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Original Article

Study of Prevalence of Hyperuricemia in Chronic Liver Disease Patients and Correlate with Severity of Chronic Liver Disease

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Abstract

Introduction: Chronic liver disease (CLD) is a disorder of varied etiology such as non-alcoholic fatty liver disease (NAFLD), chronic hepatitis due to hepatitis B and C, inherited metabolic liver diseases in which progressive destruction of liver parenchyma leads to fibrosis leading to cirrhosis. Increased serum uric acid (UA) levels have been implicated in insulin resistance, metabolic syndrome, and oxidative stress (OS), which are the risk factors for liver disease progression and are also linked to cardiovascular disease.

Aim: The aim of the study is to study the prevalence of hyperuricemia in CLD patients due to NAFLD and correlate the severity of CLD with hyperuricemia.

Materials and Methods: This cross-sectional study was conducted on 50 patients diagnosed to have NAFLD and cirrhosis based on clinical criteria. The diagnosis of NAFLD currently requires (1) evidence of hepatic steatosis by imaging or histology, (2) no significant alcohol consumption, (3) no competing causes of hepatic steatosis, and (4) no coexisting causes of CLD. Patients with prior history of alcoholic liver disease, chronic kidney disease, arthritis, cardiovascular disease and diabetes mellitus, hypothyroidism were excluded from the study. Blood samples were collected for all enrolled subjects and evaluated for serum UA.

Results: The maximum number of patients were in the age group of 41–60 years (68%). Among 50 patients with CLD, 56% of patients had fatty liver and 44% had ultrasound evidence of liver cirrhosis. In 22 patients with liver cirrhosis, 63.6% of patients had hyperuricemia and in 28 patients with fatty liver, 60.7% of patients had hyperuricemia.

Conclusion: There is a significant increase in UA levels which can induce NAFLD by stimulating endoplasmic stress, OS and insulin resistance in patients with CLD. Hence, increased serum UA levels along with the classical derangement of liver enzymes might be a risk factor for CLD in patients of NAFLD.

Key words: Chronic liver disease, Cirrhosis, Hyperuricemia, Non-alcoholic fatty liver disease, Uric acid

INTRODUCTION

Chronic liver disease (CLD) is a disorder in which progressive destruction of liver parenchymal cells leads to fibrosis and cirrhosis. It manifests with features of hepatocellular failure including jaundice, fatigue, nausea, poor appetite, abdominal distension, and intestinal bleeding. Several etiological factors have been implicated in the development of CLD.[1]

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Uric acid (UA) is a natural end product of purine metabolism. While it is naturally found in the blood in small amounts, its elevation beyond normal can indicate a metabolic disorder of late, links have been suggested between the UA level and diabetes mellitus, obesity, cardiovascular disease, and renal disease.[2,3]

Recent studies on serum UA have shown increased serum UA levels associated with the development of steatosis of the liver in the patients who had non-alcoholic fatty liver disease (NAFLD) after adjustment for various features of metabolic syndrome.

It is proposed that the role of increased UA levels in the pathogenesis of the liver disease is thought to be due to

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its increased UA could induce oxidative stress (OS), which plays an important role in the pathogenesis of NAFLD. Zhang *et al.* found that high levels of UA increased ROS levels and induced OS in cultured rat pancreatic β cells. In adipocytes, soluble UA stimulates an increase in reactive oxygen species (ROS) production, which has been recently recognized as a major causative factor for obesity-related inflammatory endocrine imbalance. UA increases the mRNA expression of monocyte chemotactic protein-1 and decreases the mRNA expression of adiponectin. A strong positive association between serum leptin and UA has been demonstrated in both diabetic and healthy subjects. These cytokines play an important role in the pathology of NAFLD. It was reported that the kidney damage caused by hyperuricemia was primarily due to OS, which can damage endothelial cells and lead to kidney dysfunction. In both kidneys of hyperuricemic Sprague Dawley rats injected with oxonic acid potassium salt and UA and human umbilical vein endothelial cells treated with UA, the level of ROS was higher, while the expression level of catalase was lower than the control group. In addition, treating HepG2 cells with UA for 30 min strongly increased ROS levels by 6.9 fold as compared with controls.[4]

High levels of UA are considered an important marker in the pathogenesis of the NAFLD and non-alcoholic steatohepatitis (NASH).[5] In addition, hyperuricemia is linked to the progressive development of hepatitis C virus-related liver diseases due to excessive alcohol consumption.[6] This strongly suggests that increased UA levels reflect and even cause increased OS, resistance to insulin, and inflammation in the systemic circulation. This has become one of the main risk factors for developing cirrhosis of the liver or hepatic inflammation due to necrosis both in alcoholic and non-alcoholic.

Aim

To study the prevalence of hyperuricemia in CLD patients and correlates with severity of CLD.

MATERIALS AND METHODS

This cross-sectional study was conducted in the department of general medicine at ESIC Medical College and PGIMSR, KK Nagar, Chennai, in which 50 patients who were diagnosed with NAFLD and cirrhosis were included in this study based on ultrasound and clinical criteria. The diagnosis of NAFLD currently requires (1) evidence of hepatic steatosis by imaging or histology, (2) no significant alcohol consumption, (3) no competing causes of hepatic steatosis, and (4) no coexisting causes of CLD. Patients with prior history of alcoholic liver disease, chronic kidney disease, arthritis, cardiovascular disease, diabetes mellitus, and hypothyroidism were excluded.

Informed consent was obtained from all patients to be enrolled in the study. In all the patients, relevant information was collected in a predesigned proforma. The patients were selected based on clinical examinations and biochemical tests.

A detailed history was elicited from the patient regarding their present complaints, associated symptoms, alcohol intake, smoking, previous history of hypertension, diabetes mellitus, arthritis, hypothyroidism, any cardiac illnesses, and chronic drug intake. Blood samples were collected for all enrolled patients and evaluated for serum UA levels.

Serum UA levels 3.50–7.20 mg/dL were considered normal. Data were presented as frequency and percentage.

RESULTS

In this study, 50 patients with NAFLD and CLD were included. The maximum number of patients was 41–60 years (68%), followed by more than 61 years (28%). The mean age of the patients was 54.28 years [Figure 1].

Among 50 patients, 82% of patients were male and 18% of patients were female [Figure 2].

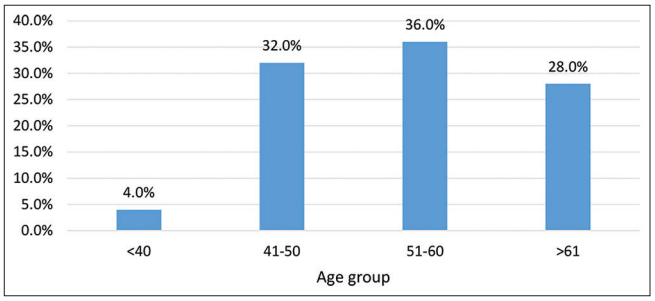

Figure 1: Distribution of age group

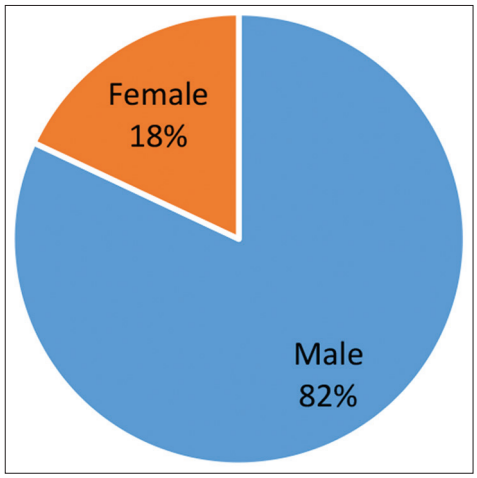

Figure 2: Sex distribution

In this study, 58% of patients have normal BMI and 26% of patients are overweight [Figure 3].

Among 50 patients with CLDs, 56% of patients had fatty liver and 44% of patients had liver cirrhosis [Figure 4].

In this study, 62% of the study group had hyperuricemia and 38% of patients in the study group had normal levels of serum UA [Figure 5].

In 22 patients with liver cirrhosis, 63.6% of patients had hyperuricemia and in 28 patients with fatty liver, 60.7% of patients had hyperuricemia [Figure 6].

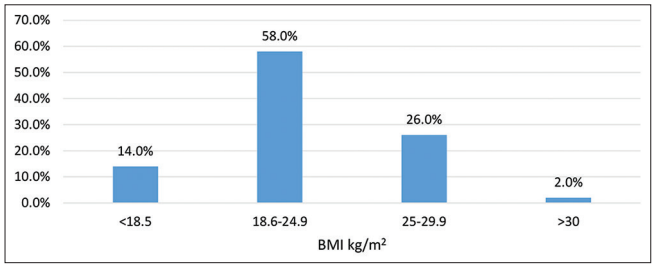

Figure 3: Distribution of body mass index

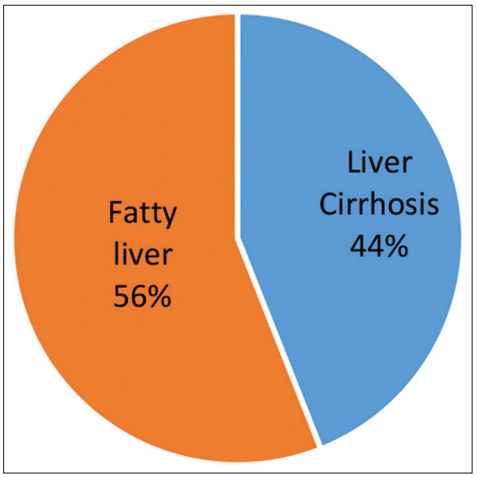

Figure 4: Distribution of chronic liver diseases

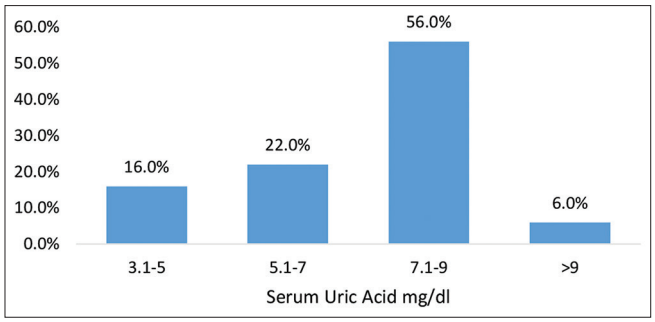

Figure 5: Distribution of serum uric acid

DISCUSSION

Cirrhosis of the liver is associated with significant morbidity and mortality.[7] Several biochemical and radiological markers such as Gamma-glutamyl transferase, Alkaline phosphatase, Alanine aminotransferase, Aspartate aminotransferase, Enhanced liver fibrosis, Fibrosis-4; Matrix metalloproteinase, Procollagen I carboxy peptide, Procollagen III amino peptide, Tissue inhibitor of metalloproteinase, imaging diagnosis, and tissue pathology diagnosis; and computed tomography, magnetic resonance imaging, and Sonography are being widely used for assessing the extent of liver injury. Using these parameters, various scoring systems such as Child-Pugh score, Model for end-stage liver disease, Monoethylglycinexylidide, and Von Willebrand Factor have been developed for prognostication. Serum UA is a well-known factor for the development of gout and contributes to the pathogenesis of chronic nephropathy and arthritis. High UA levels are associated with cardio-metabolic disease, including cardiovascular disease and all the metabolic diseases associated with metabolic syndrome.[8,9]

An increased UA level reflects OS in the tissue and is also a marker of metabolic syndrome. Furthermore, hyperuricemia has deleterious effects on endothelial function and nitric oxide bioavailability, thus causing hyperinsulinemia. Thus, it is likely that hyperuricemia and insulin resistance share a bidirectional causal effect.[4] Endoplasmic reticulum stress could induce numerous intracellular pathways leading to hepatic steatosis, insulin resistance, inflammation, and apoptosis, all of which are crucial in the pathogenesis of NAFLD.[4] Elevated serum UA levels strongly reflect and may even cause OS, insulin resistance, and metabolic syndrome, which are risk factors for the progression of liver disease.[10] Liver injury is characterized by a high blood level of ROS. It is considered a marker of OS. Similarly, in biopsy-proven Taiwanese NASH patients with fibrosis, there was a significant inverse correlation between hyperuricemia

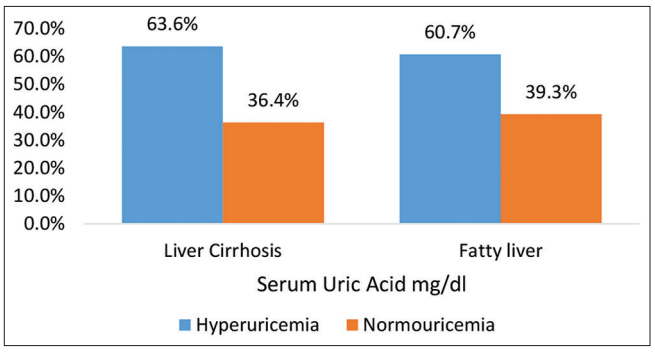

Figure 6: Cross-tabulation of hyperuricemia in chronic liver disease

and fibrosis stages, ranging from 48.4% of F0-1, 33.3% of F2, and 9.1% of F3-4, respectively. Normal UA level (OR 5.6) was one of the significant factors associated with significant fibrosis.[4] UA levels have been found to correlate with the increase of Child-Turcotte-Pugh Classification for Severity of Cirrhosis.[11] Hyperuricemia was found to induce endothelial dysfunction of reduced bioavailability of endothelial nitric oxide in rats.[10] High levels of UA induce oxidative changes in adipocytes and inflammation, this process is crucial for causing metabolic syndrome in obese mice.[12]

A study by Paul *et al*., 2013 showed that UA might be considered a marker of severity of CLD and the levels correlate with the higher Child-Turcotte-Pugh score. Serum UA acts as a surrogate marker in assessing the prognosis of CLD.[13] It is metabolized by the muscles, the intestines, and the liver is catalyzed by Xanthine Oxidase. Approximately two-thirds of UA is excreted in the urine, and the remaining one-third is excreted in feces.[13,14]

Benerji *et al*., 2013 concluded in their study that significant elevation of serum UA is observed in cirrhosis of the liver, amoebic liver abscess, and viral hepatitis. Hence the elevation of serum UA level along with the classical liver enzymes might be a risk factor for incidence of CLD.[15] Liver injury is characterized by a high blood level of oxidative marker. It is considered a marker of OS. UA levels have been found to correlate with the increases of Child-Pugh score.

In this study, the author also found a significant increase in serum UA levels with CLDs. A study conducted in Korea showed a significant correlation of UA levels with the degree of hepatic histologic change.[9] However, whether decreasing the UA level can halt the progression of the disease or prevent future hepatic or cardiac morbidity is yet unknown and needs to be investigated further.[16]

CONCLUSION

Serum UA was measured only once in this study due to the cross-sectional nature of the study. Despite these limitations, the study found a significant increase in hyperuricemia in patients with CLD. Hence, increased serum UA levels with the classical liver enzymes might be a risk factor for CLD and appropriate therapy early on may halt the further progression of CLD. However, it needs to be validated by larger studies.

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