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Liver enzymes and all-cause mortality: Open issues

See Article on Page 1566

Elevated serum levels of aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT) and alanine aminotransferase (ALT) are markers of liver injury and have been consistently related to mortality from liver disease. A possible role of liver enzymes as markers of all-cause mortality and mortality from non liver diseases, including mainly cardiovascular diseases (CVD), cerebrovascular diseases, cancer and diabetes, is yet to be clarified and quantified. In addition, although the issue has been addressed among individuals negative for viral hepatitis B (HBV) and/or C (HCV) serum markers,[1,2] limited data are available among individuals with markers of hepatitis virus infection. An additional relevant issue is the possible interaction between diabetes, vascular disease, cancer and other chronic conditions with liver disease (as defined by elevated AST, GGT and ALT) on mortality. To address this issue, Yuwaki et al present data on the relation between levels of liver enzymes and all-cause and non liver disease mortality according to HBV/HCV status using data from the Japan Public Health Center-based Prospective Study.[3]

That large, well-recognized Japanese study indicated that elevated levels of AST, GGT, but less consistently ALT, were associated to excess total mortality (which includes a small proportion of liver diseases) and, more importantly, non liver disease mortality, among HBV and HCV negative subjects. The findings on total mortality for AST and GGT were consistent in men and women, and the associations were significant after allowance for a large number of risk factors, including tobacco, alcohol, body mass index (BMI), physical activity, energy intake, hypertension, hyperglycaemia and dyslipidaemia.

The associations between liver enzymes and non liver disease mortality were however inconsistent in subjects positive for hepatitis virus infection, i.e. subjects with HBV surface antigen and/or anti-HCV antibody serum markers. In those subjects, liver disease mortality accounted for over 50% of total mortality, in both sexes combined among subjects with elevated levels of serum liver enzymes, and number of deaths were limited across strata for non liver disease mortality. Thus, an overall analysis of non liver disease mortality in both sexes combined would have been informative. For instance, the hazard ratios (HR) according to GGT were above unity for both 50-100 IU/l and >100 IU/l vs the reference category <50 IU/l, but there were only 32 deaths from non liver disease in men and six in women in the intermediate level and 18 in men and four in women in the highest level stratum. Consequently, both sex-specific trends were only of borderline significance. In any case, it is reasonable to assume that high levels of liver enzymes, as markers of liver disease, are associated to non liver disease mortality in subjects positive for hepatitis viruses markers, too.

Among hepatitis virus negative subjects, non liver disease mortality accounted for about 95% of deaths in both sexes among subjects with elevated levels of AST, ALT and GGT. Therefore, the HR for non liver disease mortality were less strong than those for all-cause mortality, but essentially reflected the patterns observed for total mortality for both levels of intermediate and high liver enzymes (AST, ALT and GGT).

Thus, the excess non liver disease mortality among HBV/HCV negative subjects with high liver enzymes levels can be due to at least four factors, i.e. (a) some misclassification of causes of death, though this is likely relatively minor in Japan; (b) the presence of liver disease, which may complicate other conditions and be a concomitant cause of death; (c) the presence of common risk factors for non viral liver diseases and other major causes of death, i.e. vascular diseases and cancer; and (d) the release by other organs of liver enzymes even in the absence of liver (hepatocellular) injury.[4]

The first two possible factors have to be mentioned and may well be important, but there is little possibility and scope for their discussion on available data.

The presence of common risk factors has however to be further discussed. In fact, besides hepatitis and alcohol, the main cause of liver disease is non alcoholic fatty liver disease (NAFLD), which is essentially due to hypertension, dyslipidaemia, overweight and type 2 diabetes, i.e. the key components of the metabolic syndrome (MetS).[5-7] These conditions are established risk factors for CVD, and CVD represents one of the major causes of death among patients with NAFLD.[8] There is also some evidence that MetS[9] and NAFLD are associated with an increased risk of colorectal cancer[10] and possibly other neoplasms.[11]

In addition, specific factors of MetS (which is the key determinant of NAFLD), notably obesity and diabetes, have been associated with the risk of some common cancers. According to the International Agency for Research on Cancer (IARC), excess body weight increases the risk of at least 13 neoplasms, including, besides liver cancer,[12] endometrial, oesophageal, renal and pancreatic adenocarcinomas, gastric cardia cancer, colorectal, post-menopausal breast, ovarian, gallbladder and thyroid cancers.[13] Type 2 diabetes is a risk factor for liver cancer and colorectal, pancreatic, endometrial and perhaps post-menopausal breast cancer.[14,15] There is also some indication for an association between dyslipidaemia and liver, as well as breast, lung, prostate and colorectal cancers.[16] In addition, MetS has been related to the development of hepatocellular carcinoma (HCC) as well as colorectal, pancreatic, endometrial, post-menopausal breast and ovarian cancer[11] and also to overall cancer death.[17] Excessive alcohol consumption is a further common risk factor for cirrhosis, and hence HCC, and several other major causes of disease and death,[18] including various types of cancer, particularly those of the upper aerodigestive tract, colorectum and breast.[19]

Thus, given the presence of common risk factors for non viral liver diseases and other leading causes of death, it is plausible that HBV and HCV negative subjects with liver injuries (elevated liver enzymes) have also an excess of mortality from non liver diseases.

The data on non liver disease mortality among HBV/HCV positive subjects were limited in the Japan Public Health Center-based Prospective Study. However, particularly in women, they were compatible to some excess deaths among subjects with elevated liver enzymes. This is reasonable, since AST, ALT and GGT are markers of liver disease, which may interact with other chronic conditions (CVD, cancer, etc) to cause death. HCV and perhaps HBV have also been related to excess lymphoma risk,[20] whose mortality may be increased by liver conditions.

Thus, the data of the Japan Public Health Center-based Prospective Study indicate that high levels of AST, ALT and GGT are related not only to total but also to non liver disease mortality in hepatitis marker negative subjects, though this essentially reflects the pattern of total mortality, owing to the small proportion of deaths from liver diseases in HBV/HCV markers negative subjects. They are also suggestive of a role of these markers as indicators of non liver disease mortality among hepatitis markers positive subjects in both sexes combined, although the numbers are small for definite conclusions.

On a mechanistic level, hypertension, dyslipidaemia, overweight and diabetes (i.e. the key components of the MetS) are associated to non HBV/HCV-related liver diseases, and are major risk factors for vascular diseases, selected cancers and hence (non liver disease) mortality. This may well explain why elevated serum levels of liver enzymes are indicators of non liver disease mortality, too.

Open issues include the mechanistic interpretation of the associations between liver enzymes and non liver disease mortality, i.e. whether elevated liver enzymes are simply markers of NAFLD and hence the MetS. An additional open issue is whether liver enzymes are related to excess non liver disease mortality in hepatitis virus positive subjects, too.

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