Gamma-Glutamyltransferase-A marker of alcohol consumption.

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INTRODUCTION.

Serum-gammaglutamyl-transferase (gamma-GT, GT, GGT, GGTP) is an enzyme which has been much used in the field of alcoholism during the last decades. Although first introduced as a liver test it has been tested as a marker for alcoholism and for heavy drinking, as a screening instrument and as a tool during long-term follow-up of drinkers. It has also been investigated in general populations and correlated with other risk factors besides alcohol consumption, and been described as a predictor of ill health in its own right. GT has been extensively used and compared with other markers of alcohol consumption. It is a cheap and easily used instrument. It can also be studied in the area of traffic safety in the drinking and driving populations and in the rehabilitation of drunken drivers.

BACKGROUND

GT catalyses the transformation of gamma-glutamyl-groups from gamma-glutamyl peptides to other peptides. It was first named and characterized by Hanes,(1950). Gluthathion (gamma-glutamylcysteinylglycin) is an important substrate, but the enzyme is not specific for this peptide. GT's physiological role is only partly understood but GT seems to contribute to the transportation of aminoacides over membranes (Orlowski,1976).

GT from different organs has the same protein structure but the difference in carbohydrate varies which make it possible to separate GT from kidney, pancreas and liver. GT in serum usually originates from the liver (Huseby,1977).
GT AND ALCOHOL CONSUMPTION.

Since 1961 GT has been used as a sensitive liver test (Szczeklik et al., 1961). The highest values have been observed in liver cancer, biliary cirrhosis and alcohol hepatitis. As with other enzymes of hepatic origin, it is raised in a multitude of hepatobiliary diseases and suffers the further disadvantage that as a microsomal enzyme, it manifests significant increments in response to enzyme inducing drugs (Goldberg, 1994).

The general significance of GT in clinical use has been critically reviewed by Rosalki (1975). GT is elevated in about 75% of anicteric patients with liver disorders, even in the absence of clinical evidence of hepatic disease and independent of recent alcohol consumption. In the alcohol dependent individual, a heavy alcohol consumption during a short period may show a pronounced acute effect on GT, but GT levels are not acutely elevated after normal social drinking in non-alcoholic subjects who have no previous history of liver damage (Rosalki, 1975).

In male out-patients attending a routine health screening, a correlation between alcohol intake and GT activity was reported (Rollason et al., 1972). A daily intake of six or more drinks showed increased GT values in half of the subjects. A subsequent report from the same group yielded somewhat different results (Robinson et al., 1979) the mean GT values at all levels of consumption were higher than those of abstainers, but there were no difference between the drinking groups themselves.

Evidence favouring a dose-dependent relationship between serum GT activities and alcohol consumption has come from other investigations. An impressive association between the frequency distribution of serum GT values and the consumption of alcohol gauged by two criteria (frequency of drinking and number of drinks on each day of consumption) was observed in males and less impressively in females (Whitfield et al., 1978). The authors also showed that the statistical probability of heavy drinking (six or more drinks daily) rose in proportion to the serum GT activity. There were also some studies from general populations showing dose-dependent realtionship, individual variations and sex differeces (Schiele et al., 1977, Bargrel et al., 1979, Kristenson et al., 1980, Papoz et al., 1981).
GT analyses are also useful for diagnostic confirmation in patients in whom excessive drinking is suspected or known but denied, and serial measurements are valuable for monitoring progress or alleged abstention from alcohol. When drinking ceases, elevated values revert towards the normal usually within three weeks (Rosalki, 1975).

In 1983 Penn and Worthington (1983) summarized much of the literature on GT and they were very pessimistic about the value of the test in screening for alcoholism in the general population. They based their calculations upon a prevalence of alcoholism of about 1% and deduced the predictive value of a positive result to be about 20%. In a recent review by Conigrave et al. (1995), however, the positive predictive value was 50%; as few as 50% of healthy people with an elevated GT may actually be hazardous drinkers. An abnormal result, therefore, is difficult to interpret until other potential causes of elevation are excluded. Nonetheless, when other laboratory tests are normal, alcohol is the commonest cause of GT elevation.

If we summarize the literature according to sensitivity and specificity is seems to be agreement of a sensitivity of 60-90% in alcohol dependence but around 20-50% in hazardous drinking, while specificity is around 55-100% in both drinking categories (Conigrave et al., 1995). GT is rarely elevated in those aged less than 30 years (Withfield et al., 1978, Bliding et al., 1982).

**FALSE POSITIVE GT VALUES.**

Another problem of GT depending of the low specificity is false positive GT values. There are many causes of elevation, several of them, such as medication and hepatobiliary disease, relatively common (Salaspuro, 1986). Drugs, in particular antiepileptics and barbiturates (Rosalki, 1975; Goldberg and Martin, 1975) obesity (Schiele et al., 1977, Peterssen, 1977) and exposure to organic solvents (Kristenson et al., 1981) are related to elevated GT.

In liver disorders (Szczeklik et al., 1961, Aronsen et al., 1970), hypertension (Beevers, 1977, Klatsky et al., 1977, Ramsey, 1977, Hennigsen et al., 1980, Saunders et al., 1981), rheumatoid arthritis and inflammatory intestinal diseases (Lowe et al., 1978, Doral et al., 1967) the GT level might be raised. In some rare disorders like dystrophia myotonica there can be reduced
liver function and high GT (Alevizos et al, 1975) and there has been a recent report on a family with elevated GT levels without alcohol etiology (Bibas et al., 1994).

Organized teetotaller have low levels of GT (Persson, 1989) and follow-up in the general population over seven years showed that change in GT in both sexes had a strong positive association with change in body mass index and hours fasting. In males, increased frequency of inebriation was positively, increased physical activity negatively associated with change in GT. In females, increased systolic blood pressure, starting use of oral contraceptives, the occurrence of menopause and decrease in consumption of bold coffee increased GT (Nilssen et al., 1990, Nilssen and Förde, 1994). In another report coffee, but not green tea, consumption was inversely related to serum GT independently of body mass index, alcohol use and smoking. The findings suggest that coffee may inhibit the inducing effects of alcohol and possibly of smoking upon GT in the liver (Kono et al., 1994).

**GT AS A RISK FACTOR.**

GT levels have also been shown to have important prognostic value. In a study from Malmoe, Sweden, middle-aged men with GT in the top decile of the GT distribution (values above 83 U/l) experienced increased morbidity and mortality compared with those with low GT results (Kristenson, 1987). Thus within three years after the screening 21% of the men had been hospitalized. Of the total days, alcohol psychosis and alcoholism made up 13.6%. Close to thirty (29.2%) of the days were caused by alcohol related and potentially alcohol influenced conditions. Alcohol related admissions were seven times as many in men with GT values in the highest quintile compared with those which had values in the lowest quintile (Kristenson et al., 1982).

Within four years follow-up of mortality in the same population evidence of alcohol abuse or an alcohol-related cause of death was present in 61% of the deaths among the attenders and 62% of those among the non-responders. GT values at the screening investigation were significantly increased in 46% of those who died, but established risk factors, such as cholesterol and triglycerides concentrations and blood pressure, had little predictive value (Peterson et al., 1980).
These results have been confirmed in an Australian study (Conigrave et al., 1993). Men attending a hospital emergency department who had a GT result of above 80 U/l were found to have a seven times increased risk of death over the next 3 years, a five times increased risk of liver disease and a 2-fold increased risk of trauma compared with men with a GT below 30 U/l. Women with higher GT levels were also reported to have increased morbidity.

Orthopedic care for fractures and low back pain was analysed six years before and six years after screening in the Malmö Study. One hundred men 28-, 38- and 48 years old in each group at each GT level. For the two oldest groups both fracture and low back pain had a correlation to the screening value of GT. Men in the highest decile of GT had five times as many fractures and 7-13 times as many visits to orthopedic surgeon as those with GT in the lowest decile (Kristenson and Johnell, 1986).

In another study trauma patients who have both elevation of GT and questionnaire evidence of a drinking problem have been shown to have 2-fold increased risk of experiencing a complication of their trauma (Jurkovich et al., 1993). All these findings indicate that GT values can be used to screen for those most likely to experience harm from their drinking.

**GT IN EARLY INTERVENTION.**

GT has also been used as a tool in intervention programmes (Kristenson, 1982, Persson and Magnusson, 1989, Romelsjö et al., 1989, Nilsson, 1991). In the Malmö Screening and Intervention Study men with GT values in the top decile were entered into a randomized trial of intervention, which included regular feedback of GT results. The treatment group had significantly reduced morbidity and mortality compared with a control group over subsequent 6-8 years (Kristenson et al., 1983). In studies in the primary health care GT has been used as a follow-up instrument during one to two years (Wallace et al., 1988, Andersson et al., 1984, Suokas, 1992).

There have been some problems in showing positive follow-up results of early intervention in some studies. To get the most accurate picture of drinking during the follow-up period one should repeat the test once every fourth months and when the time course of relapses is
important for the study the more frequent test taking is also indicated (Keso and Salaspuro, 1990).

In women the GT assay is an unspecific indicator of several metabolic abnormalities. Some of these apparently occur in individuals in whom all routine clinical and laboratory investigations give results within the health-associated reference intervals. These facts must be taken into consideration if GT values is used in a control programme for the support of alcohol abusers (Nyström et al., 1988).

A recent report from Canada, however, showed that problem drinkers entering in a intervention study, after one year had significant reductions in reported alcohol consumption, psychosocial problems and GT levels. Physician visits were reduced following counseling. Patients receiving only advice showed neither reduction in psychosocial problems nor in serum GT or physician visits, but reported a 46% reduction in alcohol consumption (Israel et al., 1996). Counseling of 3 hours given by a nurse is markedly superior to simple advice in reducing alcohol consumption and objective indicators of alcohol-related morbidity.

**GT AND AMINOTRANSFERASES AND CARBOHYDRATE-DEFICIENT TRANSFERRIN (CDT).**

The serum transaminases, asparate aminotransferase (ASAT) and alanine aminotransfease (ALAT), are less often elevated than GT, being raised in 50% of alcohol inpatients, compared with 75% for GT (Irwin et al., 1988). ASAT and ALAT are not generally used on their own for monitoring response to treatment; however, the transferases can be useful in combination with GT. The combination of these markers is a sensitive means of detecting resumption of drinking (95% sensitivity, 80% specificity) (Irwin et al., 1988). Reviews of markers used in combination with GGT have been published (Watson et al., 1986, Levine, 1990, Conigrave et al., 1995). In this paper CDT will be reported as a tool in the rehabilitation of drunken drivers in conjunction with GGT.
GT AND TRAFFIC SAFETY

It is generally acknowledged that driving under the influence of alcohol is a traffic safety problem. Studies have shown that the probability of involvement in road traffic accidents increases with increasing blood alcohol concentrations. It has also been found that drivers who are heavy drinkers are more prone than others to be involved in traffic accidents (Clare and Cooney, 1973). Therefore, prevention efforts against heavy drinking might be advantageous for the high alcohol consumers and of great value for traffic safety.

DRUNKEN DRIVING.

In an epidemiological survey in France (Papoz et al., 1986), in the Tayside Safe Drinking Project (Dunbar, 1988) and in Finnish studies (Pikkarainen and Penttilä, 1988) several groups of drinking driver have been investigated over the last fifteen years. GT values indicate that most of the intoxicated drivers were chronic drinkers and GT was raised in about 30% of the males and in professional drivers (Papoz et al., 1986, Pikkarainen and Penttilä, 1988). In a subsample of drivers over the age thirty a strong association between raised GT and road traffic accidents was found (Dunbar, 1988). The studies verify that about 30% of male drunken drivers are chronic consumers or problem drinkers. Lack of measures except legal proceedings result in raised GT level five to nine months later. Recidivism in drunken driving has also been reported to be about 30% during two-four years follow-up (Gjerde and Mörland, 1987).

In another more detailed study by Gjerde (1988), 40% of drunken driver above 29 years of age had elevated blood GT and 67% had elevated CDT. The results suggested that the mean alcohol consumption was greater than 75 g/day, and roughly 30% were heavy drinkers.

In a German report CDT, GT, methanol and acetone plus isopropanol were measured in 534 alcoholized car drivers. Alcohol problems appeared significantly more often in cases where the blood alcohol levels (BAL) were 2 per mille or higher. It was thought that 20 to 25% of the drivers had serious alcohol problems and 40% of all drivers with alcohol problems had BAL's below 1.6 per mille during offence. CDT was proved to be a valuable addition to the other indicators when detecting alcoholism in DWI drivers (Iffland and Grassnack, 1995).
REHABILITATION EFFORTS IN DRUNKEN DRIVING.

There seems to be evidence that long-term treatment is effective and that license supervision is more effective than traditional alcohol treatment programmes (Perrine and Sadler, 1987). Furthermore, the greater the duration of the license supervision, the better the long-term benefits tend to be. A recent report on a meta analysis of the efficacy of remediation with drinking/driving offenders including 215 independent evaluations, showed that the average effect of remediation on drinking/driving recidivism was a 8-9% reduction over no remediation (Wells-Parker et al., 1995).

Medical recommendation for granting or withholding a driving license has been utilised in the treatment and rehabilitation of drunken drivers (Kristenson et al., 1992). The subjects were obliged to present a medical certificate to prove to the traffic authority their fitness as drivers. Monitoring serial changes in GT levels in this group of registered problem drinkers in combination with medical control by a physician and in conjunction with license suspension were feasible as 64% of 303 subjects retained their license over five years.

This study has continued and about 1000 subjects who have been assessed and controlled in the same way. Besides GT, ASAT and ALAT, CDT and MCV have been included as well as the questionnaire Mm-MAST (Kristenson and Trell, 1982). Results are in progress.

Another study has been performed in an psychiatric outpatient clinic during one year (Kristenson and Jeppsson, 1997). Of 198 subjects who attended the clinic 57% came for Conigrave KM, Saunders JB, Whitfield JB. (1995) Diagnostic tests for alcohol consumption (invited review). Alcohol Alcoholism 30.1,13-26.

doctor's certificate and recommendation for driving license. Besides GT, CDT was measured by a new method (Jeppsson et al., 1993). CDT had higher sensitivity and specificity than GGT.

In younger men with more severe drinkig and criminal history the CDT values were higher compared with those more simple cases. In a few cases there were false positive CDT's caused by genetic heterogeneity.
REFERENCES.


