Association of serum alanine aminotransferase and γ-glutamyltransferase levels within the reference range with metabolic syndrome and nonalcoholic fatty liver disease

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Background/Aims: Nonalcoholic fatty liver disease (NAFLD) has recently been found to be a novel component of metabolic syndrome (MS), which is one of the leading causes of chronic liver disease. The serum alanine aminotransferase (ALT) and γ-glutamyltransferase (GGT) levels are suggested to affect liver fat accumulation and insulin resistance. We assessed the associations of serum ALT and GGT concentrations within the reference ranges with MS and NAFLD.

Methods: In total, 1,069 subjects enrolled at the health promotion center of Wonkwang University Hospital were divided into 4 groups according to serum ALT and GGT concentrations levels within the reference ranges. We performed biochemical tests, including liver function tests and lipid profiles, and diagnosed fatty liver by ultrasonography. Associations of ALT and GGT concentrations grading within the reference range with fatty liver and/or MS were investigated.

Results: The presence of MS, its components, and the number of metabolic abnormalities [except for high-density lipoprotein-cholesterol (HDL-C) and fasting blood glucose] increased with the ALT level, while the presence of MS, its components, and the number of metabolic abnormalities (except for HDL-C) increased with the GGT level. The odds ratios for fatty liver and MS increased with the ALT level (P<0.001 and P=0.049, respectively) and the GGT level (P=0.044 and P=0.039, respectively).

Conclusions: Serum ALT and GGT concentrations within the reference ranges correlated with the incidence of NAFLD and MS in a dose-dependent manner. There associations need to be confirmed in large, prospective studies.

Keywords: Alanine aminotransferase; Gamma glutamyltransferase; Nonalcoholic fatty liver; Metabolic syndrome

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disorder in Western countries, affecting 20-30% of the general population.¹,² The prevalence of NAFLD has increased substantially during the last 15 years in parallel with regional trends in over-nutrition central and overall obesity, type 2 diabetes mellitus (DM), and the metabolic syndrome (MS).²,³

NAFLD, characterized by elevated alanine aminotransferase (ALT) and γ-glutamyltransferase (GGT), is now considered as the hepatic expression of insulin resistance (IR),⁶ accounting for the risk of advanced liver disease observed in these patients, in addition to the well-established risk of cardiovascular disease.

Serum ALT is associated with liver fat accumulation as a...
marker of hepatic steatosis or hepatic dysfunction. Also, as a gluconeogenic enzyme, the ALT is associated with hepatic IR.\textsuperscript{7} A number of MS components, obesity, IR, and high sensitivity-C-reactive protein (hs-CRP), are strong predictors of increased ALT activity in NAFLD.\textsuperscript{5} Elevated serum ALT levels have a positive association with MS-related diseases, such as type 2 DM and cardiovascular disease.\textsuperscript{9,10}

In recent data, both normal and increased levels of ALT are associated with long-term development of multiple metabolic disorders. These results indicate the potential for ALT values within the reference interval as biomarkers for the risk of MS.\textsuperscript{11} Several prospective epidemiologic studies have demonstrated that increased concentrations of hepatic enzyme in serum, even within the reference interval, may be related to an increased risk of type 2 DM and the MS, as well as death.\textsuperscript{12} In addition, ALT is a predictor of mortality due to unrecognized liver diseases, but also due to other causes of ALT elevation, linked to non-liver health risks, such as atherosclerosis, hypertension (HTN), and type 2 DM.\textsuperscript{7} Even within the normal range, there is a positive association between the aminotransferase concentration and mortality from liver disease.\textsuperscript{13}

As GGT is a sensitive indicator of liver damage,\textsuperscript{14} excess deposition of fat in the liver is associated with an elevated serum GGT and IR.\textsuperscript{15,16} GGT is located on the external surface of most cells and mediates the uptake of glutathione,\textsuperscript{17} an important component of intracellular oxidative defenses.\textsuperscript{18} GGT is also considered a marker of oxidative stress and it may be directly involved in the generation of reactive oxygen species. The serum GGT level has been associated with many cardiovascular disease risk factors, DM, MS, and IR.\textsuperscript{13,18,19} In Korean adults, serum GGT is closely correlated with IR and the increased number of components of MS,\textsuperscript{20} as a surrogate marker of IR, inflammation, and MS.\textsuperscript{21} Some studies suggest that within its reference interval, the serum GGT concentration has been closely related to the presence of components of the MS.\textsuperscript{7} Recent reports suggest that an increased GGT level is a risk factor for advanced fibrosis in NAFLD\textsuperscript{21} and, with weight loss, a decrease in GGT activity is predictive of improved lobular inflammation and fibrosis of liver.\textsuperscript{20}

Thus, measurement of ALT and GGT may identify subjects in the general population with a risk of NAFLD and MS.\textsuperscript{7} However, limited data exist on the significance of GGT or ALT activities within reference interval in subjects with NAFLD and MS. Therefore, we assessed the association of serum ALT and GGT activities within reference range with MS and NAFLD.

**MATERIALS AND METHODS**

**Subjects**

The medical records of 2,024 subjects who attended our Center for Health Promotion for a medical check-up between 2006 and 2008 were investigated. Subjects meeting any of the following criteria were excluded: hepatic enzyme/GGT concentrations higher than the upper limit of the reference range, a positive test for hepatitis C virus antibody, a positive test for hepatitis B virus surface antigen, a daily alcohol intake of 20 g or more, liver cirrhosis, or incomplete data for determination of the MS (Fig. 1).

The subjects were classified separately into four groups according to the serum ALT and GGT activities within reference range, as in previous report.\textsuperscript{18} According to ALT and GGT activities, subjects were divided into four group respectively as below; ALT grading (first 1-14 IU/L, second 15-19 IU/L, third 20-25 IU/L, and fourth 26-40 IU/L); GGT grading (first 1-10 IU/L, second 11-15 IU/L, third 16-24 IU/L, and fourth 25-50 IU/L). Considering sexual difference, group of ALT activity was divided into male and female groups.

**Assessment of hepatic steatosis**

We used ultrasonography as a non-invasive method to diagnose fatty liver disease. All ultrasound scans were performed by two skilled operators using a high resolution B-mode scanner (SSD-5500; Aloka, Tokyo, Japan). Liver steatosis was assessed on the basis of abnormally intense, high-level echoes arising from the hepatic parenchyma, the liver-kidney difference in echo amplitude, the echo penetration into the deep portion of the liver, and the clarity of the blood vessel structure in the liver.\textsuperscript{22}

![Figure 1. Study profile.](image-url)