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CLINICAL

Liver enzymes and Aristotle's art

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TITLE Gamma-glutamyltransferase is associated with incident vascular events independently of alcohol intake: analysis of the British Women's Heart and Health Study and Meta-Analysis

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SUMMARY

Several recent studies have consistently found an association of liver enzymes such as gamma-glutamyltransferase (GGT) and alanine aminotransferase (ALT) with non-alcoholic fatty liver disease (NAFLD). There is evidence that NAFLD in turn could increase the risk of cardiovascular disease independent of other confounders. In addition, GGT reflects oxidative stress both localised within atherosclerotic plaques and in the body generally. Therefore, plasma GGT and ALT activities could be associated with an excess risk of vascular events.

The current study has tested this hypothesis by two methods. First, associations of GGT and ALT with incident coronary heart disease (CHD) or stroke were sought in a longitudinal cohort, the British Women's Heart and Health Study, which included 2,961 women aged 60–79 years without CHD or stroke at baseline. During 12,985 woman years of follow-up (median 4·6 years), 151 participants experienced CHD events and 40 suffered strokes. When association of GGT (categorised into fourths of the distribution) was examined with outcomes, the top fourth of GGT was associated with an age-adjusted increased risk of a combined end point of CHD or stroke (HR=1·49, 95% CI: 1·01–2·09). However, these associations were reduced when controlled for established risk factors for vascular events.

Investigators also performed a meta-analysis of population-based studies, which examined associations between plasma liver enzyme activities and vascular events. Results of ten prospective studies were pooled and analysed. Fully adjusted results showed that an increase of 1 U/L of GGT using a logarithmic scale was associated with a 20% increase in the risk of CHD (HR=1·2, 95% CI: 1·02–1·4), a 54% increase in risk of stroke (HR=1·54, 95% CI: 1·2–2·0) and a 34% increase in the combined risk of either CHD or stroke (HR=1.34, 95% CI: 1·22–1·48).

In a sub-group of non-drinkers, the results were similar to the main analysis, confirming that GGT is associated with vascular events independently of alcohol intake. Only two studies regarding ALT were included in the analysis, and these showed an association with CHD with a fully adjusted HR of 1·18 (95% CI: 0·99–1·41).

OPINION

> None of the arts theorise about individual cases. Medicine, for instance, does not theorise about what will help to cure Socrates or Callas, but only about what will help to cure any or all of a given class of patients. This alone is business: individual cases are so infinitely various that no systematic knowledge of them is possible.
> – Aristotle, *Rhetoric*, Book I, chapter 2, 1356b

Serum activities of liver enzymes such as ALT, aspartate aminotransferase (AST), GGT and alkaline phosphatase have for a long time been measured as components of what is popularly known as the 'liver function test'. Since the first measurement more than 50 years ago, the combinations of these enzyme activities have been used to distinguish hepatocellular from cholestatic patterns of liver injury. Although plasma liver enzyme activities have found a place in many of the diagnostic algorithms, it is a

well-known fact that their serum levels do not measure 'liver function' nor accurately reflect the degree of liver injury. Therefore, liver enzymes do not figure in any of the widely used prognostic models of liver disease.

The King's College criteria for liver transplantation in acute liver failure, the Child-Pugh classification and the Model for End-stage Liver Disease (MELD) scores have stood the test of time in their ability to predict clinical outcomes in acute and chronic liver diseases. The fact that none of these models include serum liver enzyme activities highlights the limitation of their clinical application.

The past decade has seen the tide turn in favour of liver enzymes. Cross-sectional studies, including hospital-based cohorts and population-based surveys, have suggested that both ALT and GGT are markers of NAFLD. Consistent with the interaction between NAFLD and metabolic syndrome, elevated liver enzymes have been strongly associated with other features of metabolic syndrome. Longitudinal cohort studies suggest that the elevation of liver enzymes (such as ALT) not only precedes the development of some components of metabolic syndrome, such as diabetes and hypertension, but could arguably be the best predictor of future development of type 2 diabetes.[1] Epidemiological studies even suggest that NAFLD is potentially a component cause (rather than consequence) of type 2 diabetes.[2] All these studies indicate that plasma liver enzymes closely reflect plasma insulin levels. Evidence is now mounting that hyper-insulinaemia is a critical determinant of cardiovascular risk.[3] Therefore, it follows that raised liver enzymes may be useful in identifying those at risk of cardiovascular events.

Liver enzymes, particularly plasma GGT activities, reflect biological processes that have major clinical implications well beyond our current limited understanding. The ease of their measurements and wide accessibility make them very useful screening tools. Perceived limitations of liver enzymes in reflecting the degree of liver injury may have arisen due to their use as categorical variables with cut-off values derived from apparently normal subjects. Recent studies related to liver enzymes have questioned the use of normograms to determine normal ranges, and challenge us to redefine normality.[4] Interestingly, both ALT and GGT appear to be very sensitive epidemiological tools (when used as continuous variables) within what is considered their 'normal ranges'.

In terms of their clinical application, liver enzymes exemplify the contrast between the individual and the general. While they cannot assess an individual's outcome from liver disease, liver enzymes could in a population identify a sub-group with an excess risk of developing cardiovascular events.

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