Correspondence

Letter Regarding Article by Ruttmann et al, "γ-Glutamyltransferase as a Risk Factor for Cardiovascular Disease Mortality: An Epidemiological Investigation in a Cohort of 163 944 Austrian Adults"

To the Editor:

In their article, Ruttmann et al[1] showed that γ-glutamyltransferase (GGT) was independently associated with cardiovascular (CV) mortality. GGT was significantly correlated with components of the metabolic syndrome,[2] including uric acid level, but waist circumference was not measured. Measurement of GGT activity is a very commonly used diagnostic test for liver dysfunction, and it increases with alcohol consumption and steatosis. Elevation of hepatic enzyme activities occurs frequently in patients with multiple CV risk factors. Indeed, we have shown that approximately one fourth of a population of 8501 dyslipidemic patients[3] displayed hepatic enzymatic elevations. We found correlation coefficients similar to those reported by Ruttmann et al[1] when GGT, aspartate aminotransferase, or alanine aminotransferase was selected. In subgroup analysis, the relation between waist circumference, body mass index (BMI), and GGT (n=1911) was assessed, and it revealed that the relation between GGT and waist circumference (r=0.34) was stronger than the relation between waist circumference and BMI (r=0.26) in the whole group and in men and women separately. When adjusted by accounting for waist circumference, the partial correlation coefficient of BMI with GGT was no longer significant (adjusted r=0.01). Thus, regional body fat distribution as assessed by waist circumference may represent an independent risk factor for several conditions, especially for metabolic and CV diseases involving abdominal visceral fat accumulation associated with hepatic steatosis.[4] Mild elevations of liver enzymes (GGT, aspartate aminotransferase, alanine aminotransferase) are typically associated with features of the metabolic syndrome. However, the absence of measurements of waist circumference in the Vorarlberg Health Monitoring and Promotion Program population could explain the strength of the relation between GGT and CV disease because one of the major components of the metabolic syndrome was absent in the multivariate analysis. Furthermore, because GGT activity is a signal of oxidative stress,[5] the increase in GGT may then reflect both hepatic steatosis and enhanced oxidative stress, which could constitute a deleterious factor in the metabolic syndrome.

Disclosures

None.

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Response

We agree with Giral et al that regional body fat distribution plays an important role in the development of cardiovascular diseases (CVDs). In addition, there is evidence that obesity is assessed more accurately by waist-to-hip ratio or waist circumference than by body mass index (BMI), especially in relation to CVD risk.

Waist or hip circumferences were not measured in the Vorarlberg Health Monitoring and Promotion Program, and we were unable to adjust for these variables in our analyses regarding γ-glutamyltransferase (GGT) and CV mortality.[1] Although we adjusted for BMI and a considerable number of other covariates that are related to the metabolic syndrome, such as blood pressure, cholesterol, triglycerides, and fasting glucose, we cannot rule out additional effects of missing covariates.

However, there are several arguments suggesting an independent effect of elevated GGT on the evolution or presence of CVD beyond its association with features of the metabolic syndrome and hepatic steatosis.[2] First, it has been shown that elevated GGT may be directly involved in atherosclerotic plaque formation and thus may be more than an indicator of oxidative stress in the metabolic syndrome. Second, there is a strong association between high GGT and CV mortality in people showing no evidence of increased body weight. Like Stranges et al,[3] we performed a stratified analysis investigating the effects of elevated GGT on CV mortality by groups of BMI. In contrast to Stranges et al,[3] who investigated the associations of GGT with incident hypertension, we observed significant effects of elevated GGT on CVD mortality in all BMI subgroups. Adjusted hazard ratios were 2.1 (95% confidence interval [CI], 1.2 to 3.5) per log unit GGT in persons with a BMI <20 kg/m^2 and 1.7 (95% CI, 1.4 to 2.1), 1.6 (95% CI, 1.3 to 2.0), and 1.9 (95% CI, 1.4 to 2.5) for BMI groups of 20 to 24.9, 25 to 29.9, and >30 kg/m^2, respectively.

Finally, we recently showed that a high GGT level significantly contributed to the validated European SCORE risk function that predicts CVD mortality.[4]

Disclosures

None.

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