Serum γ-Glutamyltransferase and Risk of Disease

Serum γ-glutamyltransferase (GGT) has long been used as a liver function test and a marker of excessive alcohol use; in recent years our knowledge of GGT's physiological functions has expanded and several important epidemiological associations have been reported. The paper by Ryu et al. in this issue of *Clinical Chemistry (1)* extends the range of conditions predicted by GGT to include chronic kidney disease (CKD). Such prospective associations between GGT and disease raise issues in both pure and applied science; first, the pathological significance of the wide range of GGT–disease risk associations, and second, the effects that this information may have on the clinical or preventive use of GGT determinations.

CKD is an increasingly common and important condition *(2)*. Existing laboratory markers include glomerular filtration rate estimated from serum creatinine, sex, age, and race (eGFR), and the presence of proteinuria. Because CKD tends to progress, these markers also have predictive value. Defining the pathological role of GGT in CKD will require more investigation. GGT may be a marker of the pathological process or even a contributor, but in either case, GGT is a novel predictor of CKD that could contribute to early intervention and improved outcomes.

The study by Ryu et al. *(1)* was carried out on a cohort of Korean men given a regular health check as part of their employment and followed for up to 3.5 years. Risk of CKD increased across quartiles of the GGT distribution, with the relative risk in the top quartile compared with the lowest quartile being 2.66 on the raw data and 1.7 to 1.9 after covariate adjustments. Because both GGT and the variables measured as endpoints indicating CKD (eGFR and proteinuria) are subject to biological variation and analytical error, the true association between GGT and CKD is probably stronger than this estimate implies, but the magnitude of this regression dilution effect is difficult to estimate. Another uncertainty involves the types of renal disease associated with high GGT. Because CKD is heterogeneous, these results would be compatible with either a substantial GGT effect on risk of one type of CKD or a smaller effect on all. Because CKD has a vascular component, and GGT is a known risk factor for cardiovascular and related diseases, an effect analogous to that on other vascular conditions is a significant possibility. The evidence that GGT predicts vascular disease, including both myocardial infarction *(3–6)* and stroke *(7)*, is substantial. GGT is also associated with type 2 diabetes *(8, 9)* and hypertension *(10)*, both major contributors to vascular and renal disease, and with all-cause mortality. In addition to prospective associations with disease, serum GGT correlates with known cardiovascular risk factors in cross-sectional studies *(11)* and several dietary or lifestyle measures, including fruit and meat intake, vitamin status, and markers of oxidative stress *(12–15)*. Other relevant associations include inflammation *(16)* and pollutants *(17)*. In each case, higher GGT is associated with the undesirable end of the distribution.

The most likely mechanism for these disease and dietary associations, including the newly described association with CKD, is that oxidative stress depletes glutathione stores and a compensatory increase in GGT occurs *(11, 18)*. There is some evidence, however, that GGT is not only a marker of oxidative stress but a generator of free radicals that contribute to it *(19, 20)*. Because high GGT may be a marker of clinical or preclinical disease, a causative risk factor, or both, we should consider whether people who have high GGT for genetic reasons *(21, 22)* are at higher risk for poorer health or earlier death. This possibility can be tested, once we know the detailed causes of genetic variation in GGT, by studying risk of premature death or development of disease in people with genotypes that predispose to higher or lower GGT. However, GGT is not the only liver marker to show associations with obesity, diabetes, and vascular risk. Serum alanine aminotransferase has also been found to be a risk factor for diabetes *(23–25)*, although the effect tends to be weaker than that for GGT. Because alanine aminotransferase does not have GGT's potential prooxidant effects, we can infer that much of GGT's association with disease is as a marker of preclinical effects that progress in time to overt disease.

An important practical issue is whether, and how, GGT's predictive properties can be used to identify people at high risk so that intervention to improve outcomes can be initiated. GGT retains a large part of its predictive power after adjusting for correlated risk factors such as obesity, fasting glucose, and insulin resistance. It is certainly easy and cheap to measure. How predictive is it, and how does it compare with other well-recognized risk factors? The relative risk for developing type 2 diabetes between people in the highest and lowest quartiles of GGT varies in independent studies between a 60% and a 20-fold increase, with a consensus of around a 4-fold increase. The analogous relative risks for fasting plasma glucose, and even body mass index, are substantially greater, at 7.2 and 10.8, respectively *(26)*. In the Malmo studies, however, GGT was superior to cholesterol in the prediction of cardiovascular mortality *(3)*. The relative value of these risk predictors, or combinations of them, deserves more detailed study.

Even if people who would benefit from treatment can be identified by GGT measurements, appropriate interventions must be defined. Given the spectrum of associated diseases, weight loss, changes to diet, and increased exercise are likely to be beneficial; and we know that GGT is associated, at least in cross-sectional studies, with each of these *(11)*. Because of the associations between GGT and vitamin status *(12, 13)*, vitamin supplements may be effective, although experience with supplement use in other conditions has been disappointing. Some antidiabetic drugs of the thiazolidinedione class have been shown to decrease GGT *(27, 28)*, but they have multiple metabolic and antioxidant effects, and it would be diffi-

cult to be sure which aspect of the drugs' effects has produced clinical benefits. Inhibitors of GGT have been developed and used in vitro and in animal studies for studies of GGT's normal functions, but clinical application would require massive investment in safety and efficacy studies. Perhaps the best use of GGT in risk assessment at present would be to add it to the measurements routinely done to assess prediabetes and cardiovascular risk and make treatment decisions on the accepted principle of total risk. In the renal area, replication of the results of Ryu et al. *(1)*, extension of such studies to women, and definition of the types of CKD associated with high GGT are needed before it can be applied routinely to assess risk.

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