

Insurance Testing

GAMMA GLUTAMYL TRANSFERASE (GGT) – UNDERWRITING QUESTIONS

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Gamma glutamyl transferase (GGT), also known as gamma glutamyltranspeptidase (GGTP), is normally found only in liver cells. An elevation in GGT generally signifies hepatocellular injury resulting from long-standing abusive intake of alcohol. But alcohol is not the only drug that can increase GGT, nor are drugs strictly necessary. The following discussion should answer eight of the most frequently asked questions about GGT.

Question # 1:**What is the normal range of GGT?**

Answer: The normal range of GGT is method dependent, and hence varies from one laboratory to another. It can be noted from the medical literature, as will be seen below, that this procedure is particularly temperature sensitive. The reference ranges vary depending upon the temperature under which the procedure is carried out. Please note I use the term reference ranges, as opposed to normal. We in medicine have finally understood that we really don't know what "normal" is. We study populations of persons assumed to be disease-free. We then determine the mean and standard deviation of that population. We then take the mean, plus or minus two standard deviations, as the accepted "reference range". Note, we therefore exclude the top 2½ percent, and the bottom 2½ percent of this population from the reference range. The formula depends on a normal distribution of values, the so-called "bell curve". Nevertheless, there are times when the curve of values is skewed to the right. In these instances, we try to eliminate the outlying values, and recalculate the reference range. All of us in medicine understand that at the limits of the reference range, there can be and often times is, an overlap of the normal and abnormal. In these areas, interpretation of the result is required by the person using this laboratory data.

At 30 degrees Celsius, Tietz¹⁹ gives the reference limits as 40 mu/ml for men and 25 mu/ml for women. However, Arnesen¹, in a series of 1,579 Norwegian men aged 20-54 years, and 1,654 women aged 20-49 years, found mean GGT levels of 15 mu/ml for the men and 10 mu/ml for the women, in distributions that were markedly skewed to the right, with less than 3.8% of the men and less than 0.8% of the women having GGT levels

greater than 50 mu/ml. Arnesen¹ and his colleagues attribute these unusually low figures for GGT to the low levels of alcohol consumption and low mortality rate from cirrhosis of the liver in Norway. Furthermore, Kornhuber¹⁸, in their study of 1,379 adults and 223 "other patients" who presented for glucose tolerance testing, assert that the acceptable limit of GGT has been overestimated and should actually be no more than 10 mu/ml at 25 degrees Celsius. They make this statement on the basis of positive correlation in GGT levels with blood pressure, heart rate, relative body weight, and serum insulin levels. Furthermore, they assert that even "social" drinking may be more hazardous to people's health than most of their colleagues believe, and that anyone with a GGT greater than 10 mu/ml should probably be followed for fatty liver. This assumes the determination was performed at 25 degrees Celsius.

In summary, while the acceptable upper limit of GGT in the United States would appear to be 40 - 50 mu/ml for men and 25 - 35 mu/ml for women (when run at 37 degrees Celsius), the limits in a population which, on average, drinks considerably less turn out to be much lower, standing at 15 mu/ml for men and 10 mu/ml for women (when run at 25 degrees Celsius). A GGT level of 50 mu/ml, based on Arnesen's data and Tietz's normal ranges, is probably a useful threshold above which a clinician, or a laboratorian, might legitimately suspect that the patient consumes alcohol in some quantity on a regular basis, assuming the determination was done at 37 degrees Celsius.

Question # 2:**What causes an elevated GGT?**

Answer: The cause of an elevated GGT appears to be hepatocellular injury and, to a lesser extent, enzyme induction. Ethanol induces GGT activity in the C2 rat hepatoma cell line;^{2,5} this effect is inhibited by steroids through interaction with steroid receptors. GGT may be a good histochemical marker for very early precancerous lesions in the liver,³ but GGT is not a good serum marker for premalignancy. (In other words, GGT cannot be expected to increase radically in serum in the early stages of hepatocellular CA, but antibodies to GGT may preferentially "mark" precancerous cells in, say, immunohistochemical preparations.)

GGT depends upon alcohol consumption. GGT has a "strong positive association" with body mass index and use of alcohol, and a negative association with the use of coffee.¹

Direct comparison of people with high and normal GGTs, matched by a variety of disease-related and behavioral factors, shows that alcohol consumption is the only significant factor in determining who would have an elevated GGT and who would not.⁴ Other authorities^{1,17} agree that alcohol is perhaps the most important single determinant of serum GGT levels.

However, from the Malmo Preventive Programme comes a report¹⁴ which warns that, although alcohol was responsible for 70% of the GGT elevations in their series, and that GGT was the most accurate single predictor of premature death in their population, that GGT elevation is not perfectly sensitive nor specific; many non-alcoholics present with elevated GGTs, and many alcoholics present with normal GGTs. Therefore, a GGT elevation alone is not necessarily a hard-and-fast indicator of chronic, abusive alcohol consumption. (For a possible counter argument, remember Kornhuber's⁸ assertion that a lot of people are running around with GGTs which he says are elevated while other say they're normal, and that even "social" drinking is likely to cause a lot of fatty livers. Remember also, however, that Kornhuber and his colleagues are virtually alone in making that statement.)

Salaspuro¹⁶ states that, since GGT is relatively nonspecific, it is not a good screening tool for alcoholism. Yet he also reports that a GGT/alkaline phosphatase ratio greater than 1.4 has a specificity of 78% for alcoholic liver injury.

Question # 3:

What effect does an elevated GGT have on the rest of the body?

Answer: There is report a strong positive correlation between levels of GGT and increased grade of neuropsychological impairment, and this relationship is "independent of the relative contribution of other laboratory measures of liver injury and of alcohol consumption histories." Irwin hints at a mechanism for cognitive impairment in alcohol abusers beyond liver dysfunction or alcohol consumption by themselves. Specifically, he states that one of three things maybe happening in patients with elevated GGTs⁶:

1. That the high levels of GGT may in and of themselves be altering the plasma concentrations of amino acids and, by so doing, affecting their transport across the blood-brain barrier and other barriers, or
2. That alternatively, high levels of GGT may be increasing the transport of amino acids across the blood-brain barrier in excessive amounts, or finally
3. That the GGT may be inhibiting the gamma glutamyl metabolic cycle in key CNS cells.

By any one of these means, or a combination of them, excess GGT in the bloodstream may be, in and of itself, directly responsible for the increased degree of cognitive impairment which Irwin⁶ and his colleagues found in their patients, this after adjusting for the presumed effects of liver disease and

excessive alcohol intake per se. In support of this hypothesis, Irwin et al⁶ cite studies in rats indicating significant alteration in feeding behaviors, "footshock" sensitivity, and other behavioral indices in rats with excess levels of GGT. Along that same line: From the Malmo Preventive Programme, which appears to be the equivalent of the Framingham Study for alcoholism, comes at least one report (Kristenson et al)⁹, showing a definite positive association between elevated GGT levels and increased incidence of alcohol-related orthopedic disorders. Specifically, men with more than 80 mu/ml of GGT in serum had a four to six fold increase in fractures over men with about 20 mu/ml GGT in serum, in their series of 1,151 patients.

Question # 4:

How much drinking is required to elevate GGT?

Answer: Generally, heavy (over 80 g per day) consumption of alcohol over a protracted period is required to maintain high levels of GGT. GGT elevation is higher in those whose diets are relatively rich in fat and/or poor in carbohydrates.^{10,18} The activity of GGT in the liver of the Sprague-Dawley rat (GGT units per gram of liver mass) increases by 144% with increased alcohol consumption, but that such a steep increase can be thwarted by a sufficient increase in the carbohydrate content of the diet.¹⁸ Detailed studies attempting to correlate the amount of heavy drinking with actual levels of GGT elevation (say, 65 - 100; 101 - 200; and 201 or higher) have not, unfortunately, been done, as far as I can determine. But Nemesanszky et al¹² found mean GGT levels of 86 mu/ml in a defined population of moderate (60 - 80 grams alcohol per day) drinkers, and a mean GGT level of 18 mu/ml in nondrinkers. Although the Nemesanszky group were not attempting to quantify alcohol consumption by a GGT assay, these figures may be taken as benchmarks. (Thus, if a patient presented with a GGT of 100 mu/ml or higher, I would strongly suspect that this patient is a heavy, over-80-gram-a-day drinker.) Clearly, further research is indicated, aimed at producing a function, linear or otherwise, relating mean GGT level to amount of alcohol consumed. For example, no one reports the mean GGT level in less-than-60-gram-per-day drinkers, 100-gram-per-day drinkers, etc. Weill et al²⁰ report that if GGT decreases from a patient's admission baseline after seven days in a structured (obviously alcohol-free) environment, that such a patient may indeed be an alcohol abuser, even if his GGT was within a range generally recognized as acceptable. They reported a sensitivity of 90% on the basis of observing decreases in 96 patients out of 107 admissions to a detoxification center. I am not so sure that that is a safe assumption, however, in view of the report of Nemesanszky et al¹² concerning dramatic GGT elevations in four-week abstaining moderate drinkers following an alcohol challenge, described in more detail below.

Question # 5:

How long does GGT stay elevated after a person who has been drinking heavily stops?

Answer: Most authorities report that GGT declines only after prolonged, sustained, and rigorously-practiced and/or rigorously-enforced abstinence from alcohol. Orrego¹³, calculated the mean half-life of GGT in eight-week alcohol abstainers to

be 26 days. Recall that Weill²⁰ and colleagues report significant declines in many hospitalized patients within seven days.

Question # 6:

Can a 1, 2, or 3-night binge of drinking by a person who is not a chronic alcohol abuser (e.g. party, football weekend, other examples too numerous to mention) dramatically elevate GGT? if so, how long will GGT stay elevated in such a person, after the party is over.

Answer: It depends on whether the person drinks moderately (or more heavily) or does not drink at all between such binges. Nemesanszky et al¹² report that when moderate drinkers (defined in their study as those who imbibe between 60 and 80 grams of alcohol per day) abstain from alcohol for four weeks, their mean GGT level declines from 86 mu/ml to 33 mu/ml. When these same moderate drinkers are then challenged with 1g/kg of alcohol by body weight, their GGT levels increase dramatically twenty-four hours later, to as high as 69 mu/ml on average, and decline slowly thereafter, reaching 48 mu/ml within seventy-two hours. Their AST (SGOT) levels increase significantly but less dramatically. This dramatic response to an alcohol challenge is not seen in nondrinkers, whose GGT levels increase only slightly (from 18 mu/ml to 24 mu/ml 24 hours post-challenge, falling to 20 mu/ml 72 hours post-challenge) and whose AST (SGOT) levels do not change at all. Therefore, if our hypothetical party animal was a moderate drinker to begin with, his GGT level can go up dramatically within twenty-four hours and take about a week to go down to baseline²⁰. If, on the other hand, whenever he drank except at such parties, his GGT would go up only slightly, if at all.

Question # 7:

What factors other than alcohol consumption can raise the serum GGT?

Answer: Medications known to increase GGT include: Phenytoin⁷, and other liver enzyme-inducing drugs^{7,11}, including all the barbiturates and oral contraceptives¹.

Illnesses associated with increased GGT levels include: Acute viral hepatitis¹⁹, primary and secondary neoplasm of the liver¹⁹, and obstructive liver disease¹⁵.

Dietary factors that may contribute to elevated GGT include: Low carbohydrates and/or high fat (which does not in and of itself elevate GGT but does tend to make it worse in the heavy drinker).^{10,18}

Tietz²⁰ reminds us that the transaminases (ALT, AST) are much better and faster indicators of liver disease than is GGT. Ruppert et al¹⁵ report that GGT concentration is much higher in obstructive liver disease than in liver disease due to hepatocellular injury, and furthermore, that the ratio of GGT to bilirubin is significantly higher in intrahepatic cholestasis than in extrahepatic biliary obstruction.

Question # 8:

Do any authorities have anything to say about an elevated GGT in the face of normal transaminases?

Answer: Colloredo⁴ reports that, despite earlier reports of increased prevalence of elevated GGT in diabetes mellitus, there is in fact no significant difference in prevalence of elevated GGT between diabetic and non-diabetic subjects. Specifically, 17.5 percent of male diabetics and 23 percent of male non-diabetics have elevations in GGT, while 26.1 percent of female diabetics and 14.8 percent of female non-diabetics have elevations in GGT. They also support the widely-held consensus that alcohol consumption is the prime determinant of elevated GGTs, as mentioned above. In so far as I have been able to determine, no other authority has reported anything specifically in connection with "isolated" GGTs in man.

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