

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

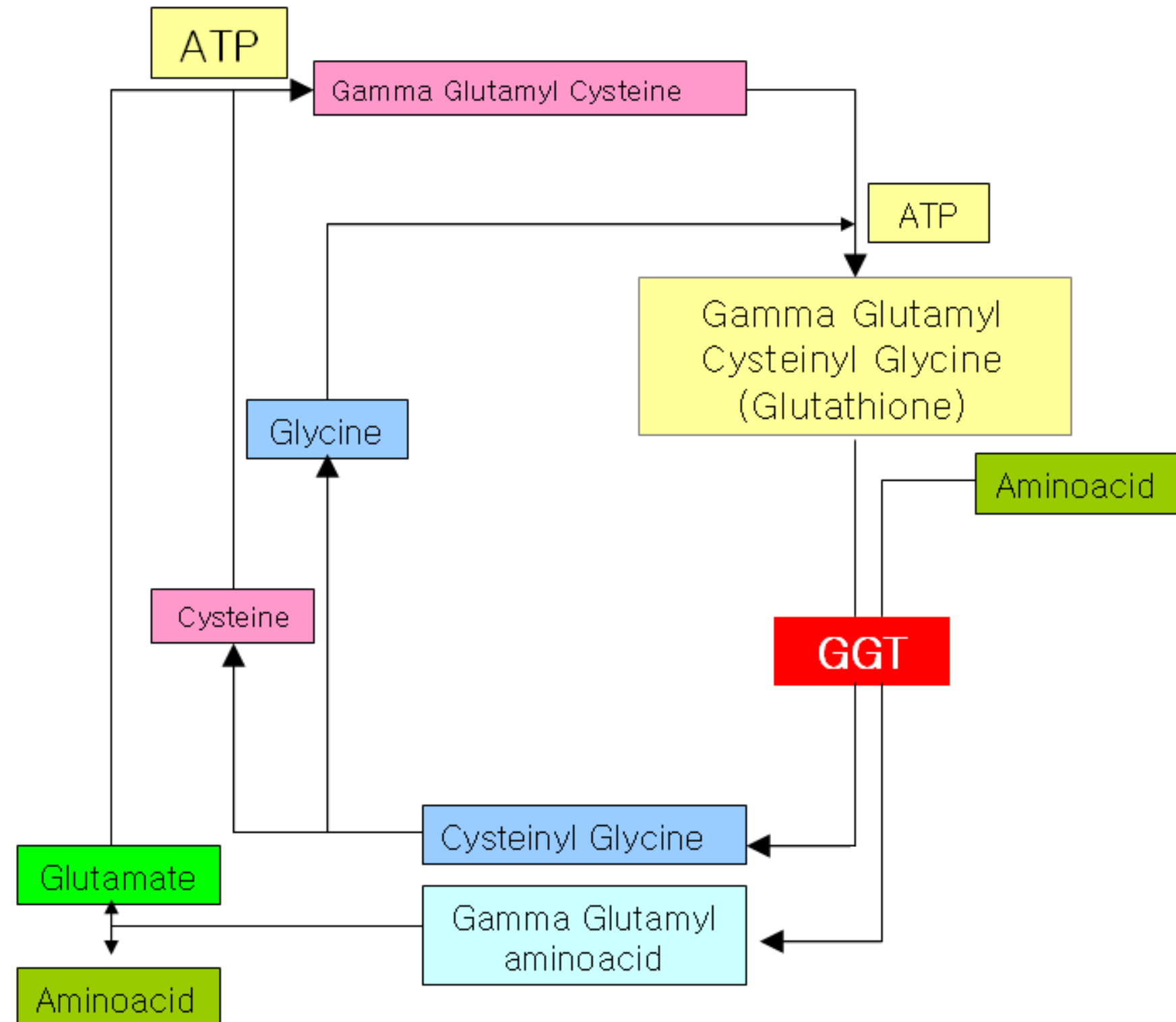
Eun Jung Rhee, Won Young Lee, Jong Chul Won, Cheol Young Park, Ki Won Oh, Sung-Woo Park, Sun Woo Kim

Department of Endocrinology and Metabolism,
Kangbuk Samsung Hospital, Sungkyunkwan
University School of Medicine

Background

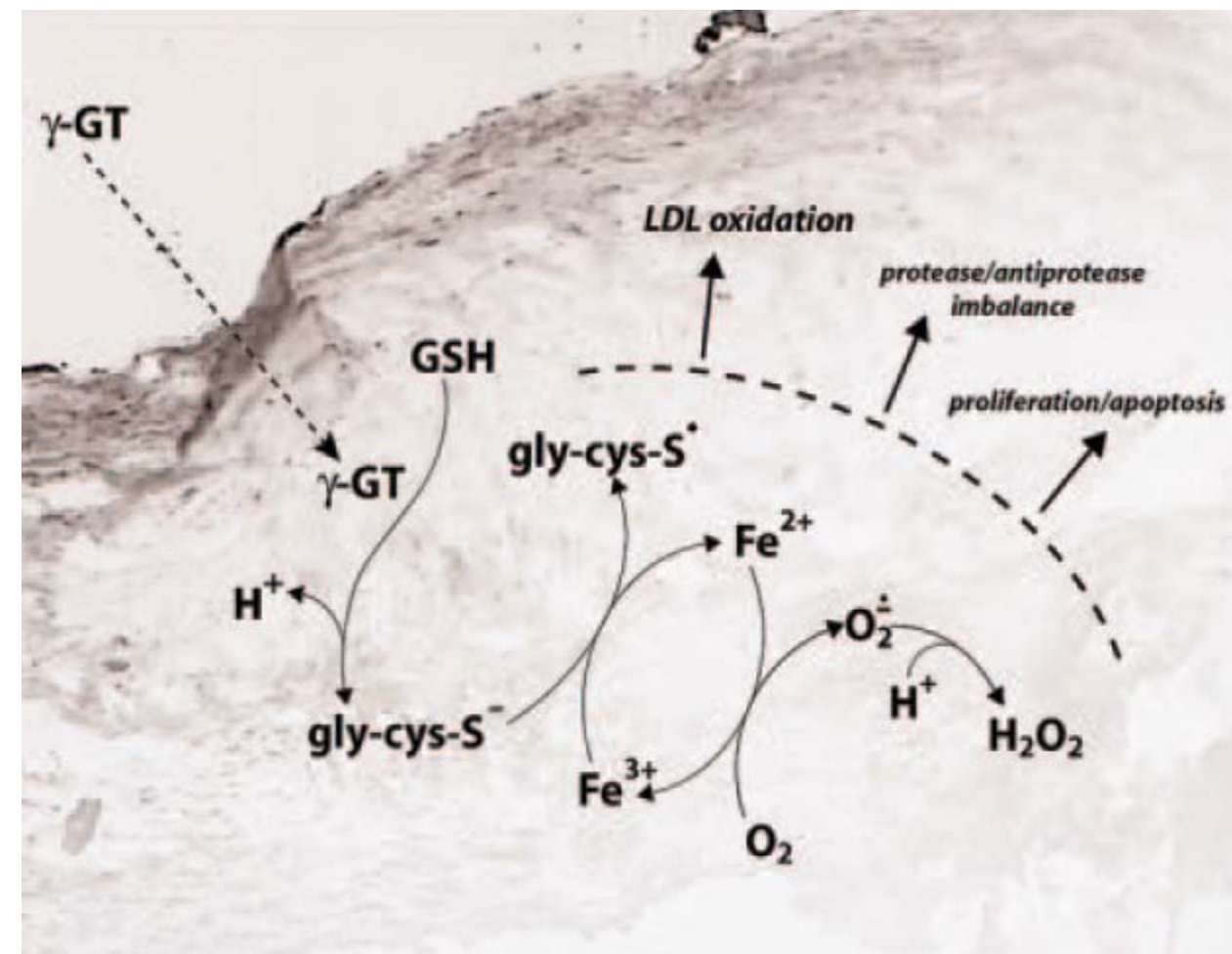
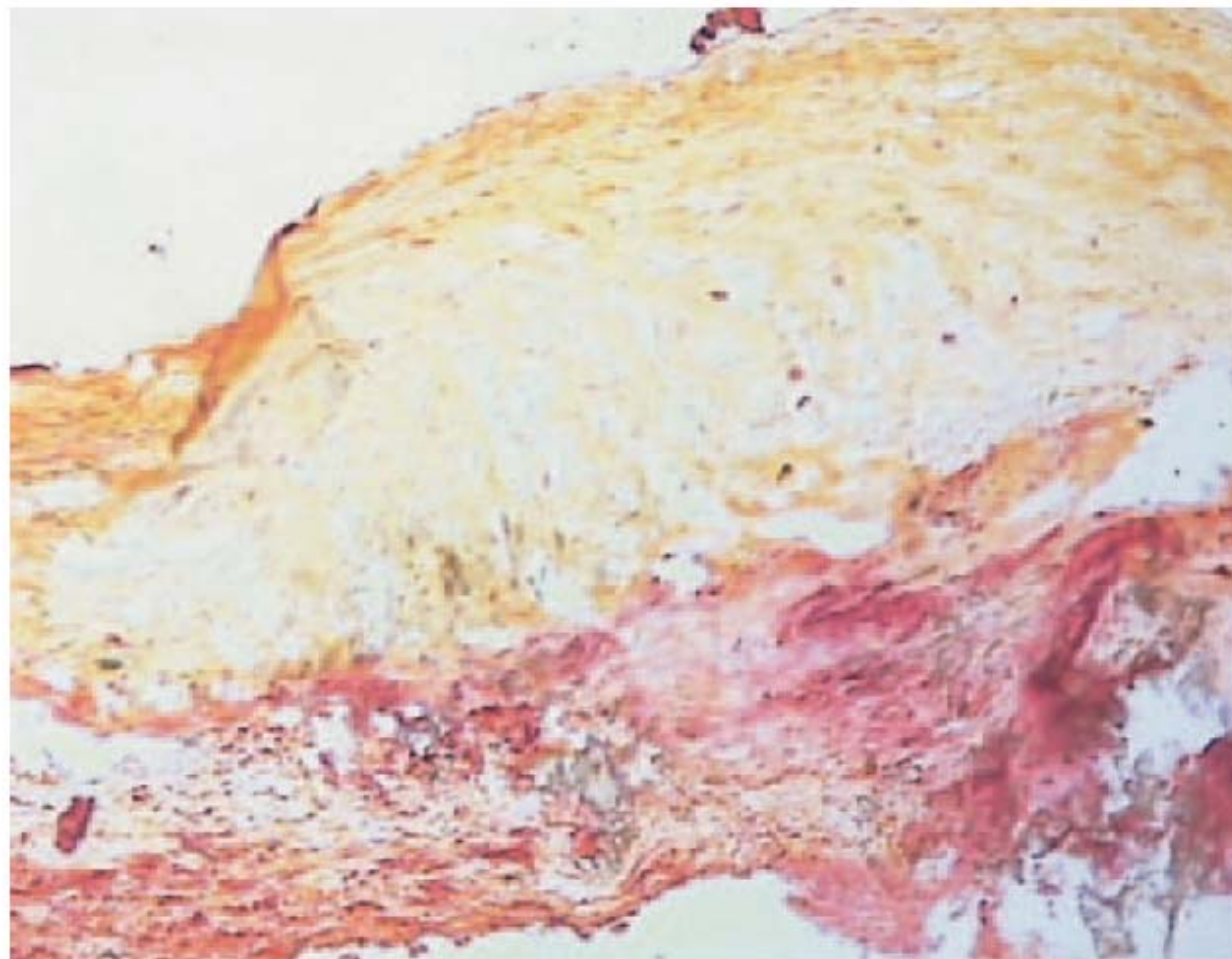
- γ -glutamyltransferase (GGT) has been regarded as a biomarker of hepatobiliary disease and alcohol consumption/abuse (*Whitfield JB, Crit Rev Clin Lab Sci, 2001*)
- GGT is the enzyme responsible for the extracellular catabolism of glutathione (GSH, γ -glutamyl-cysteinyl-glycine), the main thiol intracellular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

Reactions involved in the breakdown and synthesis of glutathione



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 \geq 90 cm
- ② Fasting glucose \geq 100 mg/dL or the presence of DM Hx
- ③ Serum triglyceride \geq 150 mg/dL
- ④ Serum HDL-C $<$ 40 mg/dL
- ⑤ Blood pressure \geq 130/85 mmHg or antihypertensive medication

- **IDF criteria**

- Abdominal obesity
: WC \geq 90 cm
plus any two of the followings
- ① Fasting glucose \geq 100 mg/dL or the presence of DM Hx
 - ② Serum triglyceride \geq 150 mg/dL
 - ③ Serum HDL-C $<$ 40 mg/dL
 - ④ Blood pressure \geq 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 Amino Transferase (ALT) levels, after adjustment for baseline confounding factors

| | Q1 | Q2 | Q3 | Q5 | <i>P</i> 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 Amino Transferase (ALT) levels, after adjustment for baseline confounding factors (continued)

| | Q1 | Q2 | Q3 | Q5 | <i>P</i> 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.**