ORIGINAL ARTICLE

ASSOCIATION OF NON-ALCOHOLIC FATTY LIVER DISEASE WITH SERUM URIC ACID

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Background: Non-alcoholic fatty liver disorder is a clinicopathological condition, characterized by macro vesicular steatosis in hepatic cells and metabolic stress related disorders without other causes of chronic hepatic disease. Uric acid is basically a heterocyclic compound of hydrogen, carbon, oxygen and nitrogen. Uric acid is the metabolic end product of purine metabolism. Hyperuricemia is considered to be related with the causes responsible for the production of metabolic syndrome. It may cause gout, impaired renal function, hypertension, hypertriglyceridemia, obesity and diabetes mellitus. The objective of study is to investigate the association of non-alcoholic fatty liver disease (NAFLD) and serum uric acid level. METHODS: This cross-sectional study was conducted at Ayub Teaching institute Abbottabad. According to predesigned questionnaire and informed consent, 100 subjects between ages 40-50 years were selected for the study. Data collected and analysis done by SPSS version 20. RESULTS: It was observed that 20 (40%) subjects developed NAFLD as compared to 30(60%) of the subjects with normal serum uric acid level. Chi-square test was applied and values found to be significant (p=0.013). CONCLUSION: Our study shows association of NAFLD with serum uric acid level.

Keywords: Non-alcoholic fatty liver disease; Serum uric acid level; Hepatic disorder

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INTRODUCTION

Non-Alcoholic fatty liver disease (NAFLD) is metabolic abnormality which mainly involves the hepatic cells with fatty infiltration. It may be associated with metabolic stress related abnormalities. The disorder mainly occurs in the absence of other chronic conditions of liver.[1]

Prevalence and incidence of NAFLD may continuously be increasing and seems to be an emerging and global problem in our region.[2,3] The disease includes different hepatic disorders, ranging from simple fatty liver disease to non-alcoholic steatohepatitis. Fatty infiltration is a benign, non-progressive condition, while steatohepatitis is a complicated condition which is converted to some other chronic conditions like hepatocellular carcinoma, portal hypertension, and may be to hepatic cirrhosis.[4] Prognosis of non-alcoholic steatohepatitis of such patients is five years, i.e., survival is estimated to be 67%.[5] It is considered to be one of the liver manifestations of metabolic syndromes[6] as it may show relationship with glucose intolerance, obesity, hypertension and dyslipidaemia. These are considered to be a group of disorders recognized as metabolic syndrome.[6,7] Early diagnosis of hepatic diseases by proper screening and followed by proper treatment is helpful for the prevention of diseases which is responsible for irreversible hepatocellular damage. During last ten years, relationship between metabolic syndrome and elevated serum uric acid levels has been determined.[8–11] "Uric acid is a heterocyclic compound of nitrogen, hydrogen, oxygen, and carbon with the formula $C_5H_4N_4O_3$. Human beings convert purine nucleosides to uric acid from adenosine and guanosine. It is an end product of purine metabolism.[12] Normal Serum uric acid level is mainly in range of 2.4–7.4mg/dl (140–440 micromole per litter) in males and in females 1.4–5.8 mg/dl (80–350 micromole per litre).[12]

Elevated serum uric acid level has been considered to be associated with factors that cause metabolic syndromes. Hyperuricemia or increased serum uric acid level causes gout, impaired renal function, hypertension, hypertriglyceridemia and obesity[12], and Diabetes Mellitus[13]. Serum Uric acid level has shown significant association with NAFLD and hyperuricemia is determined to be an independent risk factor for non-alcoholic fatty liver disease.[11]

MATERIAL AND METHODS

This is a cross sectional study carried out at Ayub Medical Institute Abbottabad, which is a tertiary health care unit. The analytical and research work was performed in research laboratories of institute which is well equipped and having advanced modern technology techniques. In this study, two groups were selected. In group A 50 NAFLD patients of age 40–50 years were selected. In group B, 50 subjects of same age group without disease were taken. These subjects were collected randomly. After taking approval from ethical review committee, study was conducted. After informed consent data was collected from subjects of both groups. Data was properly analysed by standardized methods.

Abdominal ultrasonographic examination done in outdoor subjects which are included in this study. USG examination was carried out by expert ultrasonologists by using Toshiba model probe. Fatty liver was diagnosed according to the criteria in which kidney and liver echogenicity, penetration in deeper layers of hepatic tissues and clear visibility of hepatic blood vessel considered. All study subjects in out-patient department with fatty liver disease diagnosed by sonographic examination, with no history of alcohol consumption and chronic hepatitis having normal liver function tests were included in the study. The severity of the disease sonographically was considered as mild and severe cases.

About 5 ml of blood samples were collected and coagulated. These samples were centrifuged for 10 minutes at 3000 rpm in a centrifuge machine to get clear serum. Samples were labelled properly. Serum uric acid levels analysed and measured in standardized research laboratory on daily basis. It was detected by using reagents that were provided with Ecoline diagnostic kit by enzymatic photometric method using 2, 4, 6 tribromo 3 hydroxybenzoic acid (TBHBA).

RESULTS

A total of 100 subjects, 50 with non-alcoholic fatty liver disease and 50 having no disease were included in the study. The age group is basically between 40–50 years. In this study number of males were 59 with minimum age 40 and maximum age 50 with mean 50.31±8.51. The number of females included in study were 41 with minimum age 41 and maximum 49 with mean 48.02±7.89. Various etiological and causative factors responsible for the incidence of non-alcoholic fatty liver disease were investigated amongst subjects. The serum uric acid level was divided into two categories, i.e., within normal range and high levels. Amongst those having fatty liver disease, 28 subjects have high serum uric acid levels while 22 subjects have normal serum uric acid. Statistically by applying chi-square test the relationship between serum uric acid level and NAFLD was found to be significant (*p*-value=0.000)

Table-1: Status of serum uric acid with NAFLD

Serum uric acid	Non-alcoholic fatty liver disease		Total	*p*-value
	Yes	No		
Normal Range	22	39	61	
High	28	11	39	0.000
Total	50	50	100	

DISCUSSION

Our recent study showed a significant association of NAFLD and seum uric acid level suggesting uric acid as a marker of NAFLD development (Table-1). However, it can't be determined that high seum uric acid level is considered as a causative agent of NAFLD or as a consequence of the disease. Previous studies also reveal this association[11] and suggest that high serum uric acid can develop the disorder and cause further progression of the disease.

Main reasons for considering high serum uric acid levels as a risk factor for NAFLD are firstly, serum uric acid act as an oxidant reagent[14] and secondly, the oxidative stress to liver that is produced due to the synthesis of uric acid and oxygen species, catalysed by enzyme xanthine oxidoreductase[15,16]. The oxygen species thus produced are responsible for the development and progression of NAFLD.[17] Uric acid concentration that is regulated by its synthesis excretion and reabsorption can be effected by metabolic, renal and genetic variations[18] decreasing the concentration of SUA may have beneficial effects to reduce the incidence and prevalence of NAFLD suggesting SUA as a cause or effect of disease. Certain studies also revealed that injured cells also release uric acid which then induces sterile inflammation.[19,20] Non-alcoholic steatohepatitis, however, might cause cell death, considered as important component of hepatic cell damage responsible for the release of certain molecules that are not present under normal physiological conditions, these molecules including uric acid in the extracellular environment[21] and the release of uric acid in response to tissue injury along with genetic susceptibility to inflammation happened in NAFLD patients[22]. Relationship of serum uric acid (SUA) and NAFLD is also related to the effects of metabolic syndromes that explains high serum uric acid concentration as a result of hyperinsulinemia mainly causes decrease in uric acid excretion ultimately increases the concentration[23] hence these findings may also suggest that beside uric acid other features of metabolic syndromes may cause the disease. However uric acid exerts pro-oxidant and pro-inflammatory effects in adipose tissues[24,25] and vascular smooth muscle linings[26,27]. Protein kinase pathway and nuclear factor kB are activated due to intra-cellular pro-oxidant activity of uric acid.

As discussed NAFLD is dependent on various factors, but now it is shown that raised serum uric acid levels might suggest to cause the disease, which might not be related to any metabolic diseases, age, and gender. This study reveals that mild steatosis cannot be detected by USG and has limited values in diagnosing NAFLD but benefit of USG cannot be denied in its importance for NAFLD, being cheap, readily available and non-invasive. This study can't determine any casualty among NAFLD and serum uric acid levels. Variations of hepatic fat content affect the sensitivity of liver by properly performing Hepatic USG.[28]

Certain factors like life style and diet were not measured during conducting this cross-sectional study which also contributes to increased uric acid[29] and NAFLD[30]. Decreasing uric acid levels cannot be

considered as therapeutic measures to normal life style modifications. To confirm that uric acid act as a pathogenic agent in NAFLD causation and progression needs more investigations and studies in appropriate animal and cell culture media.

CONCLUSION

Hyperuricaemia or elevated serum uric acid level is significantly associated with NAFLD irrespective of other causes including hypertriglyceridemia, hyperglycaemia and obesity. Increase in incidence and prevalence of the disease and its suspected high-risk complications needs further advanced techniques for its early detection and prevention. Certain measures in routine life like avoiding sedentary life styles, balanced diet with regular exercise and follow ups can help in prevention and progression of the disease.

AUTHORS' CONTRIBUTION

SA: Concept, literature research. NH: data analysis, interpretation. SJ: proof reading. AF: data collection.

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