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6 THE RELEVANCE OF GAMMA-GLUTAMYLTRANSFERASE AS A PREDICTOR OF CARDIO– AND CEREBROVASCULAR DISEASE IN PRIMARY PREVENTION

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Abstract

Gamma-glutamyltransferase (GGT), a well known marker of alcohol consumption and hepato-biliary dysfunction, may additionally take part in atherogenesis and evolve as a potential risk indicator of cardiovascular morbidity and mortality. This review discusses the relevance of GGT as a predictor of cardio-and cerebrovascular disease in primary prevention based on the literature published between 1995 and 2007.

Gamma-glutamyltransferase as a cardiovascular risk factor in epidemiologic research

Serum gamma-glutamyltransferase (GGT) has been well known as a marker of hepato-biliary dysfunction and alcohol abuse (Whitfield, 2001). In addition, recent longitudinal epidemiological studies have demonstrated an association of GGT with risk factors for cardiovascular disease, incident morbidity and mortality from heart disease and stroke

(Wannamethee, Ebrahim and Shaper, 1995; Jousilahti, Rastenyte and Tuomilehto, 2000; Emdin et al., 2001; Ruttmann et al., 2005; Meisinger et al., 2006; Lee et al., 2006, 2007; Hozawa et al., 2007; Kazemi-Shirazi et al., 2007).

In 1995, Wannamethee, Ebrahim and Shaper investigated the association of GGT with mortality from all causes and cardiovascular disease using data from the British Regional Heart Study. In this study, GGT levels were strongly associated with all-cause mortality, largely due to a significant increase in deaths from ischemic heart disease and other cardiovascular disease causes. In 2000, Jousilathi, Rastenyte and Tuomilehto examined the relationship between stroke, and both self-reported alcohol drinking and serum-GGT. Whereas self-reported alcohol drinking did not associate with any type of stroke, there was an association of serum-GGT concentration with the risk of total and ischemic stroke in both genders. There were also associations between GGT and intracerebral and subarachnoid hemorrhage of varying significance. The largest study, performed by our study group, was based on 163,944 male and female participants of the Vorarlberg Health Monitoring & Promotion Program (VHM&PP) published in 2005. Results of this study showed that high GGT was positively associated with incident fatal events of chronic forms of coronary heart disease, congestive heart failure, hemorrhagic and ischemic stroke. Associations of GGT with cardiovascular disease mortality were stronger in younger study participants. Hazard ratios per log GGT increase were 2.03 (95% CI 1.53-2.69) in men and 2.6 (1.53-4.42) in women younger than 60 years (Ruttmann et al., 2005). This study only investigated mortality, but results were confirmed for non-fatal cardiovascular events in three large studies: Meisinger et al. (2006) based on data from the MONICA Augsburg survey, Lee DH et al. (2006) based on data from Finish MONICA surveys and finally Lee DS et al. (2007) using data from the Framingham Offspring cohort. A study from Japan (Hozawa et al., 2007) added details regarding predictability of GGT in never-drinking women.

Gamma-glutamyltransferase as a marker for oxidative stress

The epidemiological evidence seems to be 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) (Whitfield, 2001). 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 a means for the recovery of precursors needed to reconstitute intracellular levels of GSH, the main cellular antioxidant. However, studies (Paolicchi et al., 1999, 2004) 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. Gamma-glutamyltransferase prooxidant effects are likely within atherosclerotic coronary, carotid and cerebral plaques, where catalytically active enzyme has been histochemically identified, 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 (Paolicchi et al., 2004).

The relevance of gamma-glutamyltransferase for primary prevention

In conclusion, this recent insight into the pathophysiological role of GGT seems to support the epidemiological observations of its significance as a cardiovascular risk factor. However, to be widely used as a screening parameter in primary prevention, GGT must meet the same high standard met by established risk factors such as blood pressure and serum cholesterol.

GGT can be determined by a simple, low-costs blood test. As a marker for alcohol abuse, it has been widely used in health examinations for many years, however, physicians seemed to be largely unaware of the additional relevance of this enzyme. For example, high GGT solely considered as a marker for alcohol abuse, not considering the fact that GGT is can be elevated in non-drinkers as well. There is even evidence that GGT activity is highly determined by genetic factors (Whitfield et al., 2002).

Besides low-cost and wide applicability, a screening parameter should also show a high degree of reliability. Based on data of the VHM&PP, we were able to demonstrate that the long-term stability of GGT in adults is

similar to that of total cholesterol (Ulmer et al., 2003). Recently, the persistence of liver function enzymes was confirmed for a cohort of young adults in the Bogalusa Heart study (Patel et al., 2007). Finally, a new parameter should also be compatible with existing tools and strategies of primary prevention. In cardiovascular diseases, validated risk functions such as the SCORE risk chart of the European Society of Cardiology, are in wide use (Conroy et al., 2003). We were able to demonstrate that elevated GGT contributes significantly to the SCORE risk function in order to predict cardiovascular disease mortality (Ulmer et al., 2005).

In conclusion, we consider GGT as a risk factor or at least as an early indicator for the presence of not only liver dysfunction but more importantly of the presence for cardiovascular disease. We therefore highly recommend measurement of GGT in clinical practice.

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