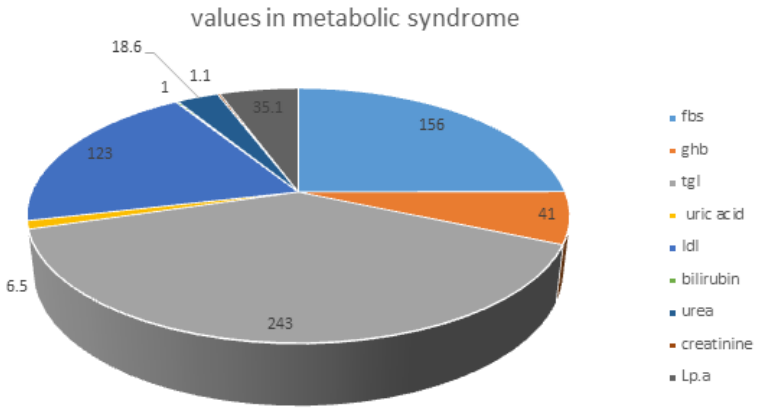
Serum LDL(P<0.002),TG(P<0.001) levels were significantly increased in Metspatients when compared withcontrols.The p-value <0.001 is comparatively highly significant. Urea(P<0.001), Creatinine(P<0.001), and Bilirubin(P<0.001)significantly increased like uric acid.the p-value <0.001 is comparatively highly significant. (Table No.1).Serum Lp a(P<0.003) was significantly increased in Met S patients when compared with controls.The p-value <0.001 is comparatively highly significant.

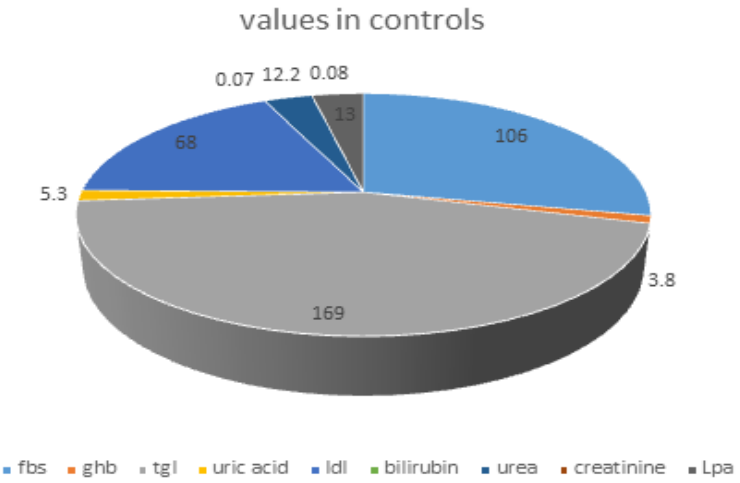
The statistical analysis was done by the unpaired two tailed't' test and the Pearson's correlation coefficient by using online calculator. The data were presented as mean with SD. The statistical significance was kept as a P value of < 0.05.ple.the p-value <0.001 is comparatively highly significant.

Table 1: The Mean±SD values of Urea, creatinine, LDL, FBS, Ghb, Uric acid, LDL, bilirubin, LP(a) in metabolic syndrome patients and control.

S.No.	Parameters	MetS(n-200) Mean±SD	Controls(n-200)	p Value
1	FBS	156.55± 4.82	106.12± 1.68	p<0.001
2	Ghb	41.1±1.2	3.86%	P<0.002
3	TGL	243±28.62	169.2±28.4	P<0.001
4	Uricacid	6.5± 0.42	5.22± 0.23	p<0.001
5	LDL	123.8±31.4	68.3±13.2	P<0.002
6	Bilirubin	1.0± 0.04	0.07 ± 0.02	p<0.001
7	Urea	18.6±1.28	12.2±1.01	p<0.001
8	Creatinine	1.1±0.06	0.08±0.02	p<0.001
9	LP(a)	35.10±13.2	13.0±6.78	p<0.003



Graph:1 Shows the values of FBS,Ghb,TGL,Uric acid LDL,Bilirubin,urea,Creatinine, and Lpa in Metabolic syndrome patients.



Graph:2 Shows the values of FBS,Ghb,TGL,Uric acid LDL,Bilirubin,urea,Creatinine, and Lpa in Control patients.

DISCUSSION AND CONCLUSION

Uric acid is one of the major endogenous water soluble antioxidants of the body. There is accumulating evidence that increased oxidative stress is closely related to diabetes and its vascular complications. Thus high circulating Uricacid(UA) levels may be an indicator that the body is trying to protect itself from the deleterious effects of free radicals by increasing the product of endogenous antioxidants. eg. Uric acid

Interestingly, UA prevents oxidative modification of endothelial enzymes and preserves the ability of endothelium to mediate vascular dilation in the face of oxidative stress. There is also same evidence that UA may have a direct role in the atherosclerotic process because human atherosclerotic plaque contains more UA than do control arteries. Inflammation is one of the features of atherosclerosis and UA crystals may induce inflammatory responses that are reduced by lipoproteins which have ability to bind UA crystals. Hyperuricemia via purine metabolism may also promote purine base formation.

In primary stage increasing purine synthesis by idiopathic & inherited metabolic disease secondary excessive dietary purine intake mainly cause for hyperuricemia. Hyperuricemia will occur due to increased ATP turnover by alcohol, tissue hypoxia. Increased nucleic acid turnover also cause for hyperuricemia by malignant disease, psoriasis, chronic renal disease, decrease renal reabsorption, decreased selection will cause for UA changes xanthine oxidase enzyme mainly cause to UA levels in serum. When increased this enzyme uricacid formation will increase, when decreased oxidase enzyme UA formation will decrease in the serum.

Hyperuricemia associated with elevated circulating endothelial levels and are of the major sites of the production of UA in cardiovascular system. High uricacid levels were independently associated with increased proximal tubular sodium reabsorption in men UA other hand cause to hypertension in metabolic syndrome and diabetes mellitus.

UA may have a direct role in atherosclerotic process because of human atherosclerotic plaque contains more UA than do control arteries. UA effects the kidney functions, this leads to kidney failure and effects as the circulatory system, this is leads to stroke and CVD. UA effects as the urate formation, and reabsorption of the proximal tubule in the kidney.

Higher UA levels may be a risk factor for HTN, and CVD, due to excess of lipids in blood leads to major complications namely atherosclerosis & hyper lipoproteinemia. Finally, increased UA levels in DM may be a response to OS in patients. This increasing UA may act in conjugation with the lipids to cause atherosclerotic complications.

The findings of our study revealed a significant increase in serum uric acid levels in cases as compared to controls ($p<0.001$). Our findings corroborates with a study conducted by Ishizaka N et al, who analyzed a cross-sectional data of 8,144 individuals and concluded that the prevalence of metabolic syndrome showed a graded increase along with increasing serum uric acid levels in both sexes [13].The findings of our study corroborates with an earlier study by Chen LY et al who have also reported a negative correlation between HDL-C and insulin resistance [14].

CONCLUSION

In the present study, we confirmed a significant correlation between the serum levels of uric acid and most of the other parameters of the metabolic syndrome. The observed correlations point to uric acid as a potential marker of metabolic syndrome. Additional studies are necessary to understand the role of uric acid in the metabolic syndrome and to determine whether the prevention of or treatment of hyperuricemia has any beneficial effects on the metabolic syndrome.

REFERENCES

[1] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: 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 adults (adult treatment panel III). JAMA 2001;285:2486-97.

[2] Ford ES. The metabolic syndrome and mortality from cardiovascular disease and all-causes: findings from the National Health and Nutrition Examination Survey II Mortality Study. Atherosclerosis. 2004; 173: 309-14.

[3] Aguilar M, Bhuket T, Torres S, Liu B, Wong RJ. Prevalence of the metabolic syndrome in the United States, 2003-2012. Jama. 2015; 313: 1973-4.

[4] Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. Current opinion in cardiology. 2006; 21: 1-6.

[5] Alberti KG, Zimmet P, Shaw J. Metabolic syndrome--a new world-wide definition. A Consensus Statement from the International Diabetes Federation. Diabetic medicine : a journal of the British Diabetic Association. 2006; 23: 469-80.

[6] Grundy SM, Brewer HB, Jr., Cleeman JI, Smith SC, Jr., Lenfant C, American Heart A, et al. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scien- tific issues related to definition. Circulation. 2004; 109: 433-8.

[7] Bhandari R, Kelley GA, Hartley TA, Rockett IR. Metabolic syndrome is asso- ciated with increased breast cancer risk: a systematic review with me- ta-analysis. International journal of breast cancer. 2014; 2014: 189384.

[8] Barbosa MC,BrandãoAA,PozzanR,MagalhãesME,CampanaEM, Fonseca FL, et al. Associac¸ão entre ácido úrico e variáveis derisco cardiovascular em uma populac¸ão não hospitalar. Arq Bras Cardiol. 2011;96:212---8.

[9] Serpa Neto A, Rossi FM, Valle LG, Teixeira GK, Rossi M. Relation ofuricacidwithcomponentsofmetabolicsyndromebeforeand after Roux-en-Y gastric bypass in morbidly obese subjects. Arq Bras Endocrinol Metab. 2011;55:38---45.

[10] Jacob S. Patient with beer belly or hypertension. Check for a metabolic syndrome! MMW Fortschritte der Medizin. 2005;147:45.

[11] Reungjui S, et al. Thiazide diuretics exacerbate fructose-induced metabolic syndrome. Journal of the American Society of Nephrology : JASN. 2007;18:2724–2731.

[12] Lee CM, Huxley RR, Woodward M et al (2008) The metabolic syndrome identifies a heterogeneous group of metabolic component combinations in the Asia-Pacific region. Diabe- tes Res Clin Pract 8:377–380

[13] Wallenfeldt, K., B. Fagerberg. Oxidized low-density lipoprotein in plasma is a prognostic marker of subclinical atherosclerosis development in clinically healthy men. Journal of Internal Medicine 2004; 256(5): 413-420.

[14] 14. Zimmet, P., K. Alberti. A New International Diabetes Federation (IDF) Worldwide Definition of the Metabolic Syndrome: the Rationale and the Results." Revista Española de Cardiología (Internet) 2005; 58(12): 1371-1375.

[15] Holvoet, P., J. Vanhaecke. Oxidized LDL and Malondialdehyde- Modified LDL in Patients With Acute Coronary Syndromes and Stable Coronary Artery Disease. Circulation 1998; 98(15): 1487- 1494.

[16] Ledwozyw, A., Michalak, J., Stepien A. and Kadziolka, A. The relationship between plasma triglycerides, cholesterol, total lipids and lipid peroxidation products during human atherosclerosis. Clin. Chim. Acta 1986; 155: 275-284.

[17] S. I. Toshima, A. Hasegawa,M. Kurabayashi. Circulating oxidized low density lipoprotein levels: a biochemical risk marker for coronary heart disease, Arteriosclerosis, Thrombosis, and Vascular Biology 2000; 20: 2243-2247.

[18] Hermsdorff HH, Puchau B, Zulet MA, Martínez JA. Association of body fat distribution with proinflammatory gene expression in peripheral blood mononuclear cells from young adult subjects. OMICS. 2010;14(3):297-307.

[19] Willett WC. Nutritional epidemiology. 2nd ed. New York: Oxford University Press; 1998

[20] Manfredi JP, Holmes EW. Purine salvage pathways in myocardium. Annu Rev Physiol. 1985;47:691-705. Review.

[21] Sautin YY, Johnson RJ. Uric acid: the oxidant-antioxidant paradox. Nucleosides Nucleotides Nucleic Acids. 2008;27(6):608-19.

[22] Hooper DC, Spitsin S, Kean RB, Champion JM, Dickson GM, Chaudhry I, et al. Uric acid, a natural scavenger of peroxynitrite, in experimental allergic encephalomyelitis and multiple sclerosis. Proc Natl Acad Sci USA. 1998; 95(2):675-80.

[23] Ford ES, Li C, Cook S, Choi HK. Serum concentrations of uric acid and the metabolic syndrome among US children and adolescents. Circulation. 2007; 115(19):2526-32.

[24] de Oliveira EP, Moreto F, Silveira LV, Burini RC. Dietary, anthropometric, and biochemical determinants of uric acid in free-living adults. Nutr J. 2013;12:11

[25] Rho YH, Woo JH, Choi SJ, Lee YH, Ji JD, Song GG. Association between serum uric acid and the Adult Treatment Panel III-defined metabolic syndrome: results from a single hospital database. Metabolism. 2008;57 (1):71-6.