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The association between increased alanine aminotransferase activity and metabolic factors in nonalcoholic fatty liver disease

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Abstract

Nonalcoholic fatty liver disease (NAFLD) has been associated with metabolic disorders, including central obesity, dyslipidema, hypertension, and hyperglycemia. Metabolic syndrome, obesity, and insulin resistance are major risk factors in the pathogenesis of NAFLD. The aim of this study was to identify the relative contribution of the metabolic syndrome, obesity, and insulin resistance to alanine aminotransferase (ALT) activity in NAFLD. A total of 3091 subjects diagnosed with fatty liver by ultrasonography were enrolled. All components of metabolic syndrome criteria, anthropometric parameters, fasting insulin levels, high-sensitivity C-reactive protein (hs-CRP) as an inflammation marker, and ALT were measured in each subject. Homeostasis model assessment—insulin resistance (HOMA-IR) as a measure of insulin resistance and body mass index (BMI) as a measure of obesity were calculated. The prevalence of increased ALT levels (>40 IU/L) was 26.7%. Increased ALT activity was significantly associated with the following characteristics: male sex, young age, increased triglycerides, fasting glucose, fasting insulin, HOMA-IR, hs-CRP, waist circumference, BMI and diastolic blood pressure, and decreased high-density lipoprotein cholesterol (HDL-C). According to the increase in the number of metabolic syndrome components, BMI, HOMA-IR, and hs-CRP, the prevalence and odds ratio for having increased ALT activity were significantly increased. Central obesity, raised triglycerides, reduced HDL-C, and raised fasting glucose were strongly associated with increased ALT activity. In conclusion, a number of metabolic syndrome components, obesity, insulin resistance, and hs-CRP, are strong predictors of increased ALT activity in NAFLD. Central obesity, raised triglycerides, reduced HDL-C, and raised fasting glucose are metabolic syndrome components that contributed to increased ALT activity.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) comprises a large part of chronic liver disease in industrialized countries after excluding alcoholic and viral liver disease. As a result of a sedentary lifestyle and westernized food choices, metabolic syndrome and obesity are increasing in prevalence in Korea, and concomitantly there is an interest in NAFLD. Its presentation ranges from simple fatty liver without fibrosis or necroinflammatory changes to nonalcoholic steatohepatitis, with various degrees of fibrosis or intrahepatic necroinflammation, which can progress to liver cirrhosis or hepatocellular carcinoma [1].

The pathophysiology of NAFLD includes the intrahepatic accumulation of fat in the form of triglycerides, in which insulin resistance is believed to play an important role by facilitating the transport of free fatty acid into the liver from visceral fat stores or peripheral lipolysis [2]. Many studies show that several metabolic conditions, including obesity, diabetes mellitus, dyslipidemia, hypertension, and insulin resistance are strongly associated with NAFLD [3-5]. Metabolic syndrome represents a chronic inflammatory state that links insulin resistance, endothelial dysfunction, and cardiovascular disease, and it has also been reported in NAFLD [6,7]. This suggests that NAFLD may represent the hepatic manifestation of the metabolic syndrome [8].

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The prevalence of unexplained hypertransaminasemia reported in the US population was 2.8% to 5.4% [9,10]. Approximately 80% to 90% of hypertransaminasemia may be explained by NAFLD, once other causes such as chronic viral hepatitis and alcohol-induced liver disease are excluded [11,12]. Therefore, nonalcoholic hypertransaminasemia, in which viral or other causes of liver disease are also excluded, has been used as a noninvasive surrogate marker for NAFLD.

The aim of this study was to identify the relative contribution of each component of the metabolic syndrome, obesity, and insulin resistance to increased alanine aminotransferase (ALT) activity in patients with NAFLD.

2. Materials and methods

2.1. Subjects

Kangbuk Samsung Hospital (Seoul, Korea), a tertiary care provider, runs a medical screening center with the aim of providing cutting-edge infrastructure to support early detection of health risk factors and eventually contributing to public health. The center accommodates about 60 000 to 70 000 people per year. Most examinees are employees of various companies and their spouses. Given their middle or higher income levels, they tend to be more attentive to their health status and undergo health checkup more often than other people of the same age range. Medical health checkup provided by the center includes urinalysis, blood cell counts, blood chemistry, measurements of hepatitis B surface antigen and hepatitis C antibody, electrocardiography, chest radiography, abdominal ultrasonography, upper and lower gastrointestinal endoscopy, and measurements of blood pressure and anthropometric parameters (height, body weight, waist circumference). A self-administered questionnaire is also served to measure medical history of the examinee and family, medication history, and lifestyles (smoking, drinking, diet and exercise). The center charges US $450 to men and US $500 to women. Employers usually pay this checkup fee, although there are some exceptions.

A total of 40 237 apparently healthy subjects who underwent a medical health checkup at the Kangbuk Samsung Hospital from January to December in 2004 were included in this study. Of those, 29 506 subjects who did not undergo ultrasonography, or who yielded abnormal ultrasonographic findings other than fatty liver, were excluded. A total of 10 731 subjects diagnosed with fatty liver by ultrasonography were included in the study. An additional 7640 subjects were excluded because of one of the following: a positive test for the hepatitis B surface antigen or hepatitis C antibody, a transferrin saturation of more than 50%, a daily alcohol intake of 20 g or more, drug-induced liver disease, or incomplete data for determination of the metabolic syndrome. Alcohol consumption was assessed by using a self-administered questionnaire concerning the amount and type of alcoholic beverages consumed per week, which was converted into the amount of pure alcohol per day. Taking drugs known to promote fatty liver disease in the past month was also surveyed by using the self-administered questionnaire. Data were not available to evaluate the presence of other less common liver diseases, such as autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, or Wilson disease. Ultimately, a total of 3091 subjects were enrolled in this study. The study protocol was approved by the institutional review board and the ethics committee of the Kangbuk Samsung Hospital, and it conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

2.2. Assessment of hepatic steatosis

As liver biopsy in apparently healthy subjects is not ethical, and the sample size was very large, we used ultrasonography (ASPEN; Acuson, PA) as a noninvasive method to diagnose fatty liver disease. The presence of steatosis was assessed on the basis of ultrasonographic findings of a bright liver, increased echogenicity of the echotexture when compared with the kidneys, vascular blurring, and deep-echo attenuation, as previous described [13-16].

2.3. Measurement of anthropometric parameters

Anthropometric measurements of height, body weight, and waist circumference were made on the same day. The height was measured to the nearest 0.5 cm. The body weight was measured in light clothing and without shoes to the nearest 0.1 kg. The waist circumference was measured to the nearest 0.1 cm with flexible tape at the midpoint between the lower border of the rib cage and the iliac crest. The systolic and diastolic blood pressures were measured in the sitting position after at least 10 minutes of rest. During the 30-minute preceding the measurement, subjects were required to refrain from smoking or consuming caffeine. The blood pressure was measured twice and the mean value was recorded.

2.4. Measurement of biochemical items

For determination of plasma concentrations of fasting glucose, fasting insulin, high-density lipoprotein cholesterol (HDL-C), triglycerides, and ALT, blood was drawn in the morning after 12 hours of overnight fast from an antecubital vein into evacuated tubes containing EDTA. The fasting glucose level was measured using the hexokinase method. The fasting insulin level was measured by an immunoradiometric assay with a BioSource INS-IRMA Kit (BioSource, Belgium). The coefficient of variation was 1.6% to 2.2% for the intra-assay and 6.1% to 6.5% for the interassay. The triglycerides level was measured with an enzymatic calorimetric test. The HDL-C level was determined using the selective inhibition method. Serum iron and total iron binding capacity were measured by a colorimetric method using ferrozine and bathophenanthroline sulfonate, respectively. All biochemical items described above were measured in an automatic analyzer (Advia 1650; Bayer,