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Serum uric acid level in postmenopausal women having non alcoholic fatty liver disease - A comparative study

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ABSTRACT

Introduction: Non Alcoholic Fatty Liver Disease (NAFLD) is the common chronic liver disorder worldwide. Postmenopausal state is associated with development of features of meta bolic syndrome and NAFLD is common in women after their menopause. NAFLD is the one of the manifestation of metabolic syndrome, which in turn is associated with increased serum uric acid levels.

Aim and Objectives: To estimate serum uric acid levels in Postmenopausal women with NAFLD and compare it with that of healthy Postmenopausal women and to correlate Waist circumference and BMI with Sr. Uric acid levels

Materials and Methods: 50 Postmenopausal women with NAFLD in the age group of 45-65 years and 50 age matched healthy Postmenopausal women from the Department of Medical Gastroenterology, RGGH, -Chennai-3 participated in the study. After obtaining informed consent blood samples were collected for determining serum uric acid levels using spectrophotometric method.

Results: All the data obtained were analyzed by unpaired t test in SPSS Software. Pearson's correlation coefficient was used to determine the correlation between uric acid levels and BMI & Waist circumference (WC). p value < 0.05 was considered significant. The results obtained in this study showed that serum uric acid levels are significantly increased in NAFLD groups than the control groups and serum uric acid levels showed a positive correlation with BMI & WC.

Conclusion: It may be concluded from the results of the study that uric acid might be involved in the etiopathogenesis of NAFLD. Hyperuricemia may be the reason for increased cardiovascular adverse effects in subjects with NAFLD.

1. Introduction

Non Alcoholic Fatty Liver Disease (NAFLD) is defined as the accumulation of fat in more than 5% of hepatocytes without the features of inflammation evidenced either by ultrasonogram or by histology in persons with no history of significant alcohol consumption. [1]

Nonalcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease, with its prevalence increasing up to 20–30% worldwide. [2] In India the prevalence is around 9% to 32% in the general population. (Ajay Duseja et al 2010[3]).

Initially it was thought that NAFLD is a benign condition but now it is one of the important reasons for liver-related morbidity and mortality. NAFLD may progress to Nonalcoholic steatohepa titis (NASH), liver cirrhosis, & failure, and even up to hepatocellular carcinoma (Adams LA et al. 2005[4]). A liver with simple fat deposition can remain silent without causing any disturbance of liver functions. But if there is any insult, it may progress to Non-alcoholic steatohepatitis (NASH). If the insult continuous for years, patients with NASH will develop liver cirrhosis, and death related to liver disease. The simple fatty liver may progress to NASH as a result of 2 liver insults.

The first hit, macrovesicular steatosis occurs due to insulin resistance and subse quent hyperinsulinemia which in turn leads to alteration in the hepatic pathway of

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synthesis, uptake, degradation and secretion of free fatty acids resulting in excessive triglyceride accumulation in the liver. The second hit is usually results of inflammatory response and oxidative stress caused by mitochondrial dysfunction which causes peroxidation of fatty acids in the hepatocytes (Day CP et al, 1998[5]) which play an important role in the progression of liver damage in NAFLD.

NAFLD is common in men and in women it is common in their postmenopausal period. Age is an independent risk factor for NAFLD in females, when the age increases the risk for NAFLD increases (Hamaguchi et al 2012[6])

Menopause is defined as absence of menstruation for 12 or more months. Menopause starts when menstruation is terminated permanently due to loss of ovary function. In each menstrual cycle serum level of specific hormones like FSH, LH and estrogen will vary widely from premenopausal period to postmenopausal period. Hence the history of attainment of menopause is more reliable indicator of postmenopausal state than measuring these hormones. In Postmenopausal women, the estrogen deficiency state causes redistribution of body fat, with excess fat gets accumulated over the lower abdomen which is called visceral obesity or central obesity.[7] Post menopausal state is associated with insulin resistance, hyperlipidemia & central obesity; all of these are also associated with more risk factor for NAFLD.

In the adipose tissue lipoprotein lipase (LPL), is the enzyme which hydrolyzes circulating triglycerides, and allows the fatty acids uptake into the adipocytes. Normally the estradiol inhibits the action of adipose tissue lipoprotein lipase (LPL). So adipose tissue lipoprotein lipase is not inhibited under the postmenopausal estrogen deficiency state, leading to triglycerides accumulation in the liver results in hepatic steatosis. After menopause**,** lipogenesis is increased and the ability of the liver to oxidize fatty acids also decreases all results in excessive accumulation of fat in the liver leading to hepatic steatosis.[8]

Due to the advanced growing medical field life expectancy has been increased and one third of the life of women spent in the postmenopausal state. Hence management of health and improving the quality of life during this period is considered essential.

1.1. Uric Acid

Uric acid is the inert end product of purine metabolism in humans. Uric acid is excreted primarily via the kidneys and smaller portion via intestinal and biliary secretion. Now no longer Serum uric acid concentration is considered as a marker of gout alone but also predictor of metabolic syndrome, diabetes and cardiovascular disease (CVD). Various studies have suggested that uric acid penetrate vascular smooth muscle fibers and reduces the endothelial nitric oxide level which in turn leads to insulin resistance.NAFLD is considered as the hepatic manifestation of the metabolic syndrome and insulin resistance. Many studies have shown that hyperuricemia is frequently associated with the development of metabolic syndrome.[9]

The prevalence of NAFLD increases with increase in serum uric acid levels. Hyperuricemia independently predicts the increased risk for the incidence of NAFLD.[10]

NAFLD can progress to Non-Alcoholic SteatoHepatitis (NASH) and hepatic fibrosis even up to cirrhosis. Apart from the mortality from cirrhosis, NAFLD individuals are also more prone for increased cardiovascular disease related mortality.[11] Hence the need for predictive factors of NAFLD and of its advanced forms is mandatory. Among the various serum markers, Serum Uric acid has emerged as possible predictor of severity of liver damage in NAFLD.[12]

The insulin resistance which is seen in Postmenopausal women with NAFLD promotes lipolysis of peripheral adipose tissue and increases free fatty acid influx into the liver. Hyperinsulinemia due to insulin resistance in them would cause lower renal uric acid excretion and eventually higher serum uric acid level.[13]Synthesis of triglycerides also increased in individuals with NAFLD which would accelerate Uric acid production and accumulation.

Hyperuricemia is defined as an uric acid level >5.7 mg/dL (360 mmol/l) in women and >7.0 mg/dL (420 mmol/l)in men. This cutoff values for hyperuricemia were taken based on previous studies about the relationship between hyperuricemia to metabolic syndrome and cardiovascular disease outcomes.

Hence this study is aimed to estimate serum uric acid levels in postmenopausal women with NAFLD and compare it with that of healthy postmenopausal women and to correlate the serum uric acid levels with waist circumference and BMI in them.

2. Materials and Methods

Fifty Postmenopausal women without NAFLD and Fifty Postmenopausal women with NAFLD of age group between 45-65 yrs participated in the study.

2.1. Inclusion criteria

Fifty postmenopausal women in the age group of 45-65 years with BMI $\leq$ 25 with ultrasonography evidence of NAFLD.

2.2. Exclusion criteria

Menopausal women with history of Alcohol intake >20g/day, Known liver disease (hepatitis, autoimmune liver disease), and renal disease and patients with history of gout. Those On statins and other lipid reducing drugs & those on fatty liver inducing drugs, on diuretics & on hormone replacement therapy for menopausal symptoms.

After obtaining informed consent they were subjected to complete general examination. BMI was calculated from the formula weight in kilograms divided by the square of height in meters (kg/m^2). Waist circumference was measured in the horizontal plane of the superior border of iliac crest. Simultaneously blood sample of 5 ml was collected in the fasting state from both the groups by venepuncture. The sample was centrifuged immediately and serum was stored at -20 degree Celsius until all the samples were collected. Then determination of serum uric acid level was done using spectrophotometric method.

The evaluations of test results were done statistically using Statistical Package for the Social Sciences (SPSS) software version 21.

3. Results

Using the Statistical Package for Social Sciences (SPSS) software version 21, all the data obtained were analyzed. Mean and standard deviations of the variables were determined for the control and NAFLD groups. Unpaired t test was employed for statistical analysis with 95% confidence interval as the test of significance. To determine the correlation between Serum Uric acid levels and BMI & Waist circumference, Pearson's correlation coefficient was used. P value < 0.05 was considered as a test of significance.

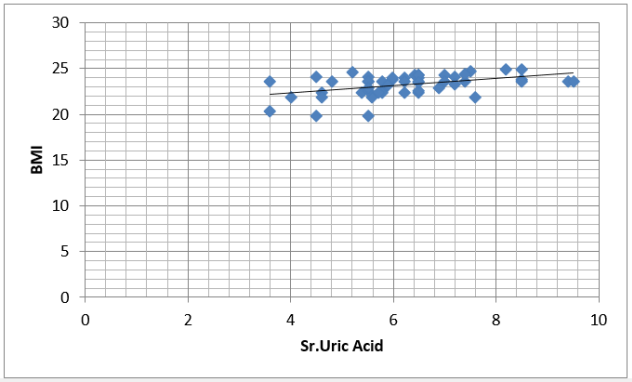

Fig. 1: Correlation between BMI and serum uric acid levels in postmenopausal women with NAFLD

4. Discussion

The current research compared the serum Uric acid levels between healthy Postmenopausal women and Postmenopausal women having NAFLD and correlated the anthropometric indices like BMI & WC with Uric acid levels. There are not much Indian studies that compared the levels of Uric acid in P ostmenopausal women with NAFLD and hence this study was done. In Our study, the results showed that Uric acid levels are significantly increased in postmenopausal women with NAFLD participants than

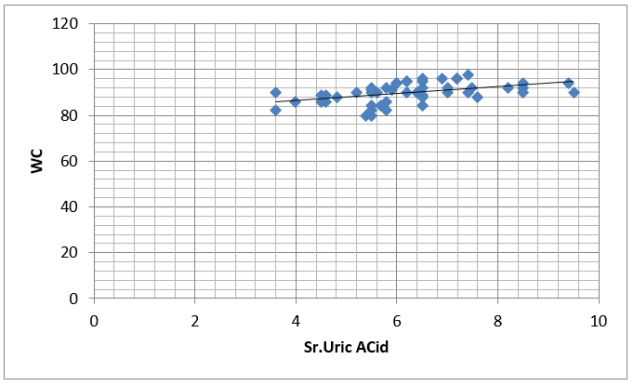

Fig. 2: Correlation between waist circumference and serum uric acid levels in postmenopausal women with NAFLD

when compared with healthy control groups. Our study results are similar to the results of Moon SS et al[14] who demonstrated that in postmenopausal women with NAFLD the mean serum Uric acid was significantly higher than in healthy Postmenopausal women and they also showed positive correlation between BMI, Waist circumference and Serum Uric acid. The results obtained in this study is also in accordance with the results of Liu PJ et al[15] who demonstrated that in Postmenopausal women with NAFLD the mean serum Uric acid was significantly higher than in healthy postmenopausal women.

This study also showed a positive correlation between BMI, WC with increased SUA levels. In individuals with NAFLD, Yuanliang Xie et al[16] also observed a positive correlation between waist circumference and Sr. Uric acid levels. Sertoglu E et al[17] who also observed a positive correlation between Sr. Uric acid levels and BMI in NAFLD individuals.

One possible explanation for this higher serum uric acid levels in NAFLD group may be that the observations are confounded by a shared background of metabolic syndrome features.[18] High serum UA levels in NAFLD group is due to insulin resistance induced hyperinsulinemia which would decreases uric acid excretion. Hyperinsulinemia also reduces the adipocytes sensitivity to insulin indirectly and then increases triglyceride lipolysis within adipose depots. This relationship is explained by various hypotheses. Uric acid may stimulate inflammation by increasing the expression of inflammatory mediators by activating multiple signal transduction pathways like production of p38 mitogen-activated protein kinases (MAPK), cyclooxygen ase-2(COX-2), chemokinemonocyte chemoattractantprotein-1. It also induces oxidative stress in adipocytes. Ketohexokinase (KHK) expression is also increased by uric acid that \accentuates the lipogenic effects of fructose which results in increased triglycerides accumulation in hepatocytes.[19] Moreover, visceral obesity causes increased influx of plasma free fatty acids into

Table 1: Comparison of baseline characteristics among the study groups

Variables	Study groups	Mean	SD	p value
Age	**Control**	58.42	4.52	0.459
	NAFLD	59.02	3.50	

The age range of the study participants was between 45-65 years. The mean age of the control group was 58.42±4.52 and the mean age of the NAFLD group was 59.02 ±3.50. There was no statistically significant difference in the mean age between the two groups and hence the two groups are comparable.

Table 2: Comparison of BMI among study groups

BMI	**Control**	21.41	1.47	0.001***
	NAFLD	23.22	1.15	

The body mass index of the controls and NAFLD groups was very highly significant.

Table 3: Waist circumference comparison among study groups

Variable	Study groups	Mean	SD	p Value
Waist circumference	**Control**	84.54	4.35	0.001***
	NAFLD	89.80	4.42	

Table 3 compares the waist circumference of the controls and NAFLD groups. The p value of waist circumference was very highly significant.

Table 4: Comparison of serum uric acid levels among study groups

Variable	Study groups	Mean	SD	p Value
Uric Acid (mg/dl)	**Control**	5.48	1.05	0.002***
	NAFLD	6.25	1.34	

Table 4 compares the serum uric acid levels of the controls and NAFLD groups. The p value of uric acid was very highly significant.

Table 5: Correlation of Serum Uric acid levels with BMI & Waist circumference using Pearson's Correlation coefficient

Correlation between Uric acid level and	Correlation value(r)	Significance
BMI of NAFLD group	0.4709	0.001**
WC of NAFLD group	0.4648	0.001**

Table 5 shows the correlation between Uric acid levels and BMI and Waist circumference in NAFLD groups. The results showed a positive correlation between Uric acid levels and BMI in the NAFLD group and the p value was <0.00 that was significant. There was also a positive correlation between Uric acid levels and WC and the p value was <0.00 that was significant.

the liver which in turn stimulates triglycerides synthesis followed by increased uric acid production through the activation of uric acid synthesis pathway.

5. Conclusion

High serum uric acid levels are seen in Postmenopausal women with NAFLD and hyperuricemia is independently associated with NAFLD. Significant positive association between SUA levels with BMI& Waist circumference is also seen in this study. High uric acid levels are associated with increased incidence of adverse cardiovascular events. Hence it is advisable to perform routine serum uric acid assay which is very simple and cost effective method in predicting and preventing the cardiovascular risk in subjects with NAFLD.

6. Source of funding

None.

7. Conflict of interest

None.

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