

Research Article

Elevated Serum Gamma-Glutamyltransferase Is a Strong Marker of Insulin Resistance in Obese Children

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Received 22 October 2012; Revised 29 January 2013; Accepted 15 February 2013

Academic Editor: Barry Posner

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Elevated levels of serum gamma-glutamyltransferase (GGT) levels have been found to predict the development of type 2 diabetes in adults. The role of GGT in insulin resistance (IR) among children is largely unknown. We investigated whether GGT among hepatic enzymes is independently associated with IR in obese Korean children. A total of 1308 overweight (above the 85th BMI percentile of Korean reference) boys ($n = 822$) and girls ($n = 486$), aged 9–15 years, were studied. Measures acquired included weight, height, percent body fat (BF%), waist circumference, blood pressure, blood glucose and insulin, C-reactive protein, total cholesterol, triglycerides, HDL-Cholesterol, GGT, aspartate aminotransferase (AST), and alanine aminotransferase (ALT). IR was calculated using the homeostasis model assessment (HOMA-IR). Serum GGT and ALT, but not AST, were positively correlated with HOMA-IR in boys ($r = 0.222$ for GGT; $P < 0.05$, $r = 0.188$ for ALT; $P < 0.05$) and girls ($r = 0.292$ for GGT; $P < 0.05$, $r = 0.258$ for ALT; $P < 0.05$). In multiple regression analysis for HOMA-IR as dependent variable, GGT ($\beta = 0.068$; $P = 0.053$ in boys, $\beta = 0.145$; $P = 0.002$ in girls) and ALT ($\beta = 0.074$; $P = 0.034$ in boys, $\beta = 0.130$; $P = 0.005$ in girls) emerged as determinants of HOMA-IR after adjusting age, BMI, Tanner stage, and triglycerides. Serum GGT level is a strong marker of IR in obese Korean children.

1. Introduction

Obesity is a risk factor for type 2 diabetes mellitus, and its prevalence is increasing worldwide. Moreover, an alarming increase in the incidence of type 2 diabetes has now been reported in very young children [1]. Insulin resistance (IR), the most common feature of childhood obesity, is a key risk factor for development of type 2 diabetes [2]. Serum activities of hepatic enzymes have been associated with obesity in adults [3] and adolescents [4], and relationships between these markers and IR or type 2 diabetes, independently of adiposity, have been shown in several studies [5–8]. In adult population, recent studies indicate that alanine aminotransferase (ALT) [8, 9] and gamma-glutamyltransferase (GGT)

are independent predictors of type 2 diabetes [6, 7, 10]. Indeed, ALT is a glucogenic enzyme and is regarded as a surrogate marker of hepatic IR, nonalcoholic fatty liver disease (NAFLD) [11, 12]. Increased ALT has been demonstrated to be an indicator of impaired insulin signaling [13]. On the other hand, serum GGT is one of the hepatobiliary enzymes and is synthesized in epithelial cells of the intrahepatic duct. Serum GGT traditionally has been used as a marker of alcohol-induced liver disease [14]. Recently, GGT has been regarded as a clinical marker for free-radical formation and proinflammation [15]. GGT-related pathomechanism is that GGT enhances the availability of cysteine to promote intracellular glutathione, the principle thiol antioxidant in humans, and resynthesis, thereby counteracting oxidant stress [16]. The

relationships of liver enzyme with IR in children are less likely to be affected by alcohol, comorbidities, and medicine, which might influence the liver function, than in adults. However, studies that clarify whether the liver plays an early role in the natural history of the disease in children with no or minimal cumulative exposure to unhealthy behaviors are rare. The aim of this cross-sectional study is to evaluate whether an independent relationship exists between insulin resistance and serum hepatic enzyme activities in obese Korean children.

2. Materials and Methods

2.1. Subjects

2.1.1. Study of Seoul Obese School Children (SSOS). This study was designed to identify the prevalence of risk factors and relationship between risk factors and metabolic profile in obese school children in Seoul. All primary and middle schools in Seoul were invited to join the study. Among them, 25 schools (15 of primary schools and 10 of middle schools) were selected by order of their responses. The target study subjects were overweight and obese students, over 85th percentile of age, and gender-specific Korean BMI references [17] in annual school examination. Anthropometric measurement, blood test, and questionnaire were performed to children whose parents and themselves agreed to join the study. A team consisting of 5 medical doctors and 3 nurses and 3 assistants were sent to the school for the measurements. After all the examination, one doctor consulted students who are regarded as having serious medical or behavioral difficulties. This study (The Study of Seoul Obese School Children) was performed as a part of children's obesity-related disease management program conducted by Seoul School Health Promotion Center, Study Group of Childhood Obesity, and Obesity Clinic in Kangbuk Samsung Hospital and Inje University Sanggye Paik Hospital. This study was approved by Institutional Review Board of Kangbuk Samsung Hospital and Inje university Sanggye Paik Hospital. Total of 1716 children (1105 boys, 611 girls, aged 9–15 years old) were enrolled.

For this study, subjects were 1308 (822 boys and 486 girls) after excluding children with established diabetes, recent infection, suspected endocrinological disease, positive for hepatitis B viral markers, and not fasted for at least 9 hours.

2.2. Study Procedures

2.2.1. Anthropometric and Blood Pressure Measurements and Physical Examinations. Height (cm) was measured to the last complete millimeter, with the subjects barefoot, using a wall-mounted stadiometer. Weight (kg) was measured to 100 g on a calibrated digital electric scale. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). BMI percentile was calculated using Korean Children BMI Chart according to age and gender [17]. Waist circumference was measured by a trained person, to the nearest 0.1 cm at the midpoint between the bottom of the rib cage and the top

of the iliac crest with the subjects standing, their weight equally distributed on both feet, their arms at their sides, and head facing straight forward. Body fat percentage (BF%) was measured by bioelectrical impedance analysis (Inbody 720, Biospace Inc, Seoul, Korea) [18]. Blood pressure (mmHg) was measured in a seated position after relaxation for 5 minutes using an automated oscillometric blood pressure recorder (Dinamap procure 100, GE medical system) [19]. Arm circumference was measured on the appropriate cuff size. Seated blood pressure was taken twice in succession (at 1-minute interval) from both arms, and an additional measurement was performed on the right arm if BP difference was more than 10 mmHg. Their means of the measurements were used in all analyses. Tanner stage was assessed by self-administered questionnaire.

2.2.2. Biochemical Measurements. After midnight fast, blood samples were drawn from an antecubital vein. Hepatitis B surface antigen (HBs Ag) was measured using a commercially available immunoradiometric assay (Riakey, Korea). Total cholesterol, glucose, HDL- (high-density-lipoprotein-) cholesterol, triglycerides, ALT, AST, and GGT were measured (Hitachi 747 automatic analyzer, Hitachi, Japan) and fasting serum insulin by immunoradiometric assay (Biosource, Nivelles, Belgium). Serum C-reactive protein (CRP) was analyzed using immunonephelometry assay (Dade Behring, Marburg, Germany). The homeostasis model for the calculation of an insulin resistance (HOMA-IR) index was used where $\text{HOMA-IR} = \text{fasting glucose (mmol/L)} \times \text{fasting insulin } (\mu\text{U/mL})/22.5$ [20].

2.3. Statistical Analysis. The data are presented as mean \pm standard deviation (SD) or the absolute number (percentages). Differences between boys and girls were assessed using *t*-tests. Correlation analyses were conducted between GGT, ALT, and AST and anthropometric, metabolic, and IR variables, after adjustment for age in boys and girls, separately. The hypothesis that GGT is a significant marker of HOMA-IR was tested using multiple linear regression analysis where HOMA-IR was the dependent variable and serum GGT or ALT, age, tanner stage, BMI, and triglycerides were independent variables. The level of significance for statistical tests was $P < 0.05$. All statistical analyses were performed using STATA version 11.0 (StataCorp LP, College Station, TX, USA).

3. Results

3.1. Baseline Characteristics. The descriptive characteristics for this study subjects are presented for boys and girls separately in Table 1.

The prevalence of obese children (BMI > 95th percentile) is more than 70% (70.2% in boys, 78.8% in girls). There were no gender differences in anthropometric variables except body fat percent. Among the metabolic variables, fasting glucose and insulin, HOMA-IR, and liver enzymes (GGT, ALT, AST) showed gender differences. Fasting glucose levels in boys are higher than those in girls, but fasting insulin

TABLE 1: Basic characteristics of the subjects (total no. = 1308).

	Boys (N = 822)	Girls (N = 486)	P value*
Age (years)	11.9 ± 1.7	12.0 ± 1.8	0.330
BMI (kg/m ²)	26.6 ± 2.9	26.2 ± 3.3	0.072
BMI percentile, no. (%)			0.003
85–89	55 (6.7)	25 (5.1)	
90–94	191 (23.2)	79 (16.3)	
>95	576 (70.1)	382 (78.6)	
BF%	36.4 ± 5.6	38.0 ± 5.3	<0.001
Waist circumference (cm)	88.4 ± 8.3	88.0 ± 8.9	0.436
Systolic blood pressure (mmHg)	116 ± 14	114 ± 13	0.002
Diastolic blood pressure (mmHg)	64 ± 7	65 ± 7	0.090
Fasting glucose (mg/dL)	87.0 ± 6.9	85.4 ± 7.8	<0.001
Fasting insulin (μU/mL)	17.9 ± 11.7	19.9 ± 12.8	0.004
HOMA-IR	3.9 ± 2.7	4.3 ± 2.9	0.025
CRP (mg/dL)	0.2 ± 0.3	0.2 ± 0.4	0.918
Total cholesterol (mg/dL)	176.9 ± 31.5	175.6 ± 29.8	0.479
Triglycerides (mg/dL)	123.8 ± 62.5	128.9 ± 63.4	0.155
HDL-cholesterol (mg/dL)	54.2 ± 12.4	53.0 ± 12.1	0.089
AST (U/L)	34.0 ± 18.1	26.4 ± 10.0	<0.001
ALT (U/L)	47.6 ± 47.5	30.9 ± 20.5	<0.001
GGT (U/L)	28.1 ± 13.8	22.4 ± 8.0	<0.001
Tanner stage, no. (%)			<0.001
1	339 (41.75)	15 (3.13)	
2	196 (24.14)	166 (34.58)	
3	225 (27.71)	199 (41.46)	
4	52 (6.40)	93 (19.38)	
5		7 (1.46)	

Data are presented as mean ± SD except BMI percentile and tanner stage. * by Student's *t*-test.

BMI: body mass index; BF%: body fat percent; CRP: C-reactive protein; HDL: high density lipoprotein; AST: aspartate transaminase; ALT: alanine transaminase; GGT: gamma-glutamyltransferase; HOMA-IR: homeostasis model assessment of insulin resistance.

levels in girls are higher than those in boys. The levels of liver enzymes in boys are higher than in girls. And there was a gender difference in tanner stage: the girls had higher tanner stage than boys ($P < 0.001$).

3.2. Relationship between Insulin Resistance and Liver Enzymes, Metabolic Variables. Tables 2 and 3 showed that serum activities of all three liver enzymes were positively correlated with BMI, waist circumference, and BF% after adjustment for age in boys and girls, respectively.

Serum GGT and ALT, but not AST, were positively correlated with HOMA-IR in boys ($r = 0.222$ for GGT; $P < 0.05$, $r = 0.188$ for ALT; $P < 0.05$) and girls ($r = 0.292$ for GGT; $P < 0.05$, $r = 0.258$ for ALT; $P < 0.05$). Waist and triglycerides was the most correlated factor with HOMA-IR in boys ($r = 0.275$ for waist; $P < 0.05$, $r = 0.275$ for triglycerides; $P < 0.05$). BMI and GGT presented the highest correlation with HOMA-IR in girls ($r = 0.347$ for BMI; $P < 0.05$, $r = 0.292$ for GGT; $P < 0.05$).

All liver enzymes were positively correlated with total cholesterol and triglycerides and negatively correlated with HDL-cholesterol in boys and girls, respectively. In boys, serum GGT, neither AST nor ALT, was positively correlated

with CRP as an inflammation marker. On the other hand, in girls, serum GGT, AST, and ALT were positively correlated with CRP. GGT was correlated with HOMA-IR and CRP more than ALT. In multiple regression analysis for HOMA-IR as dependent variable, GGT ($\beta = 0.068$; $P = 0.053$ in boys, $\beta = 0.145$; $P = 0.002$ in girls) and ALT ($\beta = 0.074$; $P = 0.034$ in boys, $\beta = 0.130$; $P = 0.005$ in girls) emerged as determinants of HOMA-IR after adjusting age, BMI, tanner stage, and triglycerides (Tables 4 and 5).

4. Discussion

In overweight and obese Korean children, we found a significant association serum GGT activity with IR. Although previous adult studies [7] including Korean people have shown similar independent relationships between GGT and insulin resistance, the relationship between GGT and insulin resistance in children has not previously been described except in small population of Pima Indian [21]. A study of 44 Pima Indian children showed GGT, neither AST nor ALT, was a significant determinant of HOMA-IR independently of age, gender, weight, body mass index, or percent body fat [21]. However, The Pima Indians are well-known high

TABLE 2: Partial correlation of serum GGT, ALT, and AST with other variables and anthropometric variables in boys.

	GGT	ALT	AST	HOMA-IR
BMI	0.3143*	0.3266*	0.1846*	0.2642*
Waist circumference	0.2395*	0.3230*	0.1851*	0.2749*
BF%	0.1584*	0.1192*	0.1278*	0.0092
Total cholesterol	0.3391*	0.2818*	0.2892*	0.0823
Triglycerides	0.2691*	0.2426*	0.2229*	0.2746*
HDL-cholesterol	-0.1342*	-0.1635*	-0.1222*	-0.0717
Fasting glucose	-0.0393	-0.0817	-0.1289*	0.4464*
Fasting insulin	0.2437*	0.2183*	0.1088*	0.9879*
HOMA-IR	0.2224*	0.1875*	0.0814	—
CRP	0.1362*	0.0950	0.0783	-0.0390
Systolic blood pressure	0.2167*	0.2189*	0.1281*	0.1578*
Diastolic blood pressure	0.2366*	0.1961*	0.1147*	0.0976*
GGT	—	0.7890*	0.6290*	0.2224*

* P value < 0.05 by Spearman's partial correlation adjusted for age. GGT, ALT, AST, Fasting insulin, HOMA-IR, and CRP were log-transformed.

BMI: body mass index; BF%: body fat percent; CRP: C-reactive protein; HDL: high density lipoprotein; AST: aspartate transaminase; ALT: alanine transaminase; GGT: gamma-glutamyltransferase; HOMA-IR: homeostasis model assessment of insulin resistance.

TABLE 3: Partial correlation of serum GGT, ALT, and AST with other variables and anthropometric variables in girls.

	GGT	ALT	AST	HOMA-IR
BMI	0.3030*	0.3395*	0.1559*	0.3471*
Waist circumference	0.2814*	0.3125*	0.1675*	0.3225*
BF%	0.1920*	0.1957*	0.1251*	0.1378*
Total cholesterol	0.3001*	0.1989*	0.2580*	0.0755
Triglycerides	0.3312*	0.2576*	0.2723*	0.1154*
HDL-cholesterol	-0.1256*	-0.1324*	-0.0664	-0.0345
Fasting glucose	0.1968*	0.1009*	0.0806	0.3393*
Fasting insulin	0.2750*	0.2541*	0.0804	0.9876*
HOMA-IR	0.2915*	0.2577*	0.0893	—
CRP	0.3392*	0.2118*	0.2153*	0.1326*
Systolic blood pressure	0.1870*	0.1954*	0.1062*	0.1563*
Diastolic blood pressure	0.1550*	0.1122*	0.0439	0.1688*
GGT	—	0.7432*	0.6642*	0.2915*

* P value < 0.05 by Spearman's partial correlation adjusted for age. GGT, ALT, AST, Fasting insulin, HOMA-IR, and CRP were log-transformed.

BMI: body mass index; BF%, body fat percent; CRP: C-reactive protein; HDL: high density lipoprotein; AST: aspartate transaminase; ALT: alanine transaminase; GGT: gamma-glutamyltransferase; HOMA-IR: homeostasis model assessment of insulin resistance.

risk population for diabetes mellitus; for example, the Pima Indians of Arizona have the highest reported prevalence of diabetes of any population in the world [22, 23]. Therefore, it may not be generalized to other population with average risk for diabetes. In Korean obese children, both GGT and ALT were significant determinants of HOMA-IR independently of age, tanner stage, and BMI in both genders.

Pubertal development is known to affect insulin status in children, but it was not significant in our obese children [2, 24]. It seems that obesity effect on IR is stronger than pubertal

stage in obese Korean children. Further investigations need to clarify the association between obesity and puberty effect to IR.

The mechanism of the relationship between insulin resistance and GGT has not been clarified. GGT is a cell-surface protein contributing to the extracellular catabolism of glutathione (GSH) [25]. This enzyme is produced in many tissues, but most GGT in serum is derived from the liver [24]. In the serum, GGT is carried primarily with lipoproteins and albumin [26]. Serum levels of GGT are determined by several factors: alcohol intake, body fat content, plasma lipid/lipoproteins, glucose levels, and various medications [25, 27]. Children are better a subject to clarify the role of liver enzyme in IR as they have less alcohol and medication. Increases in GGT activity can be a response to oxidative stress, facilitating increased transport of GSH precursors into cells. In addition, GGT is leaked into the serum possibly as a result of normal cell turnover and cellular stresses [15]. Lee and Jacobs Jr. [28] reported that in the general American population, the serum level of GGT, rather than that of ALT, was more closely associated with the plasma level of CRP, and they speculated that increased oxidative stress related to elevated serum GGT might contribute to this relationship. Our study results showed that serum GGT activity was positively correlated with CRP as an inflammation marker in children. The etiological role of the liver in later development of type 2 diabetes is debatable. Animal models support a role of hepatic insulin resistance leading to severe glucose intolerance [29, 30]. Furthermore, NAFLD, an emerging obesity-related liver disease in children, is a condition associated with elevated concentrations of serum GGT [31]. Insulin resistance is the main pathogenic factor in the etiology of NAFLD in adults [32] and in children [33]. In another Korean adult study [34], serum GGT was closely related with IR and might be more associated with dyslipidemia and abnormal glucose tolerance regardless of the presence of NAFLD, suggesting that increased serum GGT might reflect more the hepatic insulin resistance. The Mexico City Diabetes Study [10], found raised GGT to be associated with the features of metabolic syndrome and to be an independent predictor of diabetes and concluded that this association may reflect both hepatic steatosis and enhanced oxidative stress.

In our results, obesity and triglycerides were the major determinants of HOMA-IR in boys. These results are compatible with the result of Sinaiko et al., which showed heavy-insulin resistant adolescents had the highest triglycerides level [35].

Obesity and GGT were the major determinants of HOMA-IR in girls. The effect of triglycerides and GGT on IR was different by gender. Steinberger et al. originally reported that the degree of IR, as measured by the hyperinsulinemic euglycemic clamp, explained a significant portion of the variance in the levels of triglycerides, LDL cholesterol, and HDL-cholesterol in obese adolescents [36]. The gender difference of the association of GGT, TG, and IR was first described in our study in children population, as far as we know. The mechanism of gender difference also needs to further investigated.

TABLE 4: Multiple linear regression analysis in boys.

Dependent variable (log HOMA-IR)	Independent variables	B	SE	β	P value
$R^2 = 0.128$ $R^2_{\text{adjusted}} = 0.122$	Age	-0.021	0.016	-0.067	0.186
	Tanner stage	0.015	0.026	0.028	0.566
	BMI	0.045	0.007	0.253	<0.001
	GGT	0.003	0.001	0.068	0.053
	Triglycerides	0.002	0.0003	0.188	<0.001
$R^2 = 0.128$ $R^2_{\text{adjusted}} = 0.123$	Age	-0.019	0.016	-0.061	0.229
	Tanner stage	0.016	0.026	0.030	0.539
	BMI	0.045	0.007	0.249	<0.001
	ALT	0.001	0.0004	0.074	0.034
	Triglycerides	0.002	0.0003	0.191	<0.001

Dependent variables is log-transformed HOMA-IR.

ALT: alanine transaminase; GGT: gamma-glutamyltransferase; HOMA-IR: homeostasis model assessment of insulin resistance.

TABLE 5: Multiple linear regression analysis in girls.

Dependent variable (log HOMA-IR)	Independent variables	B	SE	β	P value
$R^2 = 0.172$ $R^2_{\text{adjusted}} = 0.163$	Age	-0.067	0.019	-0.210	0.001
	Tanner stage	0.020	0.040	0.029	0.612
	BMI	0.067	0.009	0.381	<0.001
	GGT	0.011	0.003	0.145	0.002
	Triglycerides	0.001	0.0004	0.075	0.090
$R^2 = 0.168$ $R^2_{\text{adjusted}} = 0.159$	Age	-0.062	0.020	-0.195	0.002
	Tanner stage	0.019	0.040	0.027	0.641
	BMI	0.067	0.009	0.378	<0.001
	ALT	0.004	0.001	0.130	0.005
	Triglycerides	0.001	0.0004	0.088	0.044

Dependent variables is log-transformed HOMA-IR.

ALT: alanine transaminase; GGT: gamma-glutamyltransferase; HOMA-IR: homeostasis model assessment of insulin resistance.

The present study has some limitations. The current findings must be interpreted with caution because of the cross-sectional study design. And our subjects are overweight/obese children, certainly not representative of the general children population. We used HOMA-IR as an index of insulin resistance, instead of euglycemic hyperinsulinemic clamp. However, HOMA-IR is more practical and less invasive than the euglycemic clamp and used in many studies in children HOMA-IR as well as indices derived from the oral glucose tolerance test were well correlated with insulin sensitivity measured by the euglycemic hyperinsulinemic clamp technique.

In summary, in overweight and obese Korean children at high risk for the development of type 2 diabetes, serum GGT activity showed a significant relationship with insulin resistance using HOMA-IR. Further investigation of the mechanisms underlying these associations in children is warranted through a prospective study.

Conflict of Interests

All authors have no conflict of interests to declare.

Acknowledgments

This study was supported by the Samsung Medical Research Institute Grant, no. SBRI C-A6-312-1 and the Grant from Inje University 2008.

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