Additive effects of moderate drinking and obesity on serum γ-glutamyl transferase¹,²

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Fatty liver (FL) is one of the most frequent hepatic conditions diagnosed in the Western world. Chronic alcohol consumption as well as overweight and obesity associated with insulin resistance, hyperinsulinemia, and the metabolic syndrome are the major pathophysiologic factors resulting in FL. Alcoholic FL (AFL) as well as nonalcoholic FL (NAFL) can progress to more advanced liver disease, including inflammation, fibrosis, cirrhosis, and hepatocellular cancer (HCC). Thus, alcoholic liver disease (ALD) and NAFL disease (NAFLD) are the most frequent types of liver diseases in North America and Europe and account for an extremely high prevalence of liver cirrhosis and related deaths.

From a public health perspective, the most successful approach to deal with these liver diseases is early detection and intervention instead of treating the complications of advanced liver disease. Early detection of FL includes its noninvasive verification, mostly done by hepatic ultrasound, and identification of its cause, which includes the patient’s alcohol history or the diagnosis of a metabolic syndrome and peripheral insulin resistance. Because it is sometimes difficult to obtain an exact history of alcohol consumption, laboratory markers of chronic alcohol misuse have been established and are frequently used. One of the best markers for chronic alcohol consumption is serum γ-glutamyl transferase (GGT), which has a relatively high sensitivity and specificity of >70–80%. Because measurement of this enzyme is easy and inexpensive, it has generally been used for early detection of chronic alcohol misuse. However, serum GGT activity loses its specificity for alcohol in more advanced liver disease (1) because its activity is elevated in hepatic inflammation and more advanced liver disease regardless of the cause. Although chronic alcohol consumption is the most frequent cause of elevated serum GGT activity, an increased activity of this enzyme can also be observed under medical treatment and in acute pancreatitis, myocardial infarction, hyperthyroidism, anorexia nervosa, certain muscle diseases, neurological disorders, porphyria cutanea tarda, and some malignancies (2).

Recently, NAFLD has become an important issue in the United States and Europe because of the striking increase in overweight and obese persons in these countries. Because these persons frequently also have increased GGT activities, a differentiation between AFL and NAFL on the basis of serum GGT activity is difficult. Furthermore, overweight is sometimes the result of chronic alcohol ingestion, and FL often results from both ethanol consumption and metabolic abnormalities. Currently, various laboratories are investigating the effect of acute and chronic alcohol intake on NAFLD in animals as well as in humans, and there is evidence that the amount of alcohol intake determines the severity of NAFLD at various stages.

In the current issue of the Journal, Puukka et al (3) showed for the first time that serum GGT activity is influenced not only by the amount of alcohol consumed but also by body mass index (BMI) and sex. The authors investigated 2419 persons and found significant effects of sex, drinking habits, and BMI on serum GGT activity. The highest serum GGT activity was found in moderate drinkers (those who consumed 1–40 g alcohol/d) with a BMI (in kg/m²) > 30. Unfortunately, heavy drinkers were not studied. In addition, they found a positive correlation between serum GGT activity and BMI and a higher serum GGT activity in men than in women.

GGT is an enzyme that metabolizes extracellular glutathione and can be induced by various xenobiotics, drugs, and ethanol. All these compounds, including free fatty acids and acetone, may also induce cytochrome P4502E1 (CYP2E1) (4). The induction of CYP2E1 is associated with an increased production of reactive oxygen species, which results in protein (5) and DNA (6) damage. It has been proposed that GGT on the sinusoidal side of the hepatocyte provides a mechanism by which glutathione released from periportal hepatocytes is metabolized to cysteine, which is needed for pericentral hepatocytes where CYP2E1 is induced and oxidative stress occurs after alcohol consumption (7). Thus, the increased GGT activity observed at the FL stage may represent a defense mechanism against an increased metabolic burden of oxidative stress (7). It is interesting that a daily alcohol intake of 40 g for 1 wk leads to a significant induction of CYP2E1 (8). This increase in CYP2E1 induction and the observed increase in serum GGT activity after moderate amounts of ethanol consumption provide support for the hypothesis of a possible correlation between CYP2E1 and GGT induction. However, such a correlation needs to be confirmed in persons who are only in the FL stage. Free fatty acids induce hepatic CYP2E1 in NAFLD (19), and, if a correlation between CYP2E1 and GGT induction exits, it is not surprising that an increase in hepatic fat content, results in increased serum GGT activities.

Many enzyme activities depend on sex. For GGT, this sex dependency could be of pathophysiologic importance and may require additional investigation. If induction of GGT activity...

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reflects the activation of body defense mechanisms due to enhanced oxidative stress, and this adaptation is lower in women than in men, it could be an interesting pathophysiologic aspect to explain, at least in part, the increased susceptibility of women to ALD (10). In addition, because oxidative stress increases with age, it would be interesting to know the effect of age on serum GGT activity in various populations.

Because both chronic alcohol consumption and obesity associated with metabolic abnormalities are increasing in Western societies, the concomitant occurrence of these factors is of considerable interest. In this scenario, advanced liver disease, including inflammation, fibrosis, cirrhosis, and HCC, may develop more rapidly. The findings by Puukka et al take this fact into consideration for the first time. Subsequently, according to the findings of Puukka et al, the determination of a normal serum GGT activity range needs to be reevaluated and adjusted to BMI to avoid wrong conclusions with respect to alcohol consumption.

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REFERENCES