MEDICAL PRACTICE

Occasional Review

Is serum γ-glutamyltransferase a misleading test?

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Although it is now 30 years since the discovery of γ-glutamyltransferase (EC 2.3.2.2.), the clinical relevance of a raised activity of the enzyme in serum remains controversial. The use of the enzyme as a potential diagnostic aid did not emerge until the early 1960s, when it was introduced as a new test of liver function.[1 2] Further work since then suggests that serum γ-glutamyltransferase activity may be a sensitive index of hepatobiliary dysfunction,[3] and the early prediction that measurement of γ-glutamyltransferase activity would be established in the laboratory repertoire seems to have been fulfilled.[4] The association between excessive alcohol consumption and raised activities of serum γ-glutamyltransferase, particularly in the absence of other abnormal results of biochemical tests of liver function, was made in the early 1970s, and a serum γ-glutamyltransferase estimation has been included in many screening programmes to detect an excessive intake of alcohol.[5 6]

It is rare, however, to find a biochemical test that is both tissue specific and disease specific, and γ-glutamyltransferase activity appears to be no exception. The serum activity of the enzyme has been shown to be affected by several factors and to rise in various clinical conditions. Also its induction by a wide variety of drugs, including alcohol, makes interpretation of test results difficult. Consequently, the claimed advantage of its sensitivity is marred by its lack of specificity. Recently, doubts have even been expressed about the clinical value of serum γ-glutamyltransferase activities in the diagnosis of hepatobiliary disease[7] and also about the dangers of misinterpreting raised activities found in screening healthy subjects or hospital patients.[8–10] We believe that serum γ-glutamyltransferase activity is estimated too often, and that clinical and laboratory staff should be much more critical about the need for assaying this enzyme.

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Location, role, and structure of γ-glutamyltransferase

The tissue and intracellular distributions of γ-glutamyltransferase are well established and widely documented.[11–14] Histochemical techniques have shown that the enzyme is present in cell membranes of many tissues, especially those concerned in secretory or absorptive processes, such as the brush border of the kidney and the bile canaliculi. The precise physiological function of γ-glutamyltransferase, which is a glycoprotein, remains to be clarified, though it is generally accepted that the enzyme facilitates amino acid transport across cell membranes and is concerned in glutathione metabolism.[15] High concentrations are found in the kidney and pancreas with a relatively low concentration (but large total quantity) in the liver.[16 17] Nevertheless, the results of kinetic and electrophoretic studies indicate that the enzyme found in serum of normal subjects originates from the liver.[18] Physicochemical differences are conferred on the enzyme by different carbohydrate moieties, and this property has led to the separation of several forms of the enzyme.[19]

Reference ranges and physiological factors affecting γ-glutamyltransferase

The determination of the reference ranges for serum γ-glutamyltransferase activity presents a problem. Besides factors

such as alcohol and drugs, the serum activity of γ-glutamyltransferase has been reported to be affected by age, sex, and body weight, although fasting does not appear to alter the value. The reference range for men is higher than for women and increases with age and body weight.[20] Many raised activities of γ-glutamyltransferase in elderly patients may in fact be normal if viewed against the correct reference population. Compounded with this is the problem of standardising enzyme assays in general.

CHILDHOOD

High values of γ-glutamyltransferase activity may be present in the serum of the neonate and reach five to eight times the upper limit of the adult reference range.[21] In premature babies the activity may transiently rise even higher than this during the first few days. Values decline rapidly and are within the normal adult range by about 7 to 9 months of age.[22 23] Serum total alkaline phosphatase values in children are invariably higher than those in adults and are therefore difficult to interpret. The circulating enzyme is derived from growing bones, and the problem is most difficult in the growth spurt associated with puberty. Perhaps the most convincing argument for retaining γ-glutamyltransferase assays is to replace those of alkaline phosphatase in children, when isolated biliary tract disease is suspected. As always, high serum transaminase activities indicate hepatocellular disease. A raised serum γ-glutamyltransferase activity is probably easier to interpret in children, since fewer children than adults are taking drugs, and if they are this is likely to be known; they are most unlikely to be alcoholics.

PREGNANCY

Serum activity of γ-glutamyltransferase is generally within the reference limits throughout normal pregnancy,[24] although a progressive decrease in activity in individual patients has been reported.[25] In a pregnant patient with suspected liver disease and a raised alkaline phosphatase value, the estimation of serum γ-glutamyltransferase activity may be useful in differentiating between the hepatic and placental alkaline phosphatase isoenzymes. Raised alkaline phosphatase values in pregnancy are difficult to interpret since the placenta contributes to the circulatory level, but if hepatocellular disease is suspected an assay of serum transaminase activities should be the first line of investigation. If these are normal then characterisation of the alkaline phosphatase isoenzymes is probably a more reliable diagnostic procedure than estimation of serum γ-glutamyltransferase activity.

Liver disease and γ-glutamyltransferase

In most liver diseases γ-glutamyltransferase activity is a sensitive, but non-specific, indicator of primary liver disease, its activity being above the reference interval in roughly 90% of such cases.[3] When various categories of hepatobiliary diseases, including alcoholic liver disease, are grouped together, the sensitivity of the estimation is variously reported to be between 87% and 95%.[7 26-29] Compared with other standard tests of liver function the serum γ-glutamyltransferase activity may be the most sensitive indicator of liver disease, but since it rises in virtually all types of liver disease the test is of little value in the differential diagnosis of hepatobiliary disease.[30] Various studies have compared γ-glutamyltransferase with other tests of liver function—for instance, serum alkaline phosphatase, 5'-nucleotidase, bilirubin, and transaminases activities—in an attempt to define the most clinically useful tests or combination of tests for differential diagnosis.[31 32] Estimation of γ-glutamyltransferase shows little or no benefit over the more traditional biochemical tests for differential diagnosis in liver disease. Although γ-glutamyltransferase activity may be raised in many cases of liver disease, the magnitude of the increase tends to be variable. The highest levels of γ-glutamyltransferase activity are found in cases of biliary obstruction, carcinoma metastatic to the liver, cirrhosis, and chronic alcoholism; but enzyme induction due to drugs and alcohol makes it difficult to rely on an isolated raised result as indicating liver disease.

HEPATITIS

The diagnostic value of serum γ-glutamyltransferase estimations in acute hepatitis is doubtful and transaminase estimations have proved superior, both as a more sensitive marker of liver cell damage and as a better guide to the progression of the disease.[33] The clinical picture and the very high serum transaminase activities are so characteristic in most cases of acute hepatitis that γ-glutamyltransferase estimations are unnecessary. γ-Glutamyltransferase activities tend to rise and return to normal later in the disease than the transaminases, and the estimation may therefore be of some use in monitoring the progress from acute to chronic hepatitis, when values remain high. The aspartate or alanine transaminase/γ-glutamyltransferase ratio is useful in differentiating acute hepatitis from extrahepatic cholestasis,[34] with a high ratio in acute hepatitis owing to the disproportionately high transaminase activities seen. Nevertheless, the ratio may not discriminate completely between viral hepatitis and intrahepatic cholestasis, since the activities of γ-glutamyltransferase in intrahepatic cholestasis are generally lower than in extrahepatic cholestasis, and therefore interpretations must be made with caution.[35] Moreover, alkaline phosphatase activity has long been used in this way with varying success and γ-glutamyltransferase activity seems no more discriminatory.

OBSTRUCTIVE LIVER DISEASE

Serum γ-glutamyltransferase activities have been compared with those of alkaline phosphatase, leucine aminopeptidase, and 5'-nucleotidase as a marker of biliary obstruction.[29 34 36] γ-Glutamyltransferase may rise to values averaging 12 times the upper reference limit and is more often raised than any of the other enzymes, although leucine aminopeptidase may be more specific for biliary obstruction.[31] The increases in serum γ-glutamyltransferase activities are more pronounced than for the other enzymes and persist longer. Mean activities are considerably higher in extrahepatic obstruction with jaundice, and when the obstruction is due to malignant disease with or without jaundice, than in other causes of cholestasis.[3 4 33 37]

It has been suggested that very high activities of γ-glutamyltransferase in a non-jaundiced patient may indicate hepatic malignancy.[37] High γ-glutamyltransferase activities are also seen in intrahepatic cholestasis, but the increase is generally much less in anicteric cholelithiasis and acute cholecystitis with jaundice.[3] Because of the variability of the rise in serum γ-glutamyltransferase activity in both intrahepatic and extrahepatic cholestasis, γ-glutamyltransferase activity cannot be solely used to differentiate between the two. Moreover, its possible induction by drugs makes interpretation difficult.

HEPATIC MALIGNANCY

The use of estimating γ-glutamyltransferase activity in detecting hepatic malignancy is well documented, but opinion varies about the clinical usefulness of the test in this context.[30] Increased serum γ-glutamyltransferase activities may be found

in both primary and secondary tumours of the liver with values averaging 18 times the upper limit of normal.[33] When hepatic secondary tumours are present the rise in γ-glutamyltransferase activity is more pronounced than that of the other liver enzyme markers.[37] A study of 153 cases with and without hepatic metastases showed a true positive rate of 90% in the diagnosis of hepatic metastases.[38] Nevertheless, the exclusion from this study of patients with extrahepatic biliary obstruction gave rise to fewer false positives than would otherwise have been obtained. In another study γ-glutamyltransferase activity was unhelpful in the diagnosis of hepatic metastases, and the authors concluded that the test gave an unacceptable number of false positives and would result in errors of classification.[39] The high prevalence of false positives decreases the specificity of the test and consequently diminishes its clinical usefulness. If, however, the γ-glutamyltransferase result is normal in a patient with established cancer, liver metastases are less likely to be present.

One drawback to the use of the test to monitor the spread of malignancy is that other variables associated with treatment may affect the serum values of the enzyme. Thus treatment with cytotoxic drugs may lead to hepatocellular damage and may also induce enzymes within the liver, both of which may increase serum γ-glutamyltransferase activity. Serum γ-glutamyltransferase values in elderly patients with cancer must also be interpreted with caution, since the rise in serum of γ-glutamyltransferase activity associated with the liver congestion of congestive cardiac failure may be misinterpreted as an indicator of hepatic metastases. One advantage offered by measuring γ-glutamyltransferase activity over alkaline phosphatase activity is that it is not raised in metastatic bone disease, and it may thus serve to define the tissue source of a raised alkaline phosphatase activity, although characterisation of the alkaline phosphatase isoenzymes is more reliable and is unaffected by drug activity.

CIRRHOSIS

It has been reported that altered serum γ-glutamyltransferase activity may be the only biochemical abnormality in cirrhosis, the later stages of resolving acute hepatitis, and chronic hepatitis. Values vary with the extent of the disease and may even be low[27 40] or very high as in alcoholics with hepatomegaly and jaundice and in patients with biliary cirrhosis.[35 41] On average the values are five times the upper reference limit.[3] γ-Glutamyltransferase activity appears to be a better indicator of the disease than transaminase activities, which are often normal. When there is extensive loss of hepatic cells γ-glutamyltransferase activity may fall to values within the normal range; this indicates a poor prognosis.[37 42]

Alcoholism and γ-glutamyltransferase

Perhaps one of the most controversial aspects concerning γ-glutamyltransferase activity is its association with hepatic damage and enzyme induction by alcohol. Long term excessive consumption of alcohol not only causes liver damage and disease but may also lead to increased serum γ-glutamyltransferase activity, either by direct damage to the liver cell or by the induction of microsomal enzymes in the absence of overt damage. Serum γ-glutamyltransferase values may be exceedingly high in alcoholics, but the precise mechanism for the rise, as for that found in epileptics taking anticonvulsants, is still not clear.[43] The finding that a raised serum γ-glutamyltransferase activity may be the only detectable abnormality[25 41 44] suggests that induction is the cause.

Since the first studies in the early 1970s there have been many reports of the value of γ-glutamyltransferase activity in the assessment of alcohol abuse. Various criteria have been used to define alcohol abuse, even though authoritative guidelines have been published for diagnosing and evaluating alcoholism.[45] This difficulty in classifying alcoholic patients means that reported studies may not be truly comparable. The sensitivity of γ-glutamyltransferase activity in detecting alcoholism, however, has been reported by several workers to range from 54% to about 85%.[26 44 46–48] Thus quite a large proportion of alcoholics do not have a raised serum γ-glutamyltransferase activity,[5 49] and the tendency for it to decrease to normal values in alcoholics of long standing has also been reported.[48 50]

Assessment of γ-glutamyltransferase activity has also been used to detect occult alcoholism in a healthy population undergoing general medical screening.[51] The reason for including measurement of γ-glutamyltransferase activity as a screening test for alcoholism was probably based on its apparent relation to alcohol consumption. These early studies had reported that serum γ-glutamyltransferase activity was raised in a large proportion of alcoholic patients. Nevertheless, the relatively low prevalence of alcoholism in the general population together with the few controls monitored in the first trials gave a false impression of the value of serum γ-glutamyltransferase activity as a screening test. If we assume that the prevalence of alcoholism in the British population is about 1%[52] and that the sensitivity and specificity of γ-glutamyltransferase activity for detecting alcoholism is 75% and 97·5% respectively, then the predictive value of a positive result is about 20%.[53] This means that in the absence of any other abnormality out of 10 patients with a raised serum γ-glutamyltransferase activity, only two will have been caused by alcohol, other factors being responsible for the raised values in the other patients. If the prevalence of alcoholism in a population is higher then the predictive value of a positive result will be correspondingly increased. With this type of calculation the definition of an "alcoholic" becomes very subjective, but clearly a person should never be classed as an excessive drinker of alcohol solely on the basis of a raised serum γ-glutamyltransferase activity. The social stigma attached to alcoholism and the effect on job prospects must never be forgotten. The diagnosis should not be made without very good evidence, and possibly the only reliable evidence is a consistently raised blood alcohol concentration. Several recent articles have reported apparently healthy people with raised γ-glutamyltransferase values, even though their alcohol intake would not be considered excessive.[10 54] For these reasons, γ-glutamyltransferase estimations are losing favour for indicating excessive alcohol intake.

In more specific investigations of alcohol abuse γ-glutamyltransferase has been claimed to be a useful enzyme to measure. It has been used to provide evidence if excessive drinking is suspected but denied by the patient,[55] to verify abstinence when used in conjunction with aspartate transaminase measurements,[56] to detect hepatic disease in suspected alcoholics,[5] and to monitor progress and abstention by serial measurements.[57 58] Even here, however, though some workers have found γ-glutamyltransferase measurement useful as an indicator of continuing alcohol consumption,[57] others have been unable to correlate estimations of γ-glutamyltransferase with alcohol intake.[59]

It has been suggested that γ-glutamyltransferase measurement may be of greater diagnostic value when combined with other markers of alcohol intake, such as serum concentrations of urate and triglycerides and erythrocyte mean corpuscular volume.[54 60 61] Raised concentrations of urate and triglyceride, however, although perhaps slightly more common in alcoholics, are also common in non-alcoholic subjects.

Drug induction and γ-glutamyltransferase

Findings similar to those reported for alcohol abuse have been reported in patients who are receiving drugs known to induce enzyme activity, such as epileptics treated with phenobarbitone and patients with heart disease taking warfarin.[62–64] A raised value of serum γ-glutamyltransferase may be the only biochemical abnormality detected. Clinical interest was aroused by the possibility of using γ-glutamyltransferase as an index of microsomal enzyme induction when there was a need to

establish a patient's compliance with drug treatment. The γ-glutamyltransferase assay is technically simpler than the other accepted indicators of enzyme induction such as urinary 6β-hydroxicortisol or D-glucaric acid. Its poor specificity is a major drawback, however, although the other indices of enzyme induction may be no better.

Other pathological factors affecting γ-glutamyltransferase

In addition to liver disease, raised serum γ-glutamyltransferase activities have been reported in several other clinical conditions and have been widely reviewed.[3 35]

PANCREATIC DISEASE

γ-Glutamyltransferase may rise to about five times the upper reference limit in acute pancreatitis with smaller rises in the chronic disease.[26 33 37] The highest activities have been observed in carcinoma of the head of the pancreas. In pancreatic disease, however, the finding of a raised serum γ-glutamyltransferase activity must be interpreted with caution as it may be neither diagnostic nor specific to the pancreas. The raised γ-glutamyltransferase activity may reflect concomitant hepatic damage in alcohol associated pancreatitis or pancreatitis after biliary obstruction.

CARDIAC DISEASE

There have been many reports of increased γ-glutamyltransferase values after myocardial infarction[30] even though the γ-glutamyltransferase content of cardiac tissue is very low. Opinion varies as to the mechanism of the increase in γ-glutamyltransferase activity, but it is generally thought to be due to tissue repair in the damaged areas of the myocardium, to hypoxic damage to the liver, or to enzyme induction in response to concomitant drug treatment. The pattern of rise and fall of γ-glutamyltransferase activity during myocardial infarction appears to be inconsistent and consequently measuring γ-glutamyltransferase activity has no advantage over creatine kinase, aspartate transaminase, or lactate dehydrogenase assays. False positives may also occur in congestive cardiac failure, in which the liver is the most likely source of the increase in γ-glutamyltransferase activity. In angina γ-glutamyltransferase activity has been claimed to be of some diagnostic use since it has been reported to be the only biochemical abnormality in 65% of cases, although the source of the enzyme is obscure.[33] The problem of poor specificity remains.

RENAL DISEASE

Although kidney tissue has a very high content of γ-glutamyltransferase activity, high serum activities of the enzyme are not common in renal disorders. Slightly raised activities may be found in acute renal failure, nephrotic syndrome, and post-transplant rejection, but they are of uncertain origin and not diagnostically useful.[3]

NEUROLOGICAL DISORDERS

Raised γ-glutamyltransferase activity in serum has been reported in cases of cerebral tumour and cerebrovascular accident.[64] A group of epileptic subjects was also included in this particular study, and it was considered that the increase in serum γ-glutamyltransferase values reflected changes in the vascular endothelium during necrotic or repair processes. The results displayed no apparent relation to drug administration. Most of the patients studied were having continuous drug treatment, however, and possibly hepatic microsomal enzyme induction of γ-glutamyltransferase by anticonvulsants or hepatotoxicity after drug treatment is the most likely explanation.

DIABETES MELLITUS

Up to 57% of diabetics, especially those with vascular complications, have raised γ-glutamyltransferase activities.[25 26 36] Such rises occur in the absence of liver disease, and the possibility of enzyme induction was put forward after a study of a group of serum enzyme values, such as alkaline phosphatase and glucose 6-phosphatase, with increased activity in some diabetic patients.[3] Like γ-glutamyltransferase these enzymes are associated with hepatic microsomes and may share a common mechanism of induction. The effects of carbohydrate metabolism on enzyme induction must also be considered.[65] Estimation of γ-glutamyltransferase activity in these patients at present serves no useful clinical function.

MISCELLANEOUS

γ-Glutamyltransferase activity may occasionally rise in chronic obstructive pulmonary disease,[66] in patients with cervical cancer after radiotherapy,[67] and in the fortnight after severe trauma.[68]

Conclusions

In the face of the widely varying factors that influence serum γ-glutamyltransferase values, it is hardly surprising that γ-glutamyltransferase estimations have not lost popularity for differential diagnosis among clinicians, even though it is one of the most sensitive indicators of hepatobiliary disease. The considerable overlap of values in many diseases coupled with the influence of so many variables on the serum enzyme activity reinforce the recent doubts that have been expressed about the clinical value of the test. Refinements to the reference ranges for serum γ-glutamyltransferase activity, together with the inclusion of serum γ-glutamyltransferase values in some discriminant function models may provide a small improvement in diagnostic value.[69 70] Examination of the multiple forms of γ-glutamyltransferase activity may also yield some information about the tissue of origin of the serum activity, although methods for their characterisation have not been reliably established.[30 71]

It is doubtful if determination of serum total γ-glutamyltransferase activity should retain a place in the diagnostic repertoire, although a case might be made for its use in children with suspected biliary tract disease. In most cases the serum transaminase activity remains the best indicator of mild hepatocellular damage and blood alcohol concentrations of alcoholism. It seems an appropriate time for laboratories performing γ-glutamyltransferase estimations to re-examine the requests for this test and assess whether the results are clinically useful.

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