Non-Alcoholic Fatty Liver Disease, Hyperuricemia and Carotid Intima-Medial Thickness: A Case Control Study

Malik Mohd Azharuddin[1], Nasar Abdali[2], Masihur-Rehman Ajmal[3], Ibne Ahmad[4], Athar Kamal[5]

ABSTRACT

Introduction: Presence of Non-Alcoholic Fatty Liver Disease (NAFLD) portends increased cardiovascular risk. A large part of this association may be due the common risk factors for both the diseases including the various components of the metabolic syndrome. Hyperuricemia is also now considered to be an established cardiovascular risk marker. The present study was designed to study the association of NAFLD and Hyperuricemia as well as its influence on the development of Carotid atherosclerosis as detected by carotid intima-medial thickness (CIMT).

Materia and Methods: The case controlled study compared 144 subjects with NAFLD (cases) with 98 control subjects. Serum uric acid (SUA), CIMT, all components of metabolic syndrome were estimated in all patients and were compared. Binary logistic regression on the whole data was also performed to assess independent predictors of development of carotid atherosclerosis.

Results: Mean SUA were significantly higher in patients with NAFLD (5.96 ± 1.19 vs.5.20 ± 0.82; P-Value <0.001). Mean CIMT was also higher in patients with NAFLD (0.89 ± 0.27 vs 0.75 ± 0.10; P-Value <0.001). The values of SUA and CIMT was also significantly higher in patients with higher grade of NAFLD.

Conclusion: Hyperuricemia was significantly more common in patients with NAFLD. Concordant with this carotid atherosclerosis was also associated with the presence of NAFLD.

Keywords: NAFLD, hyperuricimia, carotid intima-medial thickness, metabolic syndrome.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) represents a spectrum of liver disorders characterized by fatty accumulation alone (steatosis), or accompanied by signs of hepatocyte injury, inflammation and fibrosis (non-alcoholic steatohepatitis, NASH) or cirrhosis.[1,2] NAFLD is currently recognized as the most common form of liver disease in many parts of the world, the prevalence ranges from 16% to 23% using ultrasonography as tool for diagnosis.[1] The prevalence of NAFLD in India has been estimated to be 9% to 32%.[3]

Most of the deaths in patients of NAFLD are due to cardiovascular diseases making it an important risk factor for the same. It may also be considered as a hepatic manifestation of metabolic syndrome by many due their common occurrence and presence of insulin resistance, a key aspect in pathogenesis of both these conditions. NAFLD is also associated with markers of systemic inflammation which may have a contributory role in accelerated atherosclerosis.[4] Studies have also shown association of carotid atherosclerosis in the form of increased CIMT in NAFLD patients independent of metabolic syndrome.[5]

Over the past decade, an association between serum uric acid (SUA) level and cardiovascular risk has been established.[4] This increase in cardiovascular risk begins with uric acid levels even in high normal range (>5.2 to 5.5 mg/dL).[4] Hypertensive patients with carotid atherosclerosis develop hyperuricemia.[6] An association between SUA and metabolic syndrome has been repeatedly demonstrated and SUA levels increase as patients develop increasing numbers of metabolic syndrome-related disorder.[7,8] The objective of our study was to assess the association of hyperuricemia with NAFLD and carotid atherosclerosis as assessed with CIMT.

MATERIAL AND METHODS

In the present pilot study we examined 144 consecutive patients from Department of Medicine, J.N. Medical College and Hospital, AMU, Aligarh between January 2011 to October 2012, with ultrasonographically confirmed NAFLD and 98 age-matched and gender- matched control subjects with normal parenchymal liver echogenicity for determination of Carotid Intima Media Thickness (CIMT) and serum uric acid level. The study protocol was approved by the institutional ethics committee. Patients of both sex and age ≥ 18 years with NAFLD and who gave written informed consent were enrolled. Exclusion criteria were patients with history of other liver diseases including presence of hepatitis B or C infection (positive for hepatitis B surface antigen or antibody to hepatitis C virus), biliary obstruction, chronic alcohol consumption (ethanol ingestion >20 g/day) and other causes of secondary steatosis like drugs or toxins, autoimmune diseases, hereditary disease (wilson's disease), rapid weight loss etc., history of gout or any hypo/hyperuricemic drug intake.

For establishing the diagnosis of NAFLD and to rule out other possible diseases, all patients underwent a detailed clinical and laboratory evaluation including liver enzymes, hepatitis markers, autoantibodies, ferritin, and ceruloplasmin. Body mass index (BMI), waist circumference, hip circumference, waist hip ratio were measured and Blood pressure was recorded of all subjects enrolled in the study. After overnight fasting, samples were taken for blood sugar and lipid profile. Glucose dehydrogenase method was used for measuring blood glucose while enzymatic procedures were used for determination of lipid profile. Serum uric acid level was done using uricase – peroxidase method. Metabolic syndrome was defined using ATP III criteria.

[1]Assistant Professor, [3]Professor, Department of Medicine, [4]Professor, Department of Radiodiagnosis, A.M.U., Aligarh, [2]Senior Resident, L.P.S. Institute of Cardiology, G.S.V.M. Medical College, Kanpur, [5]Senior Resident, Dr RML Hospital and PGIMER, India

Corresponding author: Dr Malik Mohd Azharuddin, Assistant Professor, Department of Medicine, A.M.U., Aligarh, India

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Ultrasonography of abdomen of all the patients was done by a single experienced radiologist who was blinded to other clinical details of the patient. Patient was kept nil orally for 12 hours prior to ultrasound examination. Examination was performed in supine and semi-lateral positions, required for better visualization. Fatty liver was graded as follows according to routinely used criteria[13]:

Grade I: The basic characteristics were clear/normal visualization of the diaphragm as well as intrahepatic vessel borders, slight/mild diffuse increase in fine echoes in liver parenchyma

Grade II: Slight impairment in visualization of the intrahepatic vessels and diaphragm, along with moderate diffuse increase in fine echoes in liver parenchyma

Grade III: There was no visualization of intrahepatic vessel borders and diaphragm. The posterior portion of the right lobe of the liver was not visible. Fine echoes in hepatic parenchyma were markedly increased.

The intima-media thickness of the carotid arteries was determined using a high resolution B-mode Ultrasonography system (Logic 500 Proseries; Wipro GE) having an electrical linear transducer (multi-frequency probe of 5 to 9 MHz) by a single experienced radiologist blinded for the presence or absence of NAFLD. Imaging of the right and left common carotid artery was performed in multiple planes around the carotid bifurcation-bulb with images being obtained from the far wall of the distal 10 mm of left and right common carotid arteries at a site free from any discrete plaque. Mean of 3 readings of both right and left was taken to obtain the CIMT.

STATISTICAL ANALYSIS

All statistical data were analysed by using SPSS software version 15.0 statistical package for windows (Chicago. Inc.). Statistical significance was set at two-sided p-value≤0.05. Results are reported as the mean ± standard deviation (SD) for continuous variables and as frequencies and number (%) for categorical variable. Independent samples t tests or the Mann–Whitney U test, when appropriate, were used to compare cases and control for continuous variables. Fischer's exact test or the χ 2 test was used for categorical variables. Pearson correlation coefficient was used to compare continuous variables. The independence of the association of variables with the presence of NAFLD or atherosclerosis was assessed by multivariate logistic regression and expressed as odds ratios. Comparison of IMT values and serum uric acid level between different groups of NAFLD were done using ANOVA.

RESULTS

Patients in both of the groups with or without NAFLD were comparable with respect to age and sex distribution (Table-1). Various components of metabolic syndrome like dyslipidemia, hypertension and diabetes were significantly more common in patients with NAFLD compared to patients without NAFLD as shown in Table-1. There also was association of increasing severity of NAFLD with various components of metabolic syndrome as well (Table-2). Serum Uric acid was also higher in patients with more severe NAFLD as was CIMT. After considering CIMT>0.8 mm as a marker for atherosclerosis the data was analyzed with binary logistic regression to find out independent predictors of carotid atherosclerosis which showed SUA to be independently associated with CIMT (p-Value<0.001). Age, BMI and serum triglyceride levels were also independently associated with increased CIMT.

DISCUSSION

Recent studies have demonstrated an association between NAFLD and metabolic syndrome, NAFLD has thus been implicated in the development of atherosclerosis. Patients with NAFLD are at a higher risk for CVD than those who do not have NAFLD. Studies have found markers of early atherosclerosis, like circulatory endothelial dysfunction and carotid intima-media thickness to be increased in NAFLD patients.[9] In our case-control study, the mean serum uric acid level of subjects with NAFLD (cases) was significantly higher than the control group (5.96±1.19 mg/dl vs. 5.20±0.82 mg/dl; p-Value<0.001). Also mean uric acid level of subjects with NAFLD Grade I was 5.71±1.12 mg/dl, of grade II was 6.45±1.20 mg/dl while of grade III was 6.45+1.25 mg/dl, which was significantly different as shown by ANOVA (p<0.001). Our findings proved that SUA

	Cases (with NAFLD) N= 144	Control (without NAFLD) N = 98	p-value
Age (years)	48.82 ± 11.21	49.56±11.31	0.615
Sex (Females)	62 (43.05%)	42 (42.85%)	0.976
Waist circumference(cm)	87.99 ± 6.81	83.95 ± 4.82	<0.001
Waist hip ratio	0.91 ± 0.06	0.83 ± 0.08	<0.001
BMI	27.53± 2.95	25.32± 2.27	<0.001
Total cholesterol (mg/dl)	167.30 ± 44.16	162.15 ± 42.05	0.365
HDL (mg/dl)	38 ± 9.7	38.7 ± 9.3	0.723
LDL (mg/dl)	97.8 ± 27.4	94.4 ± 24.3	0.529
Triglyceride (mg/dl)	164.14 ± 74.68	138.60 ± 38.34	0.002
Blood Sugar(F) (mg/dl)	106.24 ± 20.52	90.07 ± 13.7	<0.001
HbA1C	6.06 ± 1.00	5.80 ± 0.78	0.024
Systolic BP(mm Hg)	135.44 ± 13.49	129.24 ± 9.46	<0.001
Diastolic BP(mm Hg)	87.79 ± 7.51	85.50 ± 5.56	0.007
AST (I.U/L)	20.19 ± 25.50	9.49 ± 4.59	<0.001
ALT (I.U/L)	21.60 ± 23.75	11.95 ± 4.99	<0.001
SUA (mg/dL)	5.96 ± 1.19	5.20 ± 0.82	<0.001
CIMT (mm)	0.89 ± 0.27	0.75 ± 0.10	<0.001

Table-1: Comparison of cases and controls.

	NAFLD Grade I (n=95)	NAFLD Grade II (n=37)	NAFLD Grade III (n=12)	p-value
Waist circumference (cm)	85.90 ± 5.75	91.02 ± 6.69	95.16 ± 7.06	<0.001
Waist hip ratio	0.89 ± 0.06	0.93 ± 0.06	0.95 ± 0.08	<0.001
BMI (kg/m2)	26.64 ± 2.58	28.93 ± 2.82	30.29 ± 2.94	<0.001
Serum Triglyceride (mg/dl)	148.47 ± 61.91	173.76 ± 76.88	258.50 ± 90.87	0.002
HbA1C	5.67 ± 0.67	6.58 ± 1.06	7.58 ± 0.80	<0.001
Blood sugar (F) mg/dl	99.47 ± 17.24	115.84 ± 18.26	130.25 ± 22.57	<0.001
Systolic BP (mm of hg)	131.56 ± 11.14	140.65 ± 14.02	150.17 ± 14.30	<0.001
Diastolic BP (mm of hg)	86.11 ± 6.61	89.62 ± 7.90	95.50 ± 7.39	<0.001
AST (I.U/L)	11.77 ± 14.23	32.11 ± 32.90	50.17 ± 33.15	<0.001
ALT (I.U/L)	13.33 ± 12.52	31.54 ± 29.59	56.42 ± 29.73	<0.001
SUA (mg/dL)	5.96 ± 1.13	6.45 ± 1.20	6.45 ± 1.25	0.001
CIMT (mm)	0.82 ± 0.18	1.00 ± 0.31	1.17 ± 0.38	<0.001

Table-2: Association of components of metabolic syndrome, Uric Acid and CIMT with severity of NAFLD.

concentrations, even within the normal range, were significantly associated with the presence of NAFLD. This was similar to the Korean study by Hwang et al in which they found mean uric acid level in NAFLD patients to be 5.6mg/dl and 4.6mg/dl in non NAFLD group (p<0.001).[10] Similar association of uric acid and NAFLD has also been reported by others.[11,12]

Despite the significant relationship between uric acid and NAFLD in the present study, prospective studies are required to conclude that serum uric acid concentration is a risk factor actively involved in the development of NAFLD. Since this study is of cross-sectional design, causal relationship cannot be determined. Insulin resistance and hyperleptinemia in patients of NAFLD may be one possible explanation for raised uric acid in them. Insulin resistance is responsible for increase uric acid synthesis as well as decrease uric acid excretion.[14] The role of leptin in hyperuricemia has also been assessed in recent studies. Leptin induces oxidative stress in endothelial cells which may lead to increase SUA levels.[15] The involvement of leptin in sodium tubular reabsorption may also result in an increase in SUA levels.[16]

In our study the mean carotid intima media thickness (CIMT) was 0.86±0.23 mm in NAFLD patients and 0.78 ±0.14 mm for control. In a study by Mohammadi et al the mean CIMT was found to be 0.81±0.14 mm in NAFLD group which had a statistically significant (p<0.001) difference with non-NAFLD group[17], which is supported by other similar studies.[5,9,18] We also found that there was a statistically significant relationship between grades of NAFLD and carotid intima media thickness of right side(p<0.001) and of left side (p<0.001).We found that in grade I,II and III NAFLD mean right CIMT was 0.81±0.18mm, 0.92±0.26mm and 1.06±0.97mm respectively. In case of left CIMT it was 0.82±0.23mm, 1.07±0.53mm and 1.22±0.72mm respectively. Mohammadi et al. also found a similar correlation with mean CIMT 0.78±0.15mm, 0.82±0.11mm and 0.85±0.97mm in grade I,II and III NAFLD with statistical significant(p=0.01) difference.[17]

A possible mechanism linking NAFLD and accelerated atherosclerosis could be represented by increased oxidative stress and subclinical inflammation, which are thought to be causal factors in the progression from simple steatosis to more advanced forms of NAFLD.[5,7,8,19] Low adiponectin plasma level, an anti-atherogenic cytokine secreted by adipocytes, may represent another possible mechanism linking NAFLD and carotid atherosclerosis.[20] Presence of abnormal lipoprotein metabolism characterized by markedly reduced hepatic apolipoprotein B-100 synthesis, a rate-determining step in hepatic VLDL formation and in hepatocyte lipid export can also result in increased levels of atherogenic triglyceride- and cholesterol-rich remnant particles.[21,22]

CONCLUSION

Our data indicate that NAFLD has a significant association with various components of metabolic syndrome, hyperuricemia and carotid atherosclerosis and this association increases with increase in severity of NAFLD. These findings are consistent with NAFLD being considered the hepatic representation of metabolic syndrome.

REFERENCES

1. Farrell GC, Larter CZ. Nonalcoholic fatty liver disease: from steatosis to cirrhosis. Hepatol Baltim Md. 2006;43:S99–S112.
2. Farrell GC. Non-alcoholic steatohepatitis: What is it, and why is it important in the Asia–Pacific region? J Gastroenterol Hepatol. 2003;18:124–38.
3. Duseja A. Nonalcoholic fatty liver disease in India – a lot done, yet more required! Indian J Gastroenterol. 2010;29:217–25.
4. Feig DI, Kang D-H, Johnson RJ. Uric Acid and Cardiovascular Risk. N Engl J Med. 2008;359:1811–21.
5. Brea A, Mosquera D, Martín E, et al. Nonalcoholic Fatty Liver Disease Is Associated With Carotid Atherosclerosis A Case–Control Study. Arterioscler Thromb Vasc Biol. 2005;25:1045–50.
6. Săvoiu G, Drăgan S, Fira-Mladinescu O, et al. Correlations between carotid intima-media thickness and serum uric acid levels in hypertensive patients. Rev Medico-Chir Soc Medici Şi Nat Din Iaşi. 2008;112:902–7.
7. Yoo TW, Sung KC, Shin HS, et al. Relationship Between Serum Uric Acid Concentration and Insulin Resistance and Metabolic Syndrome. Circ J. 2005;69:928–33.
8. Hjortnaes J, Algra A, Olijhoek J, et al. Serum uric acid levels and risk for vascular diseases in patients with metabolic syndrome. J Rheumatol. 2007;34:1882–7.
9. Targher G, Bertolini L, Padovani R, et al. Relation of Nonalcoholic Hepatic Steatosis to Early Carotid Atherosclerosis in Healthy Men Role of visceral fat accumulation. Diabetes Care. 2004;27:2498–500.
10. 1Hwang I-C, Suh S-Y, Suh A-R, et al. The relationship between normal serum uric acid and nonalcoholic fatty liver disease. J Korean Med Sci. 2011;26:386–91.

11. Xie Y, Wang M, Zhang Y, et al. Serum Uric Acid and Non-Alcoholic Fatty Liver Disease in Non-Diabetic Chinese Men. PLoS ONE 2013;8.
12. Cai W, Wu X, Zhang B, et al. Serum uric acid levels and non-alcoholic fatty liver disease in Uyghur and Han ethnic groups in northwestern China. Arq Bras Endocrinol Amp Metabol. 2013;57:617–22.
13. Fattahi, Mohammad Reza et al. The Prevalence of Metabolic Syndrome In Non-Alcoholic Fatty Liver Disease; A Population-Based Study. Middle East Journal of Digestive Diseases. 2016,8:131–137.
14. Musso G, Gambino R, Biroli G, et al. Hypoadiponectinemia predicts the severity of hepatic fibrosis and pancreatic Beta-cell dysfunction in nondiabetic nonobese patients with nonalcoholic steatohepatitis. Am J Gastroenterol. 2005;100:2438–46.
15. Modan M, Halkin H, Karasik A, et al. Elevated serum uric acid—a facet of hyperinsulinaemia. Diabetologia. 1987;30:713–8.
16. Rahmouni K, Haynes WG. Endothelial effects of leptin: implications in health and diseases. Curr Diab Rep. 2005;5:260–6.
17. Mohammadi A, Bazazi A, Maleki-Miyandoab T, et al. Evaluation of relationship between Grading of fatty liver and severity of Atherosclerotic finding. Int J Clin Exp Med. 2012;5:251.
18. Ramilli S, Pretolani S, Muscari A, et al. Carotid lesions in outpatients with nonalcoholic fatty liver disease. World J Gastroenterol WJG. 2009;15:4770.
19. Targher G, Day CP, Bonora E. Risk of Cardiovascular Disease in Patients with Nonalcoholic Fatty Liver Disease. N Engl J Med. 2010;363:1341–50.
20. Angulo P. Nonalcoholic Fatty Liver Disease. N Engl J Med. 2002;346:1221–31.
21. McCullough AJ. The clinical features, diagnosis and natural history of nonalcoholic fatty liver disease. Clin Liver Dis. 2004;8:521–533.
22. Rector RS, Thyfault JP, Wei Y, et al. Non-alcoholic fatty liver disease and the metabolic syndrome: an update. World J Gastroenterol WJG. 2008;14:185.

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