Significance of γ-Glutamyl Transferase (GGT) Activity Measurements in Alcohol-Induced Hepatic Injury

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ABSTRACT

Experimental evidence is presented that the determination of γ-glutamyl transferase (GGT) activity in serum is useful in the assessment of alcohol-induced liver disease and for demonstrating to patients the toxic effects of their drinking habits on the liver. Serial measurements of GGT activity in serum have also proved valuable in monitoring the progress of therapy as well as alleged abstention from alcohol in the known alcoholic.

Introduction

As a result of efforts by the World Health Organization, the National Council on Alcoholism and others, it is now recognized that alcoholism is an illness which is treatable. Effective treatment, however, is greatly dependent on early detection of liver involvement before permanent damage has occurred. Furthermore, it has been demonstrated that afflicted individuals are more likely to abstain from alcohol if objective evidence of liver damage can be demonstrated.

The site of pathology within the hepatic cell that results in γ-glutamyl transferase (GGT) elevation is still a matter of speculation. GGT is a membrane-bound constituent of the microsomal fraction, but it is also present in a “soluble” form in the cell cytoplasm. Rosalki and Rau8 postulated that microsomal injury is one of the earliest results of alcohol toxicity and that the microsomal location of GGT accounts for its special sensitivity in the detection of alcohol induced hepatic injury. As a result, GGT measurements have been widely used in England and, to an increasing extent, in the United States for the early detection of alcoholism as well as for monitoring progress and alleged abstention by alcoholics during therapy.

Recently Horner et al4 investigated GGT activity in 153 serum samples from 53 alcoholics, none of whom showed clinical signs of liver damage. There was a
highly significant correlation between increased levels of GGT and alanine aminotransferase (ALT) activity in serum, with GGT about three times as sensitive as ALT. However, no significant correlation was found between GGT and alkaline phosphatase (ALP) activity in serum of alcoholics. These observations point to the possible involvement of two different GGT isoenzymes. One isoenzyme form of GGT correlates with the elevated levels of ALP activity found in the serum of patients with obstructive liver disease, while another isoenzyme form of GGT, correlating with ALT, may be responsible for the increased GGT activity observed in the serum of alcoholics.

Implementation of the use of GGT as a test for early identification of alcoholism is due in great measure to Rosalki and Rau. Their studies involved patients characterized by alcoholism or heavy drinking behavior but without any other clinical evidence of liver disease. A group of 76 patients, comprised of 56 males and 20 females, was separated into 17 “heavy drinkers” and 59 “alcoholics.” Heavy drinking was defined as long-standing excessive intake of alcohol. Alcoholism was defined as excessive drinking accompanied by alcohol dependence.

GGT activity measurements on all patients revealed that serum activity was elevated in 75 percent of the 76 patients. Moreover, the degree of GGT elevation expressed as a multiple of the upper limit of normal was far greater than that shown by any of the other enzymes examined (figure 1). No abnormal GGT activity in serum was observed in blood samples taken after normal “social drinking.”

**GGT Levels in Alcoholism**

Zein and Discombe in 1970 first suggested that the measurement of GGT activity is particularly helpful in the clin-
ical assessment of alcoholic cirrhosis. They reported that GGT levels are considerably increased in chronic alcoholism even in the presence of normal transaminase levels.

The correlation of elevated GGT levels in serum and drinking habits was also confirmed by Rollason and co-workers who determined GGT activity in a total of 238 male subjects undergoing routine health screening. Based on answers to a questionnaire which related to drinking habits, the subjects were differentiated into five groups: Teetotals (TT; n = 37), social drinkers (SOC; n = 50), one to two drinks per day (n = 49), three to six drinks per day (n = 53), and more than six drinks per day (n = 49). The average age of the subjects in each group was 45 ± 8 years. GGT levels were found to correlate well with the drinking pattern; the higher the intake, the more frequently were found abnormal GGT levels. The results also suggested that even at lower levels of alcohol intake there may be a correlation between alcohol consumption and mean GGT activity.

Both Rosalki and Rollason concur in that serial measurements of GGT activity in serum are useful for monitoring progress and alleged abstention from alcohol.

A detailed study on alcohol abstention by “heavy drinkers” and “alcoholics” was performed by Lamy et al. These workers reported that after alcohol deprivation, the GGT activity of alcoholics decreased in the first few days according to an exponential law with a half-time of return to normal of 5 to 17 days (figure 2). Among past alcoholics, those who stopped drinking for a year had a lower GGT activity (mean: 21 mU per ml) than a generally healthy population. Ascitic cirrhotics known to drink at least one liter of wine per day also had a high GGT activity (mean: 139 mU per ml). In 10 out of 11 alcoholic cirrhotics who stopped drinking for a year, the half-time of return to normal was 11 to 54 days.

Our own studies were directed at the veteran population in the United States. Although an estimated three million veterans are considered alcoholics, only about 160,000 of them received treatment last year. During the course of our study serum samples from 64 patients were analyzed for GGT activity in serum using a modified Szasz procedure. Alanine transaminase and aspartate transaminase activity were determined using modified Henry procedures, lactate dehydrogenase, using a modified Wacker procedure, and alkaline phosphatase, using a modified Bowers and McComb procedure; all tests were performed at 37°.

**Patient Categories**

Patients were divided into categories of heavy, steady, or spree drinkers based on the history obtained from the patient and the family. Patients were considered heavy drinkers if they had a history of consuming at least a fifth of whiskey or wine daily; steady drinkers, if their consumption was less than a fifth, but on a regular basis; or spree drinkers if they

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<th>Enzyme Changes in the Serum of Drinkers</th>
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<tr>
<td>Degree of Increase in Enzyme Activity</td>
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<td>GGT*</td>
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<tr>
<td>Heavy drinker (n=30)</td>
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<td>Steady drinker (n=14)</td>
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<th>Percentage of Total Cases with Elevated Enzyme Activity</th>
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*GGT: γ-Glutamyl transferase †Aspartate aminotransferase §Alanine aminotransferase ‡Lactate dehydrogenase *Alkaline phosphatase
had heavy alcohol consumption but on a less than regular basis. As shown in table I, GGT activity in serum was found to be the most sensitive indicator of the amount of alcohol consumed. A five-fold increase in mean GGT activity was observed in 81 percent of the patients with a history of heavy alcohol intake. A total of 72 percent of steady drinkers were found to have a mean GGT value of approximately twice that in normals. Spree drinkers showed no elevation. During the course of treatment, GGT activity was observed to decrease regardless of the extent of the initial alcohol abuse (figure 3). Rosalki\(^7\) has recently reported similar results obtained in a study of GGT activity in the sera of hospitalized alcoholics.

A word of caution regarding interpretation of elevated GGT activity in serum has been raised by Batsakis\(^1\) who points out that GGT activity may be increased, although to a lesser extent, in a number of conditions other than liver disease (table II). Secondary liver involvement has not been ruled out completely in these disorders. These findings make clinical interpretation of GGT activity levels in serum somewhat more difficult unless the clinical picture is assessed over an extended period of time and the history of the patient is well documented.

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**References**


