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Editorial

Gamma-glutamyltransferase as a cardiovascular risk factor

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This editorial refers to 'Serum gamma-glutamyltransferase predicts non-fatal myocardial infarction and fatal coronary heart disease among 28 838 middle-aged men and women'† by D.-H. Lee *et al.*, on page 2170

The association of a novel factor with clinical vascular disease must meet the same high standard met by 'traditional' risk factors. Serum gamma-glutamyltransferase (GGT) activity is a low-cost, highly sensitive laboratory test: though it is currently considered as an index of hepatobiliary dysfunction and alcohol abuse,[1] pathology studies from our group since 1998 have indicated its possible role in the pathogenesis of atherosclerosis.[2,3] Furthermore, epidemiology studies on a total of 218 561 subjects from unselected populations[4–6] or cohorts with ascertained disease[7] have proven the role of GGT not only in predicting mortality from all causes, but also the clinical evolution of cardiac and cerebrovascular diseases towards life-threatening events, such as myocardial infarction, stroke, and cardiac death, independently from the occurrence of hepatic disease, alcohol consumption, and established traditional risk factors in multivariable analyses. As for what specifically concerns the occurrence of coronary events, first observations by Wannamethee *et al.*[4] in British middle-aged men were confirmed in 2001 in this Journal by us for patients with angiographically established coronary artery disease (CAD).[7] Serum GGT was associated with an increasing risk of cardiac death and non-fatal infarction for activity values within reference limits with a graded response relationship (from 25 up to 40 U/L). These data were further confirmed by the findings of a very large epidemiological Austrian study including data collected over 17 years (1985–2001) from 163 944 volunteers of the 'Vorarlberg Health Monitoring and Promotion Program'.[5] The latter findings confirmed the prognostic value of serum GGT activity on fatal events in chronic forms of coronary heart disease, congestive heart failure, and ischaemic or haemorrhagic stroke.[5] This was found to be true in both genders, at serum levels within normal values: the receiver operating characteristics analysis suggested GGT cut-off values of 15.5 U/L for men and 10.5 U/L for women, corresponding to 27.6 and 18.7 U/L, respectively, for measurements made at 37°C, with a clear dose–response relationship and with a stronger (from 1.5 to 2-fold) prognostic significance in younger (<60 years) participants.[5]

The epidemiological evidence is biologically plausible: GGT, which is found on all cell membranes, with the exception of erythrocytes, is the main determinant of extracellular hydrolysis of glutathione (GSH).[1] In this process, GGT releases the dipeptide cysteinyl–glycine, which is subsequently cleaved to cysteine and glycine by plasma membrane dipeptidase activities. Thus, GGT activity provides cells, first of all, with a mean for the recovery of precursors needed to reconstitute intracellular levels of GSH, the main cellular antioxidant. However, studies of our and other laboratories have shown that the reactive thiol of cysteinyl–glycine originated during GGT-mediated cleavage of GSH may cause the reduction of ferric Fe(III) to ferrous iron Fe(II), thus starting a redox-cycling process resulting in the production of the reactive oxygen species superoxide anion and hydrogen peroxide, both capable of stimulating prooxidant reactions. GGT pro-oxidant effects are likely within atherosclerotic coronary, carotid, and cerebral plaques, where catalytically active enzyme has been histochemically identified,[2,3] and can be sustained by iron storage proteins such as transferrin and ferritin, or even by free iron, shown to be present within the plaque gruel at sufficient concentrations.[2]

During the last decades, several pieces of evidence have proven serum GGT to be associated with lipoproteins, thus suggesting that the intense GGT activity found within human lesions[3], colocalized with oxidized LDL and $CD68^+$ macrophagic foam cells[2], may derive from the accumulation of LDL-associated GGT within the arterial wall. We recently showed that beta-lipoprotein (LDL, IDL, VLDL)-associated GGT activity increases with total serum GGT activity,[8] supporting the hypothesis that increasing levels of serum GGT may be linked with an enhanced influx of GGT-carrying lipoproteins into the plaque (*Figure 1*). Lee *et al.* show an independent predictive value of serum GGT activity for non-fatal myocardial infarction and fatal coronary heart disease in a large (28 838 middle-aged men and women) unselected cohort: the prognostic role is stronger among subjects

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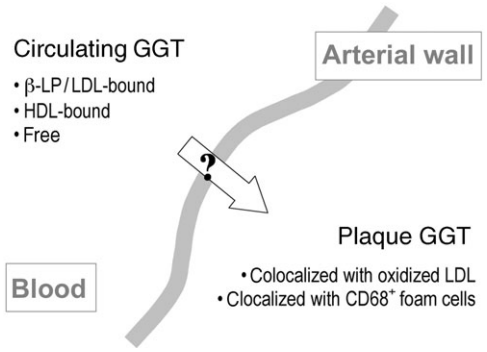

Figure 1 Lipoprotein-associated GGT activity increases with total serum GGT activity,[8] supporting the hypothesis that increasing serum GGT levels may enhance influx of GGT into the plaque (Paolicchi *et al.*[3]).

aged <60.[9] Actually, serum GGT activity is affected by strong genetic factors, with heritability estimated at 0.52.[10] Within its normal range, it has many other determinants, even stronger than liver function or alcohol consumption, and shows a positive association with several cardiovascular risk factors, such as systolic blood pressure, body weight, serum cholesterol, and others, including diabetes.[4,5,7,9] Lee *et al*. confirm GGT-independent predictive value, which is higher within the group of diabetic subjects.[9] This points out that the pathogenetic mechanism involving GGT may be additive to those specifically promoting the atherosclerotic process in diabetes (e.g. lipoprotein glycation). As regards alcohol consumption, GGT exerted a protective effect from cardiac events, in this series,[9] as in previous studies.[5,7]

Though not essential, it is relevant to assess whether the prognostic impact of a novel risk marker can be affected by therapeutical intervention, thus decreasing the occurrence of cardiac events. As for what concerns the possibility of considering GGT activity and the underlying mechanism as a therapeutical target, we recall that the coronary revascularization procedure, either percutaneous or surgical, is able to abolish prognostic value of serum GGT activity.[7] Further studies are necessary to assess the effect of drugs currently used for the treatment of atherosclerosis on serum GGT activity.

In conclusion, the recent insight into pathophysiological role of GGT and thiol metabolism concerning the evolution of atherosclerosis seems supported by the epidemiological observations of its significance as a cardiovascular risk factor. Further research is needed on the sources and biochemical characterization of GGT activity within the plaque, on its relation with global serum activity, with inflammation biomarkers, plasma lipoproteins, and other independent determinants, in order to define the most risky combination and improve the prognostic stratification of patients.

Conflict of interest: none declared.

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