Volume-4, Issue-12, Dec-2015 • ISSN No 2277 - 8160

Research Paper | Radiodiagnosis

Association Between Serum Uric Acid and Non-Alcoholic Fatty Liver Disease in a Tertiary Care Center in Northern Kerala, India

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ABSTRACT

Background: The role of elevated serum uric acid level in patients with NAFLD is increasingly noted. This study intends to determine association between NAFLD and SUA levels in healthy subjects who electively attended health checkups our hospital.

Methods: Among 3342 subjects who attended health checkups during the period of November 1 2014 to October 31 2015; 1884 subjects without other risk factors were enlisted in our study. We calculated the odds ratio of NAFLD by sex specific quartile of SUA.

Result: The proportion of NAFLD was 29.4% (33.9% in men and 23.5% in women). After adjusting the age the ORs (95% CI) for NAFLD according to each quartile of uric acid were 1.00, 1.32, 1.97, 2.82 for men and 1.0, 0.97, 1.25, 3.01 for women.

Conclusion: High SUA levels are associated with an increased risk of development of NAFLD

KEYWORDS : Uric Acid, NAFLD, Fatty liver, Ultrasound, Steatosis

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) comprises a spectrum of pathologic conditions including simple steatosis, nonalcoholic steatohepatitis and cirrhosis influencing approximately 20–30% of the general population and its prevalence is increasing worldwide[1].It has become one of the most prevalent liver diseases in Western countries, affecting 20%–30% of the general population [1,2].NAFLD is an emerging problem in the Asia-Pacific region and the prevalence is likely to increase in the future [3,4]. Simple steatosis is generally a benign condition; however, NASH can progress to cirrhosis and liver failure [5] and the 5-year survival rate for individuals diagnosed with NASH is estimated to be only 67% [6]. Recently, mounting evidence suggests that elevated serum uric acid (SUA) frequently associates with the development or progression of NAFLD [7,8]. NAFLD is now considered a part of the metabolic syndrome, a clustering of cardiovascular disease risk factors closely associated with insulin resistance and many endocrine derangements including glucose homeostasis and central obesity.[9-12]. It has been reported that hyperuricemia is related to insulin resistance and associated conditions [13-15], but its relationship with NAFLD is not well known. One recent study suggested that hyperuricemia was significantly associated with NAFLD, but the limitation of its cross-sectional study design did not permit a conclusive evaluation for its causal relationship [16] .The mechanism which is involved in the association of NAFLD and hyperuricemia was also uncertain. Insulin resistance and hyperuricemia occur frequently in patients with NAFLD. So Insulin resistance and prooxidant or antioxidant character of uric acid was suspected to be the one of causes of NAFLD[17-20].

Uric acid is the major end product of purine metabolism and is formed from xanthine by the action of xanthine oxidoreductase [21]. Serum uric acid concentrations have long been considered a marker of gout or urolithiasis. However, emerging evidence suggests that increased uric acid, despite being a major antioxidant in the human plasma [22], is associated with the prevalence and incidence of cardiovascular disease (CVD) [23], diabetes[24] and metabolic syndrome [25,26], conditions linked to increased oxidative stress, chronic lowgrade inflammation, and insulin resistance [27,28]. Non-alcoholic fatty liver disease (NAFLD) is defined as a diffuse accumulation of fat in the liver, after excluding excessive alcohol intake and other causes of liver disease. NAFLD has clinical implications because of its increasing prevalence worldwide and its potential to progress to advanced cirrhosis and hepatic failure [29,30]. Along with the "obesity epidemic", the worldwide prevalence of NAFLD, based on imaging studies, is increasing rapidly and now includes 14%–31% of the general population [31]. It is generally attributed to obesity-induced insulin resistance. The development of NAFLD is closely associated with the metabolic syndrome and the association between serum uric acid concentration and metabolic syndrome has been demonstrated in previous studies [30, 31], which leads us to speculate that there might be a relationship between uric acid concentrations and NAFLD. Although several laboratory parameters, such as alanine aminotransferase (ALT), the homeostasis model assessment of insulin resistance (HOMAIR) index, and C-reactive protein (CRP) have been reported as useful markers for the diagnosis of NAFLD [32, 33], little has been written regarding the association between uric acid and NAFLD. NAFLD contains a range of manifestations from simple steatosis, nonalcoholic steatohepatitis (NASH), fibrosis, and liver cirrhosis, which may lead to hepatocellular carcinoma (HCC) and liver failure.[34] Nutritional, metabolic and genetic factors contribute to the occurrence of NAFLD [35,36] .In addition, oxidative stress, insulin resistance and systemic inflammation are known as important risk factors for the development or progression of the liver diseases including NAFLD and NASH.

Recently, several observational studies suggest that hyperuricemia (serum uric acid (SUA) level >7.0 mg/dL in men and >5.7 mg/dL in women) is a risk factor for NAFLD among eastern Asian populations independent of the components of metabolic syndrome (MetS) [38-40]. In fact, there is some evidence that insulin resistance can lead to reduced excretion of SUA and increased SUA level[41,42] .However, data in the India have been limited to liver enzymes and advanced liver disease[43] . Thus we intend to prove a relationship between hyperuricemia and NAFLD. In addition, there is a quantitative relationship between SUA level and NAFLD. We performed a cross-sectional study to examine whether serum uric acid concentrations related to NAFLD as determined by abdominal ultrasonography in our hospital in northern Kerala.

OBJECTIVES

(1) To determine the association between ultrasound-defined NAFLD and SUA; and
(2) To determine if Hyperuricemia is associated with ultrasound-defined NAFLD independent of well-known risk factors.

MATERIALS AND METHODS

STUDY POPULATION

Our study was conducted on patients undergoing health checkup at ACME, Pariyaram during the period of November 1 2014 to October 31 2015. 3342 subjects (1824 males and 1518 females) attended the executive checkup OPD. After getting informed written consent from all the participants, subjects of both sex in the age group of 21-65 were included in our study.

EXCLUSION CRITERIA

Subjects with a history of smoking, alcohol consumption, diabetes

mellitus, hypertension, hypercholesterolemia, obesity (BMI>25), history of liver disease such as hepatitis; a history of cancer, respiratory, renal, hepatobiliary, gout and other rheumatologic disease, subjects with any missing covariate information and participants on hepatotoxic drugs (including HAART) were excluded from the study. After exclusions, 1884 subjects (1066 men, 818 women) were included in the final analysis

DATA COLLECTION

Baseline examinations included a medical history and health habit inventory taken by a physician, anthropometric measurements, hepatic ultrasonic examination, and biochemical measurements. The examinations were administered in the morning following at least 12 h fasting. Blood pressure, standing height and body weight were measured. Body mass index (BMI, kg/m2) was calculated as weight in kilograms divided by height in meters squared. Laboratory measurements included SUA, plasma glucose, serum total cholesterol, serum high-density lipoprotein cholesterol (HDL-C), serum triglyceride (TG) and liver enzymes, including serum AST and ALT.

Ultrasound was performed using GE voluson 730 using 5.0 MHz curvilinear transducer. A radiologist performed baseline ultrasound abdomen examination. Hepatic steatosis was diagnosed by characteristic echo patterns. Five criteria including liver parenchymal brightness, liver-to-kidney contrast, deep beam attenuation, bright vessel walls, and gallbladder wall definition were used to determine hepatic steatosis. Briefly, the degree of steatosis was assessed by the following five criteria: (1) the degree of the liver parenchymal brightness; (2) the presence of liver-to-kidney contrast (yes/no/not assessed); (3) the presence of posterior deep bean attenuation (yes/no/not assessed); (4) the presence of bright vessel walls (yes/no/ not assessed); (5) the definition of gallbladder (clear/ intermediate/obliterated/ not assessed) . According to the five parameters, participants with steatosis were classified as none, grade I, grade II or grade III fatty liver.

Subjects were divided according to their serum uric acid levels. Serum uric acid quartiles were defined ≤ 5.0, 5.1-6.0, 6.1-7.0, > 7 mg/dl for men and ≤ 4.0, 4.1-5.0, 5.16.0, > 6.0 mg/dl for women. Overweight was defined as BMI >/= 25 kg/m^2. Hepatic steatosis was defined as the presence of moderate or severe steatosis by ultrasound regardless of the presence of other liver diseases. NAFLD was defined as the presence of steatosis without excessive alcohol consumption, or use of zydovudine or didanosine, which were found to be associated with the presence of steatosis.

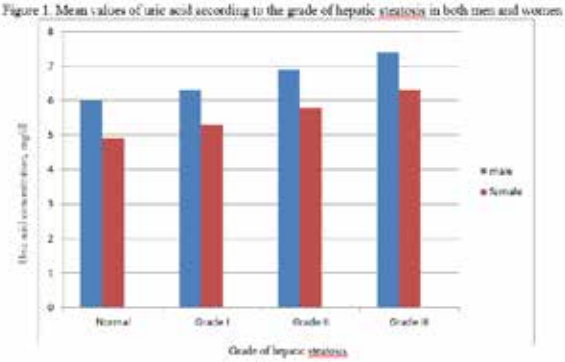
STATISTICAL METHODS

Because uric acid concentrations differ significantly by gender, uric acid quartiles were categorized separately as follows: Q1: ≤ 5.0, Q2: 5.1 – 6.0, Q3: 6.1 – 7.0 , and Q4: >7.0 mg/dl for men; Q1: <4.0, Q2: 4.1 – 5.0, Q3: 5.1 – 6.0, and Q4: >6.0 mg/dl for women. The basic characteristics of the study population according to uric acid quartiles were compared using a one way analysis of variance (ANOVA) or Kruskal-Wallis test for continuous variables, and x2-test for categorical variables. The odds ratios (ORs) and 95% confidence intervals (95% CIs) for NAFLD were calculated after adjusting for age across each quartile of serum uric acid concentration using multivariate logistic regression analysis. All analyses were conducted using SAS statistical software, version 9.1 (SAS Institute Inc., Cary, NC, USA). All statistical tests were two-sided and a p-0.05 was used for statistical significance.

RESULTS

Table 1 shows the characteristics of the 1066 men and 818 women derived after exclusion criteria. In the included population the mean age for men was 44.5 years and 43.5years for women. The mean BMI (kg/m2) was 24.4 for men and 22.9 for women. Mean uric acid concentrations (mg/dl) were 5.7 for men and 4.0 for women. Uric acid increased according to the grade of hepatic steatosis: 6.0, 6.3, 6.9, and 7.4 mg/dl in men, and 4.9, 5.3, 5.8 and 6.3 mg/dl in women with normal, grade I, grade II, grade III fatty liver, respectively as depicted in Figure 1. After adjustment for age the adjusted OR (95% CI) for the highest vs. the lowest quartile of uric acid was 2.07 (1.37–2.81) in men. Among women, the risk of NAFLD was 1.99 (1.23–3.09), after adjustment for the same variables.

Figure 1. Mean values of uric acid according to the grade of hepatic steatosis in both men and women



DISCUSSION

The proportion of NAFLD in this study was 29.4% (33.9% in men and 23.5% in women), which was similar to the data from the general population in South Korea (25.4%) [54], Italy (23%) [37], Israel (30%) [45] and Japan (29%) [53]. In multivariate logistic regression analysis, we observed independent associations between serum uric acid concentrations and the presence of NAFLD. Our results are in agreement with previous studies conducted by and Shi[44] and Li et al.[16] However, in that study, gender difference was not fully considered since separate data for both gender using multivariate analysis was not performed. As shown in the present study, there is a significant gender difference in the distribution of uric acid. Our study showed that these associations between serum uric acid concentration and NAFLD can be applied to both men and women through gender-specific multivariate logistic regression analysis.

We observed independent association between serum uric acid concentrations and the presence of NAFLD. We found that individuals with hyperuricemia had a higher proportion of NAFLD.

Many factors, including genetic, metabolic and dietary risk factors, are postulated to contribute to the development of NAFLD. Current understanding of the progression of NAFLD involves the "2-hit hypothesis."[46] The "first hit" is excessive fat accumulation in hepatocytes, which is closely linked to insulin resistance. Numerous studies have introduced significant association between serum uric acid concentration and the metabolic syndrome and its components[47] where insulin resistance is the primary problem. The significant association between serum uric acid and NAFLD suggest that insulin resistance is a possible mechanism linking serum uric acid with NAFLD. The "second hit" is a process from oxidative stress to hepatocyte injury, inflammation and fibrosis. Excessive free fatty acids in hepatocytes of patients with NAFLD generate an excess of reactive oxygen species leading to lipid peroxidation of hepatocytes, cytokine production and hepatic inflammation[47].

Uric acid is produced as the end-product of purine breakdown. People generally acquire purine from increased intake of purine-rich foods (such as meats and seafood), monosaccharide fructose, and alcohol[47]. As for fructose, once it enters into hepatocytes, it is rapidly phosphorylated and intracellular phosphate levels fall, which triggers the activity of adenosine mono-phosphate (AMP) deaminase. Finally, AMP deaminase results in substrate-dependent phosphate depletion [adenosine triphosphate (ATP) depletion], which increases uric acid production[48]. Some studies have shown that hepatic ATP depletion also leads to arrest in protein synthesis and produces inflammatory and pro-oxidative changes[46]. Another review article by Lim et al. postulates that excessive dietary fructose consumption may contribute

to the development of NAFLD. Additionally, increased SUA itself may also produce pro-inflammatory and pro-oxidative effects[48]. Ruggiero et al. showed a positive and significant relationship between SUA and many inflammatory markers in Italian men[45]. Thus ATP depletion and SUA itself may lead to hepatocellular injury (elevated liver enzymes) and progression of NAFLD. Indeed, some studies have showed that SUA levels are associated with the progression of chronic liver diseases such as NAFLD and NASH and hyperuricemia is independently associated with the severity of liver damage among NAFLD patient.

An experimental study has shown that serum uric acid stimulates the synthesis of microcyte chemo-attractant protein, interleukin-1, interleukin-6 and tumor necrosis factor-α,[48] all of which are pro-inflammatory molecules and stimulate production of C-reactive protein in the liver[49] So major factors connecting increased serum uric acid concentration with NAFLD may be due to oxidative stress and chronic low-grade inflammation.[50]

Our study has several limitations. First, given the cross sectional design, we are unable to determine causality. Second, the diagnosis of NAFLD by ultrasound is relatively insensitive as compared to that by biopsy[51] although the recent study showed that ultrasound allows for reliable and accurate in the detection of moderate-to-severe fatty liver compared to histology.[52]Thus, we are unable to determine the association between SUA and lesser degrees of steatosis. Third, we did not consider other potential confounding factors on SUA level such as diet patterns. Fourth, it should be a weakness to use in this study only around 50% of the people who attended the health checkup. Finally, individuals with more severe NAFLD, especially if hospitalized or in a nursing home, would have been unlikely to take part in the study, thus our associations are likely limited to moderate NAFLD, and not end-stage liver disease. But we were able to control for multiple confounders, including all of the components of the MetS, establishing an association independent of these factors

CONCLUSION

Our study shows a clear correlation between elevated serum uric acid levels and the development and progression (grades) of NAFLD. It is necessary to analyze serum uric acid, when a person is incidentally diagnosed to have NAFLD because recent studies have proved hypouricemic therapy clinically lowers serum uric acid levels and degree of hepatic steatosis(55).

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