

Gamma-Glutamyl Transpeptidase: a Screening Test for Alcohol Abuse and Early Liver Damage in Life Insurance Applicants

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Dimensions of our Problem

In the opening paragraph of his chapter on alcohol abuse in the *Textbook of Medicine*, Kissin observes that six million of America's ninety million imbibers drink sufficiently to produce stigmata of alcohol dependence.¹ The 1978 *Third Special Report on Alcohol and Health* from the Department of Health, Education and Welfare estimates 10% of U.S. drinkers (that is, 9 million people) should be considered problem drinkers.²

These figures are staggering in their underwriting implications, more so if one considers that the demarcation between heavy drinkers and those who are frankly alcohol-dependent is not clearcut. In the introduction to his *Natural History of Alcoholism*, Vaillant points out that drinkers cannot be divided into social drinkers and alcoholics. Rather, the categories "user" and "abuser" tend to merge. Alcohol abuse is not "... black and white; it is gray."³

A national study of drinking habits has defined "heavy drinker" as one who drinks nearly every day, with five or more drinks per occasion at least once in a while. This definition was said to apply to 12% of those surveyed.⁴ The Addiction Research Foundation in Ontario defines "hazardous drinking" as consuming the daily equivalent of 80 grams of ethanol. This translates to six mixed drinks, a half-pint of whiskey, a 750 ml. bottle of wine or a six-pack of beer.⁵ Skinner, Holt and Israel, in their 1981 paper on the "Early Identification of Alcohol Abuse," consider heavy drinking to be an early indicator of abuse when the drinker imbibes four drinks each day.⁶

A correlation between heavy alcohol consumption and significant extra mortality has been documented in several industry studies, most recently the 1983 Medical Impairment Study.⁷ Lincoln National's last alcohol study, covering issues from 1961 through 1980, showed excess mortality in all categories of alcohol criticism, including occasional excess use and "steady free user."⁸

A 1981 report from the Kaiser-Permanente system, published in the *Annals of Internal Medicine* examined the relationship between levels of

alcohol consumption and ten year mortality. As consumption increased, so did the death rate. Moreover, violent events caused 25% of the deaths among those who consumed six or more drinks each day.⁹

A 1979 study of U.S. Air Force personnel looked at serious incidents related to alcohol use. These incidents included long illnesses, accidents, "driving while intoxicated" violations, etc. Their data indicated a strong relationship between heavy alcohol intake and an increased probability of such incidents. That probability ranged from 6.5% in the lowest consumption category to 52.2% in the highest (more than 5 ounces of alcohol per day).¹⁰

An intriguing study on the causes of death among middle-aged men in a general population was conducted in Malmo, Sweden. It revealed that alcohol was the commonest etiologic factor in the deaths of these men. The authors believe the number of deaths officially caused by alcohol must be multiplied by a factor of six to eight to arrive at the true alcohol-related death rate.¹¹

The role of alcohol abuse in accidents is equally formidable. A report in the December 16, 1983 issue of *Morbidity and Mortality Weekly Report* revealed that 49.8% of drivers involved in fatal crashes whose blood alcohols were measured has concentrations in the impaired range.¹² It has been estimated that alcohol misuse is linked to 70% of falls and drownings, 50% of homicides and fires and at least 35% of suicides.

A 1979 nationwide study on the leading causes of death ranked accidents third overall in males, with suicides seventh, cirrhosis eighth and homicides ninth. Summing all deaths related to accidents and other trauma and assuming only half are alcohol-related, and then adding deaths from cirrhosis (which are predominantly alcohol-induced), one arrives at an aggregate total which puts alcohol in third place behind coronary disease and cancer as a major killer. Its impact is even greater under age 35, where accidents, homicides and suicides rank first, second and third respectively as causes of male deaths.¹³

All the foregoing data testifies to the importance

of alcohol abuse in the risk selection process. Why, then, do we direct so small a share of our screening resources to uncovering alcohol abuse among insurance applicants? We call for countless urine specimens, medical exams, chest x-rays and EKGs. Some of us ask applicants for jumbo policies to exercise on treadmills. And, if we do require blood tests at all, we are likely to go with an SMA-12 or equivalent and focus our attention on glucose and cholesterol. What little we develop pertaining to alcohol abuse is confined to confessions of the applicant, occasional fortuitous APS references and insensitive, non-specific elevations of SGOT.

Our capacity to search out chronic alcohol abuse is no longer constrained. We have laboratory technology accessible to us which permits inexpensive screening for heavy alcohol intake, hidden alcoholism and subclinical liver disease. The test which offers this opportunity is an enzyme known as gamma-glutamyl transpeptidase (GGT).

Gamma-Glutamyl Transpeptidase (GGT)

Dr. Wayne Burton, Assistant Professor of Clinical Medicine at Northwestern University and Director of that facility's Alcohol Treatment Program, has identified a battery of tests helpful in the diagnosis of alcoholism and in managing treated alcoholics. Known as MILT, this profile consists of mean corpuscular volume (M), serum iron (I), liver functions tests (L), and triglycerides (T). The liver function components were limited to LDH, SGOT, alkaline phosphatase and bilirubin but now include gamma-glutamyl transpeptidase as well. Burton added GGT to MILT because he considers GGT to be a reliable marker for alcohol abuse.¹⁴

Gamma-glutamyl transpeptidase (GGT) was discovered in 1950 and first introduced as an indicator of chronic liver disease ten years later. The enzyme is also known as gamma-glutamyl transferase. The acronyms GGT and GGTP are used interchangeably.

Like most enzymes in blood chemistry profiles, GGT is found in many organs and tissues. The highest concentration is in the kidneys, with measurable quantities also present in the pancreas, prostate gland, lungs, pituitary gland, testes and ovaries, liver cells and small bile ductules. The hepatobiliary system ranks sixth among all sites in terms of relative GGT concentration.¹⁵ Nonetheless, extensive studies have shown that most of the GGT in the serum of normal subjects originates from the liver.¹⁶

GGT elevations have been demonstrated in no fewer than 49 specific disorders. Among these impairments are 12 forms of cancer, diabetes mellitus, multiple sclerosis, angina pectoris, myocardial infarction, heart failure, Crohn's

Disease, ulcerative colitis, various systemic infectious and granulomatous processes, acute and chronic pancreatitis, most forms of liver disease and alcoholism.¹⁷ Some pregnant women in their third trimester will have elevated GGT, as will persons undergoing radiation therapy.

While similar lists could be compiled for all major liver function enzymes, GGT is distinct from the rest in one important way: it is not affected by everyday physiologic disturbances. Strenuous exercise, dehydration, fasting, low grade fever, minor muscle trauma, bone remodeling and trivial disorders (e.g., Gilbert's Disease) may distort SGOT, SGPT, LDH, alkaline phosphatase and/or bilirubin. GGT is not affected by these common conditions.

While it is reasonable to conclude that elevated GGT in an acutely or chronically ill individual is of little screening value, the vast majority of insurance applicants are essentially healthy. In ostensibly well individuals, elevation of GGT has a high probability of marking heavy alcohol intake or actual liver disease.

Most tests in routine blood profiles are affected by certain medications. GGT can be elevated by drugs that stimulate the liver's microsomal enzyme induction system and/or cause cholestasis.

Epileptics treated with dilantin and phenobarbital are expected to have mildly increased GGT after several months of therapy.¹⁸ Whitfield and his colleagues studied 49 epileptics and found that their mean GGT was 31 units (with 25 units as the limit of normal). Minimal GGT elevations should therefore be disregarded in applicants currently taking dilantin or barbiturates.¹⁹

Certain benzodiazepine drugs, particularly flurazepam (Dalmane), diazepam (Valium) and chlordiazepoxide (Librium), sometimes cause elevation of liver-related enzymes. Although the data are fragmentary, mild GGT elevations in patients taking these drugs on a daily basis could be due to transient, drug-provoked cholestasis. However, if alkaline phosphatase and bilirubin are normal and the applicant is asymptomatic, GGT levels more than minimally increased should not be overlooked.²⁰

GGT and Alcohol Abuse

Two mechanisms appear to cause excess GGT in serum. In addition to GGT leakage from injured cells, release of the enzyme may be triggered by substances which activate the liver's microsomal enzyme system. Alcohol is one of nature's most potent enzyme inducers. Hence, one would expect elevated GGT in individuals consuming large quantities of ethanol.

In their 1983 review paper, Nishimura and Teschke concluded that "... GGT has been shown to be the most reliable marker not only for alcohol-induced liver lesions, but also for alcoholism itself."²¹ Schuckit and Griffiths evaluated non-alcoholic drinking males and found that GGT is one of the first and often the only enzyme to increase after chronic heavy alcohol intake. In their study, excess alcohol intake was felt to be the cause of 70% or more of elevated GGT levels in a general population.²² When Horner and his colleagues tested patients undergoing detoxification, GGT proved to be the best single indicator of liver involvement. GGT was often elevated in patients who had normal levels of other enzymes.²³

Striking evidence for the value of gamma-glutamyl transpeptidase as an alcoholism screening test comes from Sweden. In four thousand volunteers, Peterson and his co-workers found strong associations between GGT and alcohol-related morbidity and mortality. They believe GGT identifies individuals with existing alcohol problems and others who are at high risk for developing such problems. Comparing GGT to other alcoholism markers, they concluded "... GGT is more powerful than the others as an independent screening tool for alcohol-related disturbances and GGT and assessment of alcohol background are relevant also in the investigation and care of the premorbid somatic health in middle-aged males."²⁴

In another paper, Peterson and his colleagues compared GGT to the Michigan Alcoholism Screening Test (MAST). They found GGT had a higher predictive value as a barometer of hidden alcoholism because it identified individuals with alcohol-related health problems as well as others at risk of alcohol-related disabilities.²⁵

A report published in *Preventive Medicine* in 1980 detailed the screening of two large middle-age male cohorts. Sixteen percent (16%) had elevated GGT and were evaluated further. Three-quarters (75%) were found to be alcohol abusers, leading the authors to conclude that careful interviewing of apparently healthy individuals with elevated GGT values should be expected to uncover heavy drinking as the most common etiologic factor in the large majority of cases.²⁶

Is GGT Too Sensitive?

If alcohol provokes GGT synthesis in the liver, there should be a correlation between levels of alcohol intake and serum GGT. When Whitehead and his co-workers measured GGT in 146 volunteers, 20 had elevations. All were carefully screened to exclude known alcoholics. They were business and professional men, free of lifestyle criticism. Comparing GGT to alcohol intake, the average reading for those who admitted consuming three drinks or

less daily was well within the normal range. However, those who drank four drinks per day or more had an average of 39.9 units of GGT, roughly a third higher than the upper limit of normal. SGOT was also low in the first group, but rose to an average of 40.7 units in the highest intake subset. The authors felt that if GGT was elevated in any segment of this population of non-alcoholic "social drinkers," it might be too sensitive to be used as a screening test.²⁷

Penn and Worthington reviewed the literature in 1963 and concluded that GGT is a sensitive marker for alcoholism. They cautioned, however, that one should not be labeled as an alcohol abuser solely on the basis of an elevated GGT.²⁸

In a comprehensive 1980 review paper, Goldberg came to the conclusion that three weeks of daily alcohol consumption, at a rate of one gram per kilogram of weight per day, would be required to cause pathological rise in serum GGT activity.²⁹ In other words, a 180 pound man would have to drink 80 grams of alcohol daily to significantly raise his GGT. This level of consumption has been identified as hazardous by several authorities (see above, notes 4, 5 and 6).

Morse and Hurt, writing on "Screening for Alcoholism" in 1979, determined that moderate amounts of alcohol do not cause elevation of GGT.³⁰ Dr. Paul Hill of the Scott and White Clinic in Texas found that GGT does not elevate with mild to moderate use of alcohol, but is often four times higher than normal in alcoholics.³¹

Scottish researchers evaluated employees of alcoholic beverage firms and reported that GGT rose with alcohol intake. At a GGT level of 90 IU/l, the probability of consuming more than 450 grams per week was estimated to be 60%.³² A study done in Romania supports these findings.³³

GGT is a sensitive indicator of heavy alcohol intake. Borderline elevations may occur in individuals whose drinking habits might be considered socially acceptable. This does not diminish the value of GGT as a screening test any more than the possibility of benign and non-pathological causes of inverted T waves or proteinuria make electrocardiograms and urine specimens useless to the risk selection process. It is sufficient, for our purposes, to establish a "gray zone" wherein minimal GGT elevations are overlooked in the absence of additional evidence of alcohol abuse, liver damage or other diseases.

Is GGT Too Non-specific?

Several studies have questioned the clinical value of GGT. The issue is its apparent non-specificity. Dragosics and her co-workers found that when they

evaluated adults who did not have any history of acute hepatitis, many individuals with slight changes in their liver function were detected by GGT.³⁴ Penn and Worthington argued that GGT is of little value in the assessment of hepatobiliary disease simply because it rises with virtually all liver and bile duct lesions.³⁵ Ruppin, Frydman and Lunzer studied alcoholic in-patients in Australia and reached similar conclusions.³⁶

As screeners of large populations and appraisers of insurance risks, we do not require that a test pinpoint definite diagnosis. It is satisfactory to be able to conclude that, given an abnormal test result, the probability of some type of potentially significant impairment is affirmed. We are not in the diagnostic business. We need not be dismayed by our inability to establish specific diagnoses.

Horner and his colleagues recognized that the value of GGT is not its specificity, but rather the sensitivity with which it responds to changes in liver status. They strongly endorsed GGT as a screening test.³⁷ The finding by Morris and Hurt that "... most alcoholics with abnormal GGT values have hepatocellular necrosis on liver biopsy specimens" further underscores the value of GGT to life underwriters.³⁸

GGT and Binge Drinking

The usefulness of GGT as a marker for alcohol abuse would be severely compromised if it were possible to substantially raise GGT with a single binge drinking. The explanation that the applicant "had one too many at a party the night before the test" would become a recurring "explanation," forcing us to retreat.

A report by Schuckit and Griffiths in the *American Journal of Psychiatry* addressed this question from the clinical perspective. They realized that if GGT rose significantly from one episode of drinking, the number of false positives would be too great to make the test useful. To settle the issue, they tested 78 male volunteers, ages 21-25. All volunteers were screened to eliminate alcoholics. Each consumed 0.75 ml of ethanol per kilo of weight. The results showed that GGT levels are not likely to increase after moderate drinking. Their recommendation was that GGT be considered a valuable tool to screen for potential alcoholism.³⁹ Other researchers have come to the same conclusion.⁴⁰

Italian investigators measured GGT in intoxicated drivers who caused accidents and compared the results to GGT levels of volunteers who agreed to become intoxicated for testing purposes. Seventy-eight percent (78%) of the drunk drivers had elevated GGT, but GGT did not rise in the volunteers. This prompted the authors to endorse

GGT as a screening test to identify chronic alcohol abusers among inebriated motor vehicle violators.⁴¹

Freer and Statland administered 0.75 grams of alcohol per kilogram of weight each night for three consecutive nights to nine subjects. GGT did rise, but in only three did the highest level exceed baseline pre-test values by more than 40%. The individual with the greatest rise (50% increase after 60 hours) also had the lowest pre-test GGT. The two male subjects with the highest baseline GGT's had negligible changes despite the three days of drinking. It appears from these findings that individuals who normally consume little alcohol will experience a rise in GGT following several days of increased intake. However, the degree of that rise is modest and compatible with an underwriting practice which disregards minimal, isolated GGT elevations.⁴²

Given Abstinence, When Does GGT Normalize?

GGT is not as labile as glucose, triglycerides and some other components of blood profiles. Once a pattern of heavy alcohol intake is established and the GGT has elevated, it takes several weeks to a month for GGT to return normal.⁴³ It is particularly significant that GGT normalizes more slowly than SGOT. In a study of inpatient alcoholics, normal transaminase levels were realized in 10 days of enforced sobriety. It took 80 days to get normal GGT readings in these same subjects.⁴⁴ Other authors document similar findings.⁴⁵ This should put to rest any serious question of antiselection. Few abusers will stop drinking for several weeks or longer in order to lower telltale GGT readings!

GGT and Fatty Liver

Fatty liver is the earliest physical complication of heavy drinking. Although generally considered benign and reversible, it is associated with later hepatocellular inflammation, necrosis and fibrosis.⁴⁶

Histologically, fatty liver involves fat and protein accumulation within liver cells, causing them to distend and resulting in liver enlargement. Other than vague complaints of tenderness over the right abdomen, most patients are asymptomatic. Serious complications generally do not develop until alcoholic hepatitis and/or cirrhosis supervene.

When Nishimura and Teschke compared routine liver tests in patients with alcohol-induced fatty liver, only GGT showed a pronounced increase in serum.⁴⁷ Dragosics and her co-workers assayed 35 patients with fatty liver and found that elevated GGT and abnormal BSP retention were the only lab findings in many cases.⁴⁸

The sensitivity of GGT to fatty liver is important in

underwriting because this lesion is a common alcohol-induced condition in otherwise healthy insurance applicants who are abusing ethanol. Once that abuse leads to alcoholic hepatitis and cirrhosis, the likelihood of major symptoms and a documented history is much greater. The advantage lies in detecting early damage. GGT enhances our capacity to screen for such damage.

One might add that GGT is also an excellent marker for alcoholic hepatitis and cirrhosis. In fact, it may be a better indicator of cirrhosis than the transaminase enzymes, as the latter are often normal in cirrhotic patients.⁴⁹

GGT? Alkaline Phosphatase? SGOT? Which is the Best at Detecting Alcohol Abuse?

Various researchers have compared GGT, SGOT, alkaline phosphatase and other tests with regard to their relative utility in identifying alcoholics. Reding, Thys and DeKeyser found that GGT had a clearcut advantage over the others in distinguishing known abusers from non-alcoholic controls.⁵⁰ When Bagrel and his associates studied the relationship between admitted alcohol consumption and screening test results in a large unselected population, they found GGT consistently had the highest correlation coefficient related to the amount of alcohol consumed.⁵¹ Other researchers have documented similar findings.⁵² The imposing evidence for the superiority of GGT over other tests led Rosalki to conclude his review paper by observing:⁵³

In the nonjaundiced patient, GGTP is a sensitive screening test for liver disease and is superior to alkaline phosphatase... and the transaminases for this purpose. The high incidence of elevation in liver disorders suggest that liver disease is unlikely to be present if the plasma level (of GGT) is completely normal.

Considering the sensitivity of GGT, it may even be appropriate to moderate adverse underwriting action in cases where an elevation of SGOT or alkaline phosphatase coexists with a normal GGT reading.

MCV and GGT

If gamma-glutamyl transpeptidase is the best available screening test for alcohol abuse, mean corpuscular volume (MCV) may be a close second. MCV is one of the three red blood cell indices usually reported on blood counts. Individuals with high MCV are said to have macrocytosis. In anemia, this correlates with Vitamin B-12 or folate deficiency. In non-anemic patients, however, the direct toxic effect of ethanol on erythrocytes is thought to be the cause of macrocytosis.

A Belgian study of beer drinkers who regularly consumed more than two liters per day revealed that

91% had increased MCV. And only 5% returned to normal MCV values one week after enforced alcohol withdrawal.⁵⁴

Papoz and co-workers studied alcohol consumption in healthy patients at two Parisian clinics and found that although GGT was the best overall predictor of heavy drinking, MCV was also a dependable marker.⁵⁵ Investigators in Britain and Scotland have come to similar conclusions.⁵⁶

Underwriters should be aware of the relationship between MCV and alcohol abuse. Unfortunately, mean corpuscular volume is not reported on routine blood profiles and consequently will mainly be available on some APS's. Still, if MCV is elevated in an applicant who also has elevations of GGT and/or SGOT and SGPT, there is an increased probability that the findings relate to alcohol abuse. This is further underscored by the fact that macrocytosis is a common finding in chronic alcoholism due to nutritional deficiencies, chiefly inadequate folic acid intake.

HDL and GGT

High density lipoproteins (HDL) are best known for their inverse relationship to the risk of premature atherosclerosis. Given elevated cholesterol and/or a strong family history of early heart attacks, underwriters generally ease off somewhat if the applicant has a high HDL reading.

HDL synthesis is related to alcohol intake. Ninety-two patients entering an in-patient treatment program at a Milwaukee rehabilitation hospital were matched to controls based on HDL findings. None of the patients or controls were receiving hypolipidemic drugs. The average HDL in the alcoholics was 66 for males and 83 for females. Corresponding readings in the controls were 48 and 56 respectively. HDL fell promptly when alcohol was withdrawn, leading the investigators to conjecture that HDL in conjunction with tests such as GGT may be a more reliable indicator of alcoholism than either test used alone.⁵⁷

It is well known that alcoholics are prone to high levels of triglycerides. HDL may be an even better lipid marker for heavy drinking. One would be disinclined, however, to react adversely to high HDL in the absence of other liver-related findings because of the favorable underwriting implications of the anti-atherogenic properties of HDL.

Conclusion

Alcohol abuse and alcohol-induced liver disease represent major mortality risks. As risk appraisers, our capacity to identify these impairments has, until now, been greatly limited. Gamma-glutamyl transpeptidase (GGT) is a highly sensitive indicator

of heavy drinking and fatty liver, the most common pathological condition associated with alcohol abuse. Although challenged by some as too sensitive and too non-specific for diagnostic purposes, it has been endorsed for use in alcoholic treatment programs. In combination with SGOT, SGPT, alkaline phosphatase, MCV and HDL, its value is considerably enhanced. Overall, GGT offers an inexpensive and readily available tool for screening insurance applicants for chronic alcohol abuse and early, subclinical liver disease.

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Calendar of Events

October 15-17, 1984

The Ninety-Third (93rd) Annual Meeting of ALIMDA will be held at the Sheraton-Hartford, Hartford, Connecticut from October 15 through October 17, 1984.

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Editor's Note

We welcome Dr. Isobel D. Moon, Excelsior Life, Toronto, Ontario, Canada, who has joined the Regional Editorial Board as the representative for Canada.