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Gamma glutamyl transferase “To be or not to be” a Liver function test?

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Liver function tests or LFTs are commonly requested blood tests, usually as a panel or group request rather than as individual components. The term is a misnomer since many of the individual analytes measured as part of the panel have no relationship to liver function, but reflect tissue damage to the liver and other organs. Liver function testing has become almost a routine reflex test added on to any venepuncture performed on a patient, often being used as a test of “wellness”; this has led to an explosion in the number of patients tested. In Tayside, Scotland, over 60% of the resident population had LFTs checked in a 20-year period (1). As the rate of testing has increased, the proportion of abnormality has remained the same at 17-20%. In tandem with this increase in testing there has been a significant rise in liver disease, being the only major cause of death to be increasing in those under the age of 65 (2). So there are calls for initiatives to use LFTs to identify significant liver disease early, when interventions for alcohol, antiviral treatment for hepatitis C or B virus (HCV or HBV) and weight loss for non-alcoholic fatty liver disease (NAFLD) can have significant beneficial effects.

The composition of the “LFT” panel varies, but bilirubin, albumin, alanine aminotransferase (ALT) and alkaline phosphatase are amost ubiquitous; aspartate aminotransferase (AST) and gamma glutamyl transference (GGT) are only occasionally included. GGT is present in the cell membranes of many tissues, including kidneys, bile duct, pancreas, gallbladder, spleen, heart, brain and seminal vesicles. It consists of two polypeptide chains, a heavy and a light subunit, with the active site in the light subunit. GGT is involved in the transfer of amino acids across the cellular membrane and

leukotriene metabolism. It is also involved in glutathione metabolism by transferring the glutamyl moiety, leaving the cysteine product to preserve intracellular homeostasis of oxidative stress (3).

The contraction of the LFT panel has been driven in part by cost considerations. For example with respect to evidence of hepatocyte damage, the argument is that the clinical information derived from AST is similar and less specific for liver than for ALT, so that only the ALT is required to be measured. A similar argument is advanced for the GGT and alkaline phosphatase, both reflecting biliary disease. However this view of AST and GGT as simple surrogates of ALT and alkaline phosphatase respectively are over-simplifications that only hold true if each test is looked at in isolation, which is not what happens in clinical practice. GGT has a sensitivity for the diagnosis and prognosis of liver disease beyond its association with biliary disease and the alkaline phosphatase. This may be due to its function in the control of redox status. It is a well-known marker of alcohol excess; more recently, slightly elevated serum GGT has also been found to correlate with cardiovascular disease and is under active investigation as a cardiovascular risk marker. GGT in fact accumulates in atherosclerotic plaques, (4) suggesting a potential role in pathogenesis of cardiovascular diseases. This correlates with its strong association with the metabolic syndrome and NAFLD. It remains unclear if NAFLD drives the cardiovascular risk, with GGT merely a surrogate biomarker, or if GGT has a more direct pathogenetic role.

GGT can be used in different diagnostic and prognistic algorithms or scores for liver disease. It is one of the most powerful predictors of development of presence of liver disease in patients discovered to have first-time abnormal LFTs (5). The Abnormal Liver Function Investigations Evaluation (ALFIE) diagnostic algorithm was developed in a cohort of nearly 90,000 patients and validated in a group of nearly 11,000. Baseline characteristics which were significant predictors of liver disease included increased GGT, decreased albumin, alcohol dependency, female sex, increased alkaline phosphatase, socioeconomic deprivation, and younger age. Albumin had the greatest percentage prediction of risk in the model followed by GGT. The prognostic index had a negative predictive value of nearly 100% for liver disease. Such prediction tools could substantially reduce the referral and work-up of liver disease, and focus investigation on those with much higher diagnostic yield.

GGT also appears to be a more sensitive detector of NAFLD than ALT. It contributes to several algorithms for the diagnosis of NAFLD, non-alcoholic steato-hepatitis (NASH) or fibrosis within the NAFLD disease spectrum. In the diagnosis of NAFLD, the Fatty Liver Index (FLI), an algorithm derived from the Dionysos Nutrition & Liver Study (6), is calculated through a formula incorporating body mass index (BMI), waist circumference, triglycerides and GGT. It showed good accuracy in detecting NAFLD and avoids the use of abdominal ultrasound in diagnosis. Recently, a study on 2,075 middle-aged Caucasians from the Regional Health Registry, followed for 15 years, showed that FLI independently associates with overall, cardiovascular and cancer-related mortality (7). Similarly, the commercially available test SteatoTest (Biopredictive, Paris, France) which incorporates GGT has diagnostic utility NAFLD. GGT also has a role in several diagnostic algorithms for fibrosis. For example Fibrotest® (Biopredictive, Paris, France) is a patented formula combining α-2-macroglobulin, GGT, apolipoprotein A1, haptoglobin, total bilirubin, age and gender, which has been validated in hepatitis C infection and several other chronic liver diseases. Similarly the Zeng score incorporates α-2-macroglobulin, age, GGT and hyaluronate and has been validated in the staging of HBV infection.

The context in which LFTs are requested determines what they are being used to achieve and should perhaps dictate what the LFT panel contains. The patient who presents for the first time with non-specific symptoms would benefit from having the complete or extended panel of LFTs performed, so that any abnormality could trigger investigation and algorithms to stratify risk of liver disease and fibrosis, allowing decisions to be made about further investigation. By contrast, frequent repeats of

the whole panel are unnecessary in patients with an established diagnosis of liver disease who are being monitored.

So in conclusion we have ever-increasing testing of LFTs and a pressure to perform more tests to detect liver disease at an earlier stage. The removal of AST and GGT from the LFT panel was done at a time and in an environment when the focus was on saving resource within the laboratory service. With changing technology and increasingly 'intelligent' automated laboratory analysers, the unit cost of the measurement of a single analyte has fallen. It is important to consider the whole system cost and impact on patient care rather than the biochemical analyte in isolation. Measurement of GGT and AST may allow intervention to prevent the development of cirrhosis and associated morbidity, mortality and costs (of variceal bleeding, ascites, encephalopathy and hepatocellular carcinoma etc). Using the technological advances in real-time control of laboratory analysers allows reactive changes in testing panels of analytes. For example first-time LFTs can have GGT added to increase detection of liver disease and an AST test to allow calculation of the non-invasive fibrosis scores to detect fibrosis that may be present in those with normal LFTs. Thus both increasing detection of liver disease and its advanced stages as well as containing costs. So to answer the question our title posed; GGT should be a liver function test, some of the time!

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