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GUIDELINES FOR CLINICAL PRACTICE

Liver function tests: Association with cardiovascular outcomes

Yusuf Yilmaz

Yusuf Yilmaz, Department of Gastroenterology, Marmara University, School of Medicine, Altunizade 34662, Istanbul, Turkey
Author contributions: Yilmaz Y contributed solely to this paper.
Correspondence to: Yusuf Yilmaz, MD, Department of Gastroenterology, Marmara University, School of Medicine, Altunizade 34662, Istanbul, Turkey. yusufyilmaz@uludag.edu.tr
Telephone: +90-533-4403995 Fax: +90-216-6886681
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Abstract

An association between nonalcoholic fatty liver disease and cardiovascular disease has been repeatedly reported. Several studies have focused on levels of gamma-glutamyltransferase (GGT) and alanine aminotransferase (ALT) in relation to cardiovascular outcomes. Evidence indicates that GGT may have a potential role for cardiovascular risk stratification while the role of ALT for cardiac prognosis remains controversial. A conceptual framework that includes not only GGT and ALT but also markers of hepatocyte apoptosis such as cytokeratin-18 fragments should be developed.

Key words: Nonalcoholic fatty liver disease; Liver function tests; Cardiovascular disease; Outcomes

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INTRODUCTION

The evidence in favour of an association between nonalcoholic fatty liver disease (NAFLD) and cardiovascular disease is now considerable[1]. For example, NAFLD patients diagnosed on ultrasonographic findings have an increased risk of incident cardiac events[2]. The nature of the association between NAFLD and cardiovascular events has generated a great deal of interest in the scientific community and levels of common biomarkers of NAFLD, including gamma-glutamyltransferase (GGT) and alanine aminotransferase (ALT), have been repeatedly studied in relation to cardiovascular outcomes. The objective of this editorial is to give an overview of the current evidence linking levels of GGT and ALT to cardiac prognosis. The overview provided in this paper is not intended to be exhaustive; rather, a brief summary of some key findings is provided.

CURRENT EVIDENCE

In a previous meta-analysis of 10 population-based cohort studies, it was reported that an increase in 1 unit of log-transformed GGT was associated with an adjusted hazard ratio of 1.34 (95% CI: 1.22-1.48) for incident vascular events[3]. Besides being an early subclinical marker of fatty liver, GGT may act as a marker of oxidative stress and exposure to environmental chemicals[4]. It has thus been suggested that increased GGT levels may be linked to cardiovascular disease *via* different biological processes such as oxidative stress or lifestyle behaviours[3].

In contrast, the association of serum ALT, an enzyme more specific to the liver than GGT, with cardiac outcomes appears more controversial. There are at least six published studies that have addressed the association between serum ALT and incident cardiovascular events[3,5-9]. Figure 1 shows that the results have been quite divergent, casting doubts on an independent association between ALT and incident cardiac events. There are

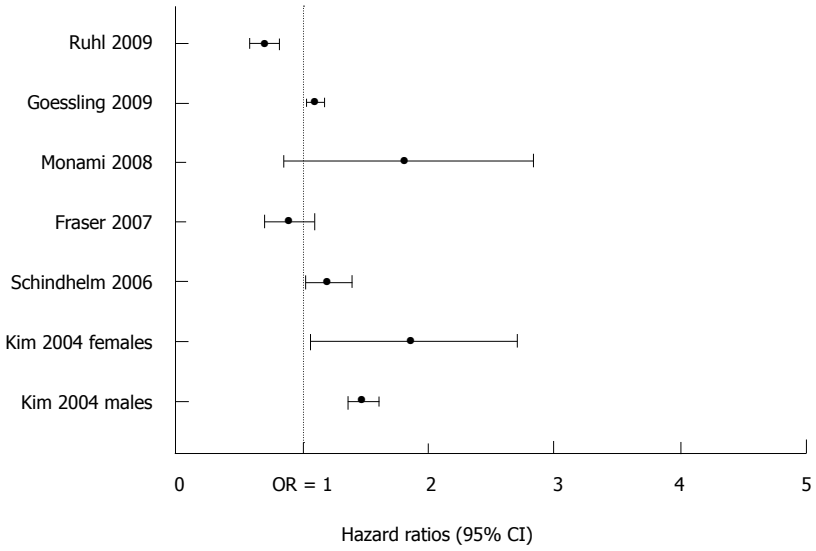

Figure 1 Fully-adjusted hazard ratios and 95% confidence intervals for incident cardiovascular disease for an increase in 1 unit of log-transformed ALT in six published prospective studies. OR indicates odds ratio and CI confidence interval.

several possible explanations for this lack of association. Firstly, significant heterogeneity between studies could have resulted in null findings. Secondly, ALT is not only a marker of NAFLD but also of ectopic fat in general[10]. Finally, the association between ALT and cardiac risk may be confounded by other cardiovascular risk-equivalent such as diabetes[11].

CONCLUSION

In summary, GGT may have a potential role for cardiovascular risk stratification but its predictive power appears modest overall. Evidence suggests that a doubling of GGT is associated with a 34 percent increase in the risk of incident cardiovascular events[3]. In contrast, there is not enough evidence that ALT may predict future cardiovascular events. As scientific evidence is insufficient, more research is needed into the prognostic significance of liver function tests for incident cardiovascular events. In particular, there are a number of issues that should be systematically addressed in the future. For example, it will be necessary to clarify the association with cardiovascular events of elevated GGT or ALT for initially healthy individuals compared with patients with NAFLD diagnosed by ultrasound. Future detailed analysis of the current studies will provide better discrimination on who is at increased risk and who is not. Another open issue is whether there are sex-related effects or relative risks. Even after adjustment for known risk factors, associations of GGT/ALT with cardiovascular events appear stronger in males than in females. A conceptual framework that includes not only classical markers of NAFLD but also markers of hepatocyte apoptosis such as cytokeratin-18 fragments[12,13] or other non-invasive liver tests such as Fibroscan[14] should form the basis for this research agenda.

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