SERUM GAMMA GLUTAMYLTRANSFERASE, A MARKER OF METABOLIC SYNDROME AND CORONARY DISEASE LIKELIHOOD

Altan Onat\textsuperscript{1,2}, Gülay Hergenç\textsuperscript{3}, \textsuperscript{1,2}Turkish Society of Cardiology, \textsuperscript{2}Cerrahpasa Medical Faculty, Istanbul University, Biology Department, \textsuperscript{3}Yildiz Technical University, Istanbul, Turkey

Gamma glutamyltransferase (GGT), present on the surface of most cells and in serum, mediates cellular glutathione uptake which is an important element of intracellular protective antioxidant mechanisms, but at the same time is also regarded as a “pro-oxidant” \cite{1}. Serum GGT is partly adsorbed on LDL particles by which it may be delivered into the plaques \cite{2}. Elevation in serum GGT activity can predict morbidity and mortality independent of alcohol intake or liver disease. Modest increases within normal range may be an early marker of cellular oxidative stress \cite{3} and explain the strong associations of serum GGT with many cardiovascular risk factors and disease. Hypertension, incident diabetes, all-cause mortality, and coronary heart disease (CHD) mortality were shown to be predicted by elevated GGT activity independent of alcohol intake or liver disease. Metabolic syndrome (MS) was also found to be associated with increased GGT activity in both genders cross-sectionally \cite{4} and in a prospective study in men \cite{5}.

In the cohort of the Turkish Adult Risk Factor Study, a prospective survey on the prevalence of cardiac disease and risk factors in a representative sample of adults in Turkey carried out periodically since 1990 throughout all geographical regions of the country \cite{6}, serum GGT concentrations were determined among 1,881 participants, aged ≥33 years in the course of the 2003/2004 screening. After exclusions (17\%) were made for frequent alcohol consumption, hormone replacement therapy, use of lipid lowering drugs, diabetes, recent myocardial infarction, known hepatic disease, individuals with GGT values over 100 U/L, 1,556 non-diabetic persons (754 men and 802 women) remained for analysis \cite{7}.

Metabolic syndrome was identified according to the criteria of National Cholesterol Education Program (ATP III), modified for pre-diabetes, abdominal obesity (cutpoints of ≥95 cm in men and ≥91 cm women), and HDL-cholesterol (in women < 45 mg/dl). Diabetes was diagnosed with the criteria of the American Diabetes Association. Drinking alcohol once a month to 4 times per week was considered as moderate user.

Our Findings

The non-diabetic sample population (mean age 52 ± 10.7 years) tended to central obesity (mean waist circumference 94 cm), and to metabolic syndrome (prevalence 34\%) in both sexes. Nineteen newly developed nonfatal and fatal CHD were identified during a brief follow-up which, along with those having CHD at baseline, resulted in a total of 135 participants with CHD.

Median (and interquartile range) GGT values were 24.4 (17-34.3) U/L in men and 17.0 (12.1-24) U/L in women \cite{7}. Sex-specific GGT tertiles were formed with cutoff points of 19.1 and 30.2 U/L in men, and 13.1 and 21.0 U/L in women. The mean GGT gradient across the upper and lower tertiles was 3.2-fold in men and women. GGT values were significantly correlated with age, positively in women, and inversely in men, declining past the fifth decade. Highest correlations for GGT concentrations were with fasting insulin, complement C3 and waist
circumference. Correlations with MS, C-reactive protein (CRP), triglycerides, total cholesterol, body mass index (BMI) and, in men, with uric acid were of intermediate strength. Multivariate analysis revealed waist circumference to be the main determinant of GGT activity among a set of biologic and lifestyle variables. Complement C3 and uric acid, also linked to abdominal obesity, were weaker independent determinants of GGT activity (Table 1). Genes affecting release of GGT from the hepatocyte surface have been reported in adult pairs in the Australian Twin Registry [8].

**Likelihod of GGT for Metabolic Syndrome**

Sex- and age-adjusted odds ratio (OR) of GGT for MS in a logistic regression analysis among 1,537 adults, adjusted also for smoking status, moderate alcohol usage, total cholesterol, and uric acid proved to be 2.43. This meant a doubling of serum GGT activity was associated with a rise by 74% in the likelihood of MS, independent of confounding variables. The association attenuated with the introduction of waist circumference to the model, but a residual association persisted in women: OR 1.51, p = 0.077 (in men 1.30, p = 0.12). This indicated a link of GGT to MS in part independent of waist circumference.

**GGT and Coronary Disease Likelihood**

Compared to the referent lower GGT tertile, the top tertile disclosed a significant 1.81-fold likelihood for CHD in men and women combined, independent of age, sex, waist circumference, moderate alcohol usage, smoking status, systolic blood pressure, total cholesterol, and impaired fasting glucose. An even stronger OR (2.03, p = 0.047) was noted in men. Thus a doubling of GGT activity represented an adjusted 1.45-fold increment in CHD likelihood in the entire group [5].

A significant 45% of excess CHD likelihood was elicited in this sample of a general population for a doubling of serum GGT, after adjustment for covariates including age, waist circumference, and 3 major risk factors. The magnitude of the excess likelihood is congruent with a hazard ratio ~ 1.5 of multi-adjusted serum GGT for CHD risk found in two large prospective cohort studies, namely, on over 28,000 Finnish men and women [9] and the KORA study in which GGT activity was a predictor of acute coronary events in men (women not investigated) from the general population [10]. Similar to the Finnish study, we provided evidence that increasing CHD likelihood associated with increasing serum GGT activity is not confined to patients with a prior myocardial infarction or to association with acute coronary events.

After adjusting for age, BMI, and other confounders, Nakanishi et al. [5] found prospectively an excess relative risk of MS in men, which corresponded to ~ 24% with doubling of GGT concentrations. After similar adjustments in hypertensive Finnish adults, GGT activity was an independent determinant of MS, albeit in a cross-sectional analysis [4]. Our adjusted finding of a high (74%) excess MS likelihood for a doubling of serum GGT activity, though partly mediated through abdominal obesity, is of interest.

In the present study, the association of raised GGT levels with MS in men is exclusively mediated by insulin resistance and central obesity, and is likely due to hepatic steatosis concomitant to hepatic insulin resistance. Insulin resistance was indeed found a determinant of raised serum GGT in obese subjects, and was also independently determined by serum GGT
levels among patients with hepatic steatosis of varied etiology. Among Turkish women in whom insulin resistance plays a more limited role in MS than men, and a tendency to a residual MS likelihood persisted after adjustment for waist girth, a component independent of liver steatosis, namely enhanced oxidative stress, may be operative. This is consistent with the findings in Japanese women [11] or in Korean adults in whom MS seemed to be directly (not via a fatty liver) associated with raised GGT levels. The association of raised GGT levels with CHD likelihood in this study being independent of and additive to central obesity, and by inference of a fatty liver, may be accounted for by enhanced oxidative stress inducing vicious cycles leading to inflammation. This parallels the Mexico City Diabetes study [2] which found raised GGT associated with the features of MS and an independent predictor of diabetes, and concluded that this association may reflect both hepatic steatosis and enhanced oxidative stress.

We conclude that moderately elevated serum GGT activity is likely reflects hepatic steatosis due to insulin resistance, as well as enhanced oxidative stress, hence, is both a marker of MS and may contribute actively to athero-thrombogenesis.

References

Table 1. Determinants of GGT* by multiple linear regression (n = 1068)

<table>
<thead>
<tr>
<th></th>
<th>Coeff. $\beta$</th>
<th>$P &lt;$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference (cm)</td>
<td>1.008</td>
<td>0.001</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>1.002</td>
<td>0.001</td>
</tr>
<tr>
<td>Complement C3 (g/L)</td>
<td>1.227</td>
<td>0.003</td>
</tr>
<tr>
<td>Moderate alcohol intake (y/n)</td>
<td>1.107</td>
<td>0.04</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>0.991</td>
<td>0.032</td>
</tr>
<tr>
<td>Gender, F/M</td>
<td>0.733</td>
<td>0.001</td>
</tr>
</tbody>
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Model comprised also age, systolic BP, HDL-C, impaired fasting glucose, body mass index, smoking status and physical activity grade as nonsignificant variables

* log-transformed