Editorial

Gamma-Glutamyl Transferase
Another Biomarker for Metabolic Syndrome and Cardiovascular Risk

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Gamma-glutamyl transferase (GGT) is a cell-surface protein contributing to the extracellular catabolism of glutathione (GSH).[1] The enzyme is produced in many tissues, but most GGT in serum is derived from the liver.[1] In the serum, GGT is carried primarily with lipoproteins and albumin.[2] Serum levels of GGT are determined by several factors: alcohol intake, body fat content, plasma lipid/lipoproteins and glucose levels, and various medications.[1,3,4]

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High levels of GGT have been associated in populations with increased risk of atherosclerotic cardiovascular disease (CVD).[5,6] In the current issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Lee et al[7] report that in 3451 Framingham Study participants (mean age 44 years, 52% women) an increased serum GGT predicted the onset of metabolic syndrome and the occurrence of CVD and death; moreover, the highest GGT quartile experienced a 67% increase in CVD incidence. In this study the association of GGT concentrations with CVD and mortality remained significant after adjustment for traditional cardiac risk factors and C-reactive protein (CRP).

One hypothesis for the relation of GGT levels and CVD holds that GGT itself is proatherogenic.[1] GGT has been reported to occur in atherosclerotic plaques,[8] which might support this hypothesis. The origins of GGT in plaques could be through influx of lipoproteins that carry it into lesions. One of the products of GSH hydrolysis produced by GGT is cyseinyl-glyceine, which can generate superoxidide anion radicals through its interaction with free iron.[9] This effect could promote atherogenesis via LDL oxidation. At present the postulated pathogenic pathways remain hypothetical and are yet to be substantiated.

An alternative hypothesis that appears to be consistent with the findings of Lee et al[7] is that elevations of GGT are a marker of the presence of the metabolic syndrome. Other workers have reported that high levels of GGT are associated with fatty liver, insulin resistance, type 2 diabetes, obesity, and other metabolic risk factors. There is growing evidence that the liver, which is the primary source of circulating GGT, is a key target organ for the development of the metabolic syndrome. An elevation of GGT is seemingly closely related to hepatic steatosis[10–13]; the latter in turn is strongly associated with the metabolic syndrome.[14–18] The mechanisms whereby elevated GGT is related to hepatic steatosis have not been determined, but several possibilities have been proposed by Ortega et al.[19] For example, fatty liver could cause hepatocellular damage that would simulate the synthesis of GGT. Alternatively, excess fat in the liver could enhance oxidative stress, leading to overconsumption of GSH with a compensatory increase in GGT synthesis. Finally, a higher GGT production could be secondary to a low grade hepatic inflammation induced by hepatic steatosis.

It must be noted that high levels of GGT are not the only hepatic biomarker of hepatic steatosis. Elevations of transaminase are common in patients with fatty liver with or without histological evidence of inflammation.[20–24] In addition, higher levels of serum transaminases in populations have been associated with the metabolic syndrome[25–30] and a higher risk for CVD.[31,32]

Other lines of evidence support a relationship between elevated serum GGT and the metabolic syndrome.[33] Thus the higher GGT levels are accompanied by more insulin resistance and greater risk for developing type 2 diabetes.[34–38] Another important association between GGT and the metabolic syndrome is the finding that higher GGT levels occur in obese persons, particularly those with abdominal obesity.[39–44] The connection between GGT and the metabolic syndrome extends to an association of higher GGT levels with hypertension.[45–49] Thus, it appears that all of the major components of the metabolic syndrome are linked to elevations of serum GGT.

The metabolic syndrome consists primarily of a group of atherogenic factors that commonly cluster in individuals.[50] These include elevations of remnant lipoproteins, glucose, blood pressure, circulating inflammatory cytokines, and prothrombotic factors and low levels of high density lipoproteins (HDL) (Table). In addition, a large number of biomarkers have been reported to be associated with the metabolic syndrome (Table). These include parameters of obesity and products released by adipose tissue, plasma insulin levels and insulin-like growth factors, liver enzymes, C-reactive protein and circulating metabolites, several components of circulating lipoproteins, microalbuminuria, and markers of increased cellular inflammation.[51–66] The status of these biomarkers as causative factors, either in generation of the metabolic syndrome or directly in atherogenesis, at present is uncertain. Some of them have been implicated as causes, but others as a reflection of a metabolic abnormality.

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(*Arterioscler Thromb Vasc Biol.* **2007;27:4-7.**)

***Arterioscler Thromb Vasc Biol.* is available at http://www.atvbaha.org**
DOI: 10.1161/01.ATV.0000253905.13219.4b

TABLE 1. Atherogenic Metabolic Risk Factors and Biomarkers for the Metabolic Syndrome

Atherogenic Metabolic Risk Factors	Metabolic Syndrome Biomarkers
Elevated remnant lipoproteins (50)	Waist circumference (50)
Low HDL levels (50)	Non-esterified fatty acids (50)
Elevated blood pressure (50)	Leptin (53)
Elevated glucose (50)	Adiponectin (53)
Elevated cytokines (50, 51)*	Resistin (53)
Elevated prothrombotic factors (50, 52)†	Angiotensinogen (53)
	Insulin (54)
	Insulin-like growth factor binding protein-2 (IGFBP-2) (55)
	IGF-1 (56)
	Gamma glutamyl transferase
	Transaminases
	C-reactive protein (57)
	Sialic acid (58)
	Uric acid (Salonen) (59)
	Ferritin (60, 61)
	Ghrelin (62)
	Sex hormone-binding globulin (SHBG) (63)
	Triglycerides (50)
	Apolipoprotein CIII (64)
	Small LDL particles (50)
	Microalbuminuria (50)
	Soluble CD36 (65)
	Soluble CD40 ligand (66)
	Soluble P-selectin (66)

*Inflammatory cytokines reported to be increased in in the metabolic syndrome include IL-6, IL-10, IL-18, and TNF alpha.

†A prothromobotic state is characterized by a series of abnormalities that can enhance coagulation, inhibit fibrinolysis, and alter platelet function, such as increases in plasminogen activator inhibitor-1 (PAI-1), fibrinogen, Factor VII, Factor VIII, Factor X, prothrombin fragments F1+2, and vWF (50).

Certainly elevations of serum GGT belong on the list of biomarkers linked to the metabolic syndrome. It appears to be largely a reflection of ectopic liver fat or secondary hepatic inflammation. Although high levels of GGT have been postulated to be directly atherogenic,[1] as have several other biomarkers for the metabolic syndrome, a direct role in causation of atherosclerosis remains to be determined. Nonetheless, it is clear that the pathways whereby various biomarkers are connected to the causation and complications of the metabolic syndrome represent a rich field for future research.

Disclosures

None.

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