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The relationship between γ-glutamyltransferase and adiponectin in nonalcoholic women

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Abstract

The relationship between adiponectin and γ-glutamyltransferase (GGT) has yet to be clearly demonstrated especially in women. Among the parameters of the liver function test (LFT), it has become increasingly evident that GGT is associated with metabolic disease. The objective of this study was to characterize the relationship between adiponectin and GGT in nonalcoholic women without liver disease. The subjects in this study were recruited from participants in routine health examinations during February of 2004. Among the total of 115 subjects considered for recruitment, we ultimately included 86 patients without liver disease in the study after performing LFT and abdominal sonography. After a 12-hour overnight fast, levels of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, GGT, total cholesterol, high-density lipoprotein cholesterol, triglycerides, fasting plasma glucose, fasting insulin, and adiponectin were measured in all subjects. We found a significant negative correlation between adiponectin and GGT ($r = -0.35$, $P < .001$) and a significant positive correlation between GGT and homeostasis model assessment (HOMA) ($r = 0.29$, $P < .01$) after controlling for the confounding influences of age and fat mass. Although GGT is clearly related to adiponectin and HOMA, we determined aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase were not significantly associated with adiponectin and HOMA. The present study suggests that only GGT among the LFTs is related to adiponectin in nonalcoholic women without liver disease.

1. Introduction

γ-Glutamyltransferase (GGT) has come into the spotlight because of its association with metabolic disease [1-9]. γ-Glutamyltransferase is the enzyme responsible for extracellular glutathione catabolism and has previously been used as a sensitive indicator of hepatobiliary disorders, including both alcohol-related liver disease and fatty liver [10].

Recently, mounting evidence has suggested that serum GGT levels are more than a marker for alcohol consumption. Several studies have reported that GGT levels might also constitute a risk factor for metabolic disease [5-7]. These studies have determined that a correlation exists between GGT levels and several metabolic risk factors, including body mass index (BMI), systolic blood pressure, physical inactivity, serum triglycerides (TGs), and total cholesterol (TC), as well as fasting plasma glucose (FPG) levels [5-7,11]. Therefore, it is interesting to investigate the relation of GGT and adiponectin, which has been proposed to be correlated with the development of insulin resistance and has been implicated as a critical molecule in the pathogenesis of live disease [7]. This study was conducted only on female subjects, as there are significant sex differences with regard to adiponectin concentrations in the circulation [12,13].

The objective of this study was to elucidate the relationship between adiponectin and GGT levels in nonalcoholic female subjects, none of whom currently has liver disease.

2. Patients and methods

The subjects of this study were recruited from patients undergoing routine health examinations at the Department of Family Medicine of the Korea University Hospital during February of 2004. The protocols of this study were approved

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Table 1
Physical and metabolic characteristics of the study population (n = 86)

Variables	Mean ± SD or median (minimum, maximum)
Age (y)	46.60 ± 11.37
BMI (kg/m^2)	23.56 ± 2.98
Total fat mass (kg)	29.92 ± 4.82
Fasting serum insulin (IU/mL)	7.53 ± 3.07
Insulin resistance (HOMA)	1.68 ± 0.71
Systolic blood pressure (mm Hg)	115.52 ± 14.00
Diastolic blood pressure (mm Hg)	72.27 ± 10.81
TC (mg/dL)	195.50 (166.00-210.00)
HDL-C (mg/dL)	55.23 ± 14.31
TG (mg/dL)	112.00 (65.75-161.50)
FPG (mg/dL)	88.00 (83.00-94.25)
AST (IU/L)	19.00 (16.00-23.00)
ALT (IU/L)	17.00 (12.00-22.25)
ALP (IU/L)	51.50 (42.75-60.25)
GGT (IU/L)	15.00 (11.00-19.25)
Adiponectin (μg/mL)	7.28 (4.76-10.22)

Data are mean ± SD or median (25th-75th percentiles).

by the ethics committee, and the study was conducted in accordance with the guidelines established by the Helsinki Declaration. Written informed consent was obtained from all participants before the commencement of the study.

A total of 115 subjects were screened for recruitment into this study. After a standard interview, some of the candidates were excluded because of the following criteria: (1) positive serologic finding for the hepatitis B or C virus (2 subjects); (2) aspartate aminotransferase (AST) 75 IU/L or greater or alanine aminotransferase (ALT) 75 IU/L or greater (2 subjects); (3) alcohol intake more than twice per week, or more than 20 g/d (7 subjects); (4) any history of another known liver disease (1 subject); (5) any history of hypercholesterolemia or hypertension (15 subjects); (5) any abnormal finding in liver on abdominal ultrasonography (2 subjects).

Height, weight, and waist and hip circumferences were measured by one nurse, rounding off the numbers to 2 decimal places. Waist circumference was measured at the midpoint between the lower border of the rib cage and the iliac crest, and hip circumference was acquired at the widest point between the hip and the buttock. BMI was calculated as weight (kilograms) divided by height (meters squared).

Hepatitis B surface (HBs) antigen and antibody status and hepatitis C virus (HCV) antibody status were assessed via chemiluminescence enzyme-linked immunosorbent assays. One experienced radiologist conducted the abdominal ultrasonographies. Blood pressure was measured in the right arm, using an appropriately sized cuff and a standard mercury sphygmomanometer, after the subject had been seated for at least 10 minutes. Blood was obtained from all patients after a 12-hour overnight fast. A routine biochemical evaluation was performed measuring serum AST, ALT, alkaline phosphatase (ALP), GGT, TC, high-density lipoprotein cholesterol (HDL-C), TG, FPG, and fasting insulin levels. Serum AST, ALT, ALP, GGT, TG, HDL-C, and FPG levels were measured via the enzymatic method, using a chemical analyzer (Hitachi 747, Tokyo, Japan). The glucose oxidase method was used to measure plasma glucose levels, and a human insulin–specific RIA kit (Linco Research, St Charles, MO) was used to determine the insulin levels. Serum was recovered from supernatant resulting from 15 minutes of centrifugation at 3000 rpm in a clinical centrifuge. The insulin resistance indices were measured via the homeostasis model of assessment (HOMA) method according to the following formula [14]: (fasting glucose level [mg/dL] × fasting insulin level [μU/mL])/405. Plasma adiponectin protein levels were quantified by using a commercially available enzyme-linked immunosorbent assay kit (Quantikine, R&D Systems, Minneapolis, MN) in accordance with the manufacturer's instructions after each of the serum samples had been diluted 100-fold.

2.1. Statistical analysis

Data were summarized via standard procedures. Any missing values resultant from insufficient samples or values outside the assay range were excluded from the analysis. The results were expressed as means ± SD for Gaussian variables. Each of the variables was checked for normality of distribution via Kolmogorov-Smimov tests. Any parameters that did not fall within a normal distribution (ie, TC, TG, AST, ALT, ALP, GGT, FBS, insulin, homeostasis model assessment of insulin resistance [HOMA-IR], and adiponectin) were then log transformed for subsequent analyses. Pearson correlation and partial correlation analyses were used to test the associations between plasma adiponectin levels and GGT, lipid profile, and HOMA-IR values after controlling for age and fat mass.

Table 2
Partial Pearson correlation coefficients between adiponectin and various potential predictors after adjusting for age and fat mass

	GGT (IU/L)	AST (IU/L)	ALT (IU/L)	ALP (IU/L)	Adiponectin (μg/mL)
AST (IU/L)	0.42***				
ALT (IU/L)	0.53***	0.81***			
ALP (IU/L)	0.23*	0.25*	0.28*		
Adiponectin (μg/mL)	−0.35***	−0.17	−0.13	0.03	
HOMA	0.29**	−0.02	0.09	0.21	−0.22*

Adiponectin, GGT, AST, ALT, ALP, and HOMA were log transformed.
* $P < .05$.
** $P < .01$.
*** $P < .001$.

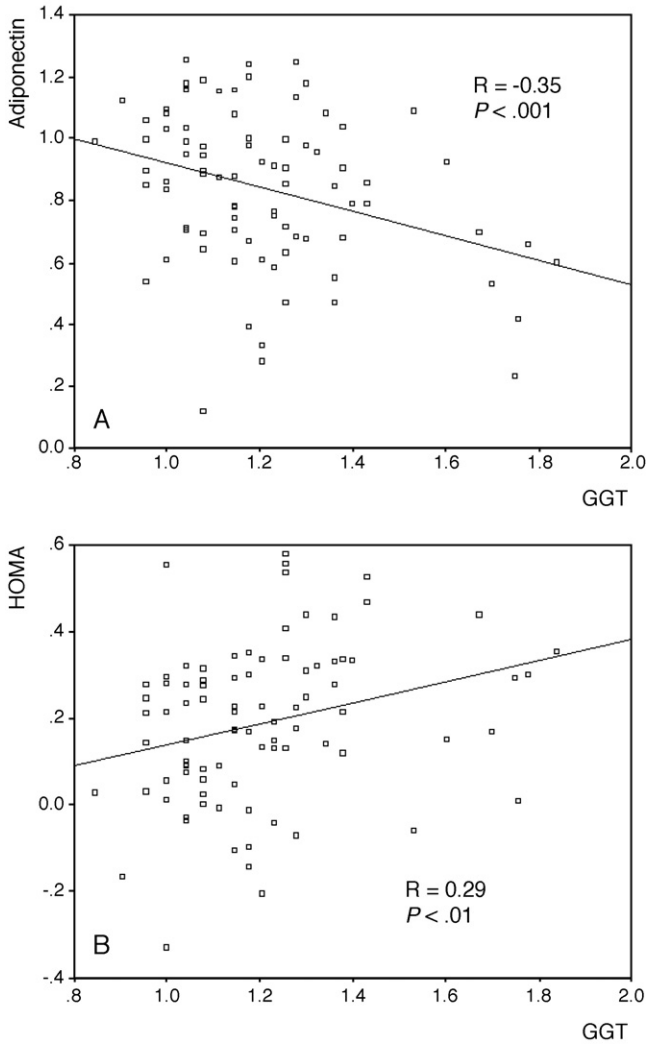

Fig. 1. Relation between insulin sensitivity and GGT after adjusting age and fat mass. Adiponectin, GGT, and HOMA-IR were log transformed. A, Relation between HOMA-IR index and GGT. B, Relation between adiponectin and GGT.

The level of statistical significance was set at $P < .05$. All statistical analyses were conducted by using the SPSS computer analysis program (version 10.0; SPSS, Chicago, IL).

3. Results

The physical and metabolic characteristics of the study population are provided in Table 1.

Table 2 shows a significant negative correlation between adiponectin and GGT ($r = -0.35$, $P < .001$) after controlling for the confounding influences of age and fat mass. A significant positive correlation between GGT and HOMA ($r = 0.29$, $P < .01$) was detected, whereas AST, ALT, and ALP were not found to be related with adiponectin and HOMA.

Fig. 1 shows the relation between GGT and HOMA and between GGT and adiponectin after adjusting for age and fat mass. γ-Glutamyltransferase is positively related to HOMA ($R = 0.29$, $P < .01$) and negatively related to adiponectin ($R = -0.35$, $P < .001$).

4. Discussion

This study was targeted specifically toward the elucidation of the relationship between adiponectin and GGT. Thus, drinkers were excluded from the study, as were any subjects who apparently had liver disease. These selection criteria appear to have attained the considerably desired end, as adiponectin was significantly negatively related to GGT.

Our study revealed no significant relationship between adiponectin and liver function test (LFT), with the exception of GGT levels. By way of contrast, a study conducted with Japanese male workers indicated that AST, ALT, and GGT are all negatively correlated with adiponectin [15]. However, abnormal LFT groups were not excluded in their study, as they were from ours. Therefore, in their study, there might be a possibility of a relationship between adiponectin and AST or ALT because the subjects might have some liver diseases.

In addition, some studies showed plasma adiponectin is decreased in non-alcoholic fatty liver disease (NAFLD) [16,17]. However, their concerns have been limited to adiponectin, not GGT. The important point of our report is GGT as well as adiponectin. Because we wanted to research more about GGT as a metabolic marker, we excluded the subject who had abnormal transferase values; thus, our results clearly showed the relationship between GGT and adiponectin. Serum GGT has classically been used as an objective indicator for excess alcohol consumption, and high GGT level has been interpreted as a surrogate of the correlation between alcohol consumption and disease [18,19]. Recently, a growing body of evidence has suggested that serum GGT is more than simply a marker for excess alcohol consumption. Previous studies have shown that GGT is significantly positively associated with certain metabolic factors, implying that elevated GGT level belongs in the metabolic syndrome cluster [2-9].

The mechanisms underlying the associations observed in this study remain largely unknown. Changes in the liver associated with insulin resistance have been discussed as a possible mechanism [2,3,20]. More than 90% of patients with NAFLD have at least one factor of the metabolic syndrome [21,22], and the prevalence of NAFLD increased in the person who had metabolic features [21-24]. Obesity, type 2 diabetes mellitus, and hyperlipidemia are major predisposing factors leading to the development of NAFLD [25-27]. However, this relation is insufficient to adequately explain our results. Other possibilities may include the relationship of the GGT levels with oxidative stress [7]. γ-Glutamyltransferase plays a pivotal role in the maintenance of intracellular antioxidant defenses via its ability to mediate the transport of extracellular glutathione into most cell types [28]. An increase in oxidative stress could be one mechanism of nonalcoholic steatohepatitis, which is clearly

related to low adiponectin level [29-31]. Therefore, these mechanisms might also play important roles with regard to the relationship existing between adiponectin and GGT.

The limitation of our study was that it was predicated on a cross-sectional design, thereby rendering it difficult to differentiate reason from result. However, the importance of this study lies in the fact that our results imply that adiponectin is associated negatively with GGT, even in subjects with normal LFT. To the best of our knowledge, this is the first study to elucidate the association between adiponectin levels and GGT activity in women.

Second, the subjects were limited to women. However, in the general population, plasma adiponectin is known to have apparently higher values and GGT is documented to have lower values in women than in men [32-37]. Therefore, we only included female subjects for clarifying the relation of GGT and adiponectin. Future studies are needed to prove whether this relationship is similar in male subjects.

In conclusion, only GGT level is related to adiponectin level in nonalcoholic women without liver disease.

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