The predictability of serum gamma-glutamyltransferase levels on future development of metabolic syndrome defined by two different criteria in Korean men

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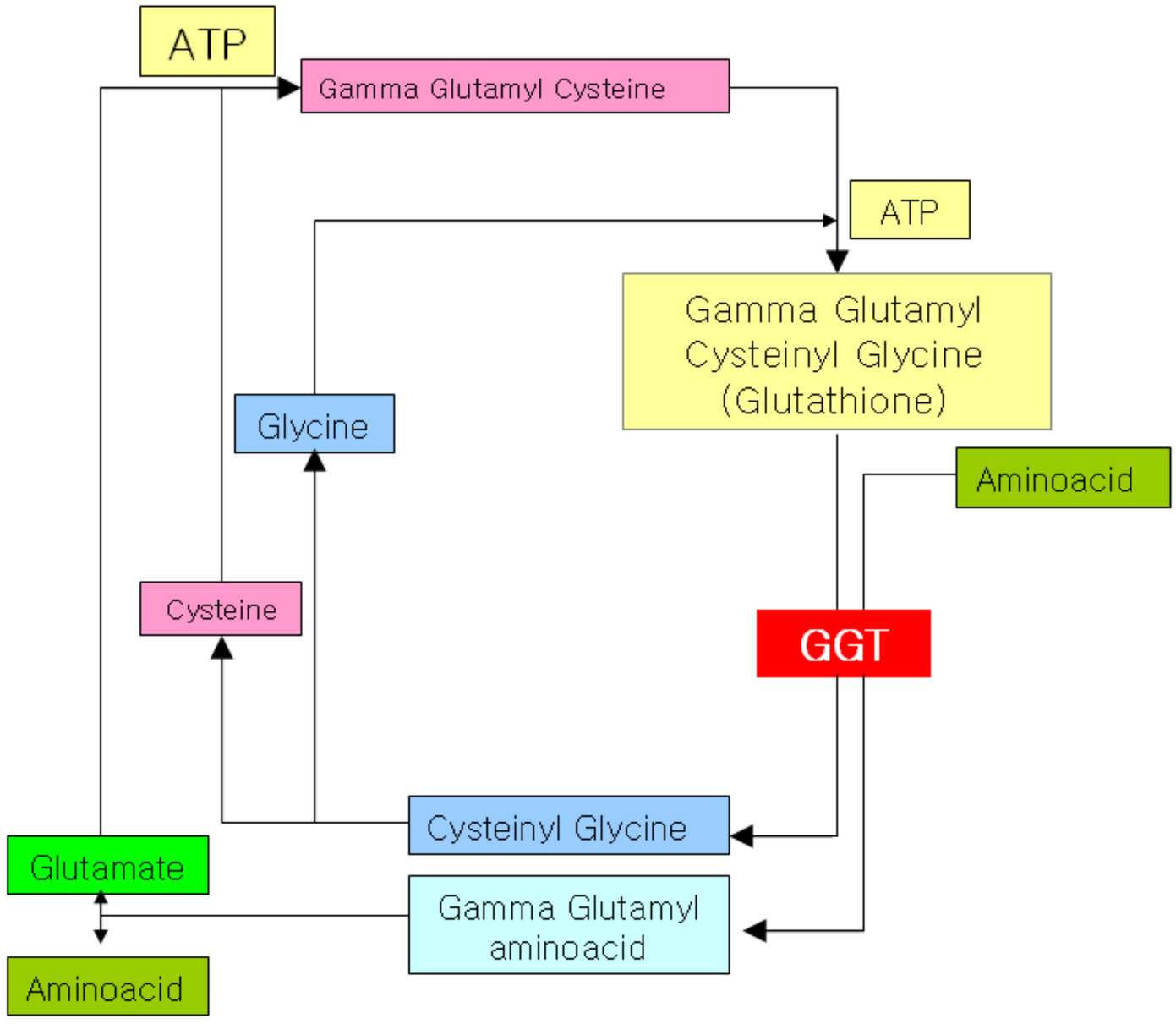
Background

- γ-glutamyltransferase (GGT) has been regarded as a biomarker of hepatobiliary disease and alcohol consumption/abuse *(Whitfield JB, Crit Rev Clin Lab Sci, 2001)*
- GGT is the enzyme responsible for the extracellular catabolism of glutathione (GSH, γ-glutamyl-cysteinyl-glycine), the main thiol intracellular antioxidant agent in mammalian cells *(Whitfield JB. Crit Rev Clin Lab, 2001)*

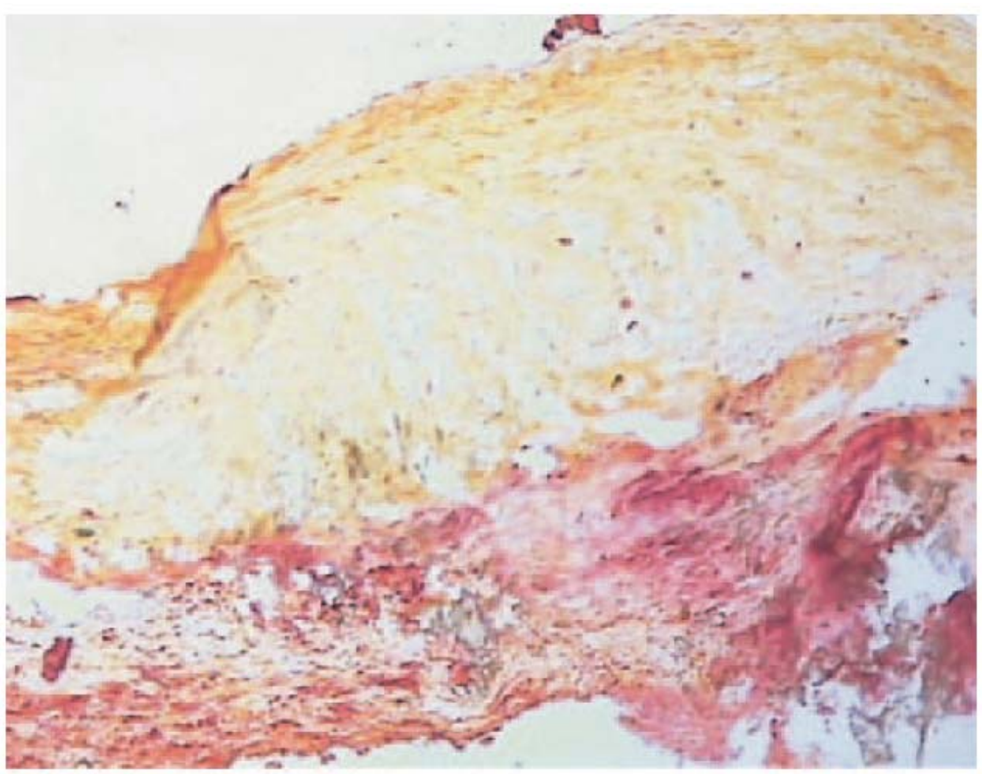
Reactions involved in the breakdown and synthesis of glutathione

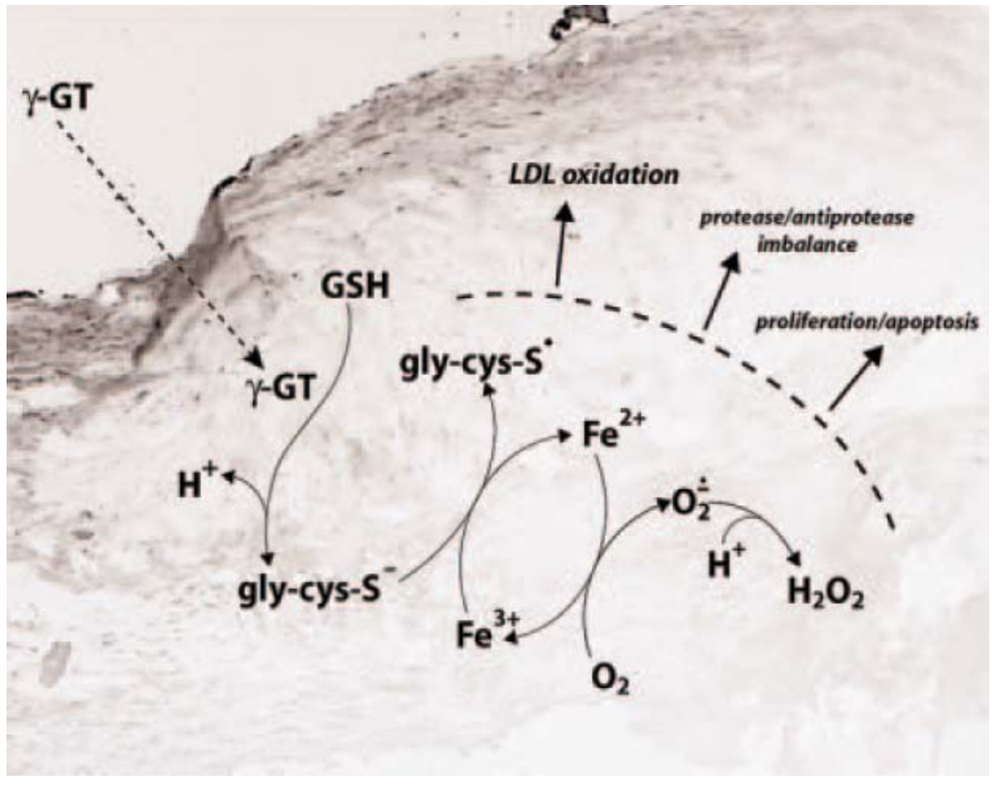


Whitfield JB. Crit Rev Clin Lab Sci 38:263-355, 2001

GGT and Atherosclerosis

- Catalytically active GGT has been found within atherosclerotic plaques from cerebral, carotid, and coronary autopsy specimens, colocalized with oxidized LDL
- The previous study results of the association of GGT to lipoproteins suggest that LDL lipoproteins can carry GGT activity inside the plaques





Paolicchi et al., Circulation 109:1440, 2004,
Emedin et al., Circulation 112:2078-2080, 2005

GGT and Insulin Resistance, cardiovascular disease

- Decreased insulin sensitivity is associated with nonalcoholic fatty liver disease (NAFLD)*(J Obes Relat Metab Disord, 2004).*
- Serum activities of hepatic enzymes (ALT, AST, GGT) have been associated with obesity and insulin resistance, and hepatic insulin resistance is one of the primary pathologic mechanisms of T2DM *(Nat Clin Pract Endocrinol Metab, 2006).*
- Serum GGT is closely related with the presence of metabolic syndrome, and the presence of diabetes *(DRCP, 2007, Diabetic Medicine, 2006).*
- In individuals with a history of ischemic heart disease, elevated GGT was associated with a significant increase in mortality from all causes and from IHD *(Am J Epidemiol, 1995).*
- In 469 pts with MI Hx, increased GGT level was a significant risk factor for increased cardiac mortality with the cutoff of 40 IU/L *(Eur Heart J, 2001)*
- In a cohort study performed in 163,944 Austrian adults with a follow-up period of 17 years, ROC analysis suggested predictive cutoff values of 15.5 U/L of GGT levels for men and 10.5 U/L for women, for future cardiovascular events within normal values *(Circulation, 2005)*

Aim of the study

- We studied the association of GGT and ALT with the development of the metabolic syndrome (MetS), according to newly recommended criteria from International Diabetes Federation (IDF) and National Cholesterol Education Program-Adult Treatment Panel (NCEP-ATP) III definition

Methods

- A total of 15,250 males (mean age 38 years, aged 19-86 years), who visited the Health Promotion Center at Kangbuk Samsung Hospital for medical check up in 2002, were followed-up for 4 years
- Subjects with diabetes by self-report or by fasting glucose higher than or same with 126 mg/dL in the year 2002, were included in the analysis to avoid other biases from the exclusion.
- Waist circumference, height and weight were measured and BMI was calculated from dividing the weight (kg) with height (m) squared.
- In all subjects, systolic and diastolic BP were measured and after 12 hours of fasting, glucose, insulin, lipid profiles were measured
- Serum GGT levels were measured by modified Szasz method using an ADVIA 1650 auto-analyzer (Bayer, Tarrytown, USA).
- Serum AST and ALT levels were measured using IFCC recommended UV methods on a Cobas Integra® 800 (Roche. Diagnostics, Basel, Switzerland) and ADVIA 1650 auto-analyzer (Bayer, Tarrytown, USA).

The Definition of Metabolic syndrome

•The presence of metabolic syndrome was assessed from 2 diagnostic criteria

- **AHA/NHLBI criteria**

① WC≥90 cm

② Fasting glucose≥100 mg/dL or the presence of DM Hx

③ Serum triglyceride ≥150 mg/dL

④ Serum HDL-C < 40 mg/dL

⑤ Blood pressure ≥130/85 mmHg or antihypertensive medication

- **IDF criteria**

Abdominal obesity
: WC ≥90 cm
plus any two of the followings

① Fasting glucose≥100 mg/dL or the presence of DM Hx

② Serum triglyceride ≥150 mg/dL

③ Serum HDL-C < 40 mg/dL

④ Blood pressure ≥130/85 mmHg or antihypertensive medication

Table 1. General characteristics of the participants

	mean±SD
Age(years)	37.7±6.50
Body weight(kg)	70.9±9.11
BMI(kg/m^2)	24.0±2.81
Waist circumference (cm)	82.4±6.40
Systolic blood pressure (mmHg)	115.9±13.0
Diastolic blood pressure (mmHg)	75.7±10.4
Fasting glucose (mg/dL)	92.7±15.5
Total bilirubin (mg/dL)	1.14±0.5
AST (IU/L)	26.7±15.1
ALT (IU/L)	33.2±27.1
GGT (IU/L)	36.4±31.4
Total cholesterol (mg/dL)	204.0±35.0
Triglyceride (mg/dL)	152.1±88.8
HDL-cholesterol (mg/dL)	52.3±11.6
LDL-cholesterol (mg/dL)	120.9±29.5
Fasting insulin (μIU/mL)	7.77±2.90
HOMA-IR	1.79±0.79
Drinker (%)	821 (5.4)
Smoker (%)	1782 (11.7)
Diabetes mellitus in 2002 (%)	321 (2.1)

Table 2. Odds ratios of 4-year incident metabolic syndrome according to quartiles of baseline γ-Glutamyl Transferase Activity (GGT) and Alanine AminoTransferase (ALT) levels, after adjustment for baseline confounding factors

	Q1	Q2	Q3	Q5	*P* for trend
GGT quartiles (IU/l)	<19.0	19.0~26.0	26.0~38.0	>38.0	
IDF (n=656)					
Cases/individuals at risk	48/3360	112/4153	191/3909	305/3826	
Model 1	1	1.83 (1.30-2.58)	3.36 (2.43-4.63)	5.54 (4.07-7.56)	〈0.001
Model 2	1	2.05 (1.27-3.32)	3.36 (2.07-5.22)	5.40 (3.41-8.53)	〈0.001
Model 3	1	2.02 (1.21-3.37)	2.97 (1.81-4.87)	4.60 (2.81-7.53)	〈0.001
Model 4	1	2.05 (1.23-3.42)	3.05 (1.86-5.00)	4.56 (2.76-7.48)	〈0.001
AHA/NHLBI (n=183)					
Cases/individuals at risk	12/3348	24/4129	42/3867	105/3721	
Model 1	1	1.54 (0.77-3.09)	2.84 (1.49-5.41)	7.22 (3.96-13.2)	〈0.001
Model 2	1	1.13 (0.49-2.60)	1.76 (0.81-3.83)	4.16 (2.01-8.62)	〈0.001
Model 3	1	1.01 (0.42-2.45)	1.67 (0.74-3.77)	3.55 (1.63-7.73)	〈0.001
Model 4	1	1.04 (0.43-2.52)	1.74 (0.77-3.92)	3.63 (1.67-7.90)	〈0.001

Model 1: adjusted for age
Model 2: adjusted for age, alcohol intake, physical activity, smoking status and ALT
Model 3: adjusted for age, alcohol intake, physical activity, smoking status, ALT, and fasting insulin
Model 4: adjusted for age, alcohol intake, physical activity, smoking status, ALT, and HOMA-IR

Table 2. Odds ratios of 4-year incident metabolic syndrome according to quartiles of baseline γ-Glutamyl Transferase Activity (GGT) and Alanine AminoTransferase (ALT) levels, after adjustment for baseline confounding factors (continued)

	Q1	Q2	Q3	Q5	*P* for trend
ALT quartiles (IU/l)	<18.0	18.0~27.0	27.0~43.0	>43.0	
IDF (n=656)					
Cases/individuals at risk	57/3403	134/3920	202/3984	263/3942	
OR adjusted for age	1	1.96 (1.43-2.69)	3.16 (2.34-4.27)	4.74 (3.53-6.36)	〈0.001
OR adjusted for age and GGT	1	1.88 (1.37-2.58)	2.79 (2.06-3.78)	3.65 (2.68-4.97)	〈0.001
AHA/NHLBI (n=183)					
Cases/individuals at risk	11/3392	33/3887	48/3936	91/3851	
OR adjusted for age	1	2.44 (1.23-4.85)	3.75 (1.94-7.25)	8.19 (4.36-15.4)	〈0.001
OR adjusted for age and GGT	1	2.33 (1.17-4.63)	3.26 (1.68-6.33)	6.16 (3.22-11.8)	〈0.001

Table 3. Age-adjusted odds ratios for the 4-year incidence of each individual MetS components according to quartiles of baseline γ-Glutamyl Transferase Activity (GGT)

	Q1	Q2	Q3	Q4	P for trend
GGT quartiles (IU/l)	<19.0	19.0~26.0	26.0~38.0	>38.0	
Abdominal obesity					
Cases/individuals at risk	111/925	217/1196	274/1083	276/941	
Odds ratio	1	1.62 (1.26-2.07)	2.46 (1.94-3.14)	3.00 (2.35-3.83)	〈0.001
Low HDL-C					
Cases/individuals at risk	155/3047	248/3731	228/3418	241/3381	
Odds ratio	1	1.36 (1.10-1.67)	1.38 (1.12-1.70)	1.51 (1.23-1.86)	〈0.001
High triglycerides					
Cases/individuals at risk	346/2819	528/2933	508/2081	426/1448	
Odds ratio	1	1.61 (1.39-1.86)	2.41 (2.07-2.80)	3.20 (2.72-3.76)	〈0.001
High blood pressure					
Cases/individuals at risk	243/2828	358/3302	425/2940	513/2589	
Odds ratio	1	1.26 (1.06-1.49)	1.71 (1.44-2.02)	2.44 (2.07-2.88)	〈0.001
High fasting glucose					
Cases individuals at risk	338/3015	535/3560	559/3163	599/2665	
Odds ratio	1	1.38 (1.19-1.56)	1.65 (1.42-1.91)	2.19 (1.90-2.54)	〈0.001

Table 4. Optimal cut-off points of risk factors defined by maximizing sensitivity and specificity to predict future metabolic syndrome defined by two different criteria and their area under the curve (AUC)s

	GGT (IU/L)	ALT (IU/L)	BMI (kg/m^2)	WC (cm)	SBP (mmHg)	DBP (mmHg)	Fasting glucose (mg/dL)	TG (mg/dL)	HDL-C (mg/dL)	HOMA-IR
IDF definition										
Cut-off point	31.5	29.5	25.3	85.5	115.0	76.0	92.5	150.5	49.1	1.935
Sensitivity (%)	63.1	61.1	70.7	71.4	61.3	70.1	57.6	63.4	43.4	65.2
Specificity (%)	67.0	60.1	70.5	71.2	53.6	49.5	57.3	62.5	43.3	64.0
AUC (%)	67.7	63.4	76.4	77.5	61.0	62.3	60.5	69.3	42.4	69.2
95% CI	65.7-69.7	61.3-65.4	74.9-78.0	75.6-79.4	58.8-63.2	60.1-64.4	58.3-62.7	67.4-71.2	40.2-44.6	67.0-71.4
AHA/NHLBI criteria										
Cut-off point	34.5	30.5	25.3	85.5	115.0	72.5-78.5	94.5	155.5	48.0	2.035
Sensitivity (%)	66.7	64.5	71.0	71.9	67.2	72.7	61.2	64.5	41.5	67.1
Specificity (%)	65.4	62.0	70.1	68.7	53.2	48.9	65.4	64.0	37.5	67.8
AUC (%)	71.8	67.9	77.8	76.6	63.6	65.0	67.6	72.7	35.4	74.4
95% CI	68.2-75.5	64.2-71.5	75.1-80.4	73.3-80.0	59.8-67.4	61.1-69.0	63.5-71.6	69.6-75.8	31.4-39.3	70.6-78.1

Summary

- Future risk for MetS defined by the two criteria increased as the baseline serum GGT quartiles increased even after adjustment for confounding factors.
- Serum ALT level also showed significantly positive correlation with development of MetS even after adjustment for age and GGT in both groups
- Risk for the individual MetS components increased as the baseline GGT levels increased.
- In receiver operating characteristic (ROC) curves, the area under the curves (AUC) for cutoffs of GGT and ALT to predict future MetS by both criteria, were larger than the AUCs of blood pressure, fasting glucose and high-density lipoprotein cholesterol.

Conclusion

- In this large prospective study in Korean men, high baseline GGT and ALT levels predicted future development of MetS defined by IDF and AHA/NHLBI criteria in 4 years of follow-up.