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Liver enzymes and risk of cardiovascular disease in the general population: A meta-analysis of prospective cohort studies

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ABSTRACT

Background: Gamma glutamyltransferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP), commonly used markers of liver dysfunction, have been implicated with risk of cardiovascular disease (CVD). However, the strength and consistency of their associations in the general population have not been reliably quantified.
Methods: We synthesized available prospective epidemiological data on the associations of baseline levels of GGT, ALT, AST, and ALP with CVD [composite CVD, coronary heart disease (CHD), or stroke outcomes]. Relevant studies were identified in a literature search of MEDLINE, EMBASE, and Web of Science up to December 2013. Pooled relative risks (RRs) with 95% confidence intervals (CIs) were calculated using random effects models.
Results: Twenty-nine unique cohort studies with aggregate data on over 1.23 million participants and 20,406 cardiovascular outcomes were included. The pooled fully adjusted RRs (95% CIs) for CVD were 1.23 (1.16–1.29) and 1.08 (1.03–1.14) per 1-standard deviation change in log baseline levels of GGT and ALP levels respectively. There was no evidence of an association of ALT or AST with CVD, however, ALT was somewhat inversely associated with CHD 0.95 (0.90–1.00) and positively associated with stroke 1.01 (1.00–1.02) in stratified analysis. Tests for nonlinearity were suggestive of linear relationships of GGT and ALP levels with CVD risk.
Conclusions: Baseline levels of GGT and ALP are each positively associated with CVD risk and in a log-linear fashion. There may be variations in the associations of ALT with cause-specific cardiovascular endpoints, findings which require further investigation.

1. Introduction

Liver enzymes -gamma glutamyltransferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) – are commonly used as markers of liver dysfunction. Over the past decade, these enzymes have sparked great interest as emerging markers for cardiovascular risk, but uncertainty exists because important questions pertaining to their aetiological relationships with cardiovascular disease (CVD) remain unresolved. Whereas several studies have observed associations of these markers of liver dysfunction with risk of CVD [1–5], others have shown threshold effects or even no association at all [1,6–13]. While some of these studies have reported log-linear associations, others have reported nonlinear relationships or have failed to evaluate nonlinearity, leaving great uncertainty regarding the aetiological nature of these associations. Although GGT is a less specific marker of liver dysfunction, several reports suggest that among the liver enzymes, it is the strongest risk indicator for CVD. Fraser and colleagues have previously reported positive independent associations between GGT levels and subsequent risk of CVD outcomes [coronary heart disease (CHD), stroke, and a combined outcome of CHD or stroke] by synthesizing data from available prospective studies [6]. In the same review, they also pooled the results of the only two studies that evaluated the association of ALT with incident vascular outcomes and reported no significant associations. Since this review, several large prospective studies evaluating the associations of GGT and ALT levels with risk of cardiovascular outcomes have been published and their results have been inconsistent [7,10,14,15]. Data on the association of AST and ALP levels with risk of CVD are comparatively limited and also

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inconsistent, and no reviews quantifying their aetiological associations have been performed to date.

Evaluation of all four common liver enzymes is important, because their assays are sensitive, well standardised, simple, inexpensive, do not require a fasting state prior to venepuncture, are commonly measured together, and are emerging risk markers for CVD. Furthermore, they may hold potential for CVD risk prevention, either as validated causal therapeutic targets or as markers of risk prediction. In this context, we have carried out a comprehensive systematic literature review and study-level meta-analysis of available prospective epidemiological data to quantify the aetiological associations of baseline circulating levels of GGT, ALT, AST and ALP with risk of CVD in the general population.

2. Methods

2.1. Data sources and searches

This systematic review and meta-analysis of studies was conducted using a predefined protocol and in accordance with PRISMA and MOOSE guidelines [16,17](Appendix Supplements 1,2). We searched MEDLINE, EMBASE, and Web of Science for prospective (cohort or "nested case control") population-based studies that evaluated associations of baseline circulating levels of GGT, ALT, AST, or ALP with risk of composite CVD, CHD or stroke outcomes among adults up to December 2013. The computer-based searches combined free and MeSH search terms and combination of key words related to the exposures (e.g., "gamma glutamyltransferase", "alanine aminotransferase", "aspartate aminotransferase", "alkaline phosphatase", etc) and outcomes (e.g., "cardiovascular disease", "coronary heart disease", "stroke", etc). There were no restrictions on language or the publication date. Reference lists of retrieved articles were manually scanned for all relevant additional studies and review articles. We searched and contacted several investigators for unpublished studies on the associations. We restricted the search to studies of humans. Further details on the search strategy are presented in Appendix Supplement 3.

2.2. Study selection

Observational cohort studies were included if they had at least 1 year of follow-up, assessed associations of GGT, ALT, AST, or ALP with risk of composite CVD, CHD, or stroke in adults, with samples measured at baseline, and recruited participants from approximately general populations (i.e., they did not select participants on the basis of confirmed pre-existing medical conditions such as CVD, diabetes mellitus, liver disease, or chronic kidney disease at baseline). Retrospective cohort studies were not included. For findings published only in abstract form, we contacted the investigators to determine if the results were still considered to be valid.

2.3. Data extraction, endpoints, and quality assessment

Data were abstracted, where available, on study, publication date, geographical location, population source, time of baseline survey, sample population, study design, sample source (plasma/serum), nature of sample (fresh or frozen and storage temperature), assay type and source, case definition, sample size, number of cases, number of participants, mean age, duration of follow-up, degree of adjustment for potential confounders (defined as '+' when RRs were adjusted for age and/or sex; '++' further adjustment for established risk factors such as smoking status, body mass index, blood pressure, lipids; and '+++' additional adjustment for alcohol consumption, other liver markers, or inflammatory markers) and risk estimates reported for greatest adjustment for potential confounders. Two authors (H.K. and T.A.A.) independently abstracted data and performed quality assessments. A standardized predesigned data collection form was used for data extraction. Each article was assessed using the inclusion criteria above and any disagreement regarding eligibility of an article was discussed, and agreement reached by consensus with a third reviewer (S.K.K.). In the case of multiple publications involving the same cohort, the most up-to-date study or study with the most comprehensive information was abstracted. We contacted authors of eligible studies where the published data were insufficient, to provide relevant missing information. The primary outcome of this analysis was a composite endpoint of CVD (i.e., a combined outcome of CHD, stroke, cardiovascular death, angina, heart failure, and other CVDs). If a composite endpoint of CVD was not reported or indeterminable, CHD or stroke outcomes were used as reported. Studies that reported on only heart failure as a distinct primary outcome were not included. Appendix Supplement 4 provides details of study-specific outcome definitions. Study quality was assessed based on the nine-star Newcastle–Ottawa Scale (NOS) [18] using pre-defined criteria namely: selection (population representativeness), comparability (adjustment of confounders), and ascertainment of outcome. The NOS assigns a maximum of four points for selection, two points for comparability, and three points for outcome. Nine points on the NOS reflects the highest study quality.

2.4. Data synthesis and analysis

Analyses involved only within-study comparisons (i.e., cases and controls were only directly compared within each study) to limit potential biases. The relative risk (RR) with 95% confidence intervals (CIs) was used as the common measure of association across studies. To enable a consistent approach to the meta-analysis and enhance interpretation of the findings, reported study-specific risk estimates (per-unit change, quintiles, quartiles, thirds, or other groupings) were transformed using standard statistical methods [19,20]. As there is evidence of linear associations of some of these markers with cardiovascular risk and to ensure consistency, we pooled estimates per 1-standard deviation (SD) change in logarithmically transformed baseline levels of these enzymes. Briefly, the log risk ratio for a 1-SD change being equivalent to the log risk ratio for a comparison of extreme thirds divided by 2.18 (equivalently, as the log risk ratio for a comparison of extreme quarters divided by 2.54 or as the log risk ratio for a comparison of extreme quintiles divided by 2.80). Log risk estimates were transformed assuming a normal distribution (or that a transformation of the explanatory variable for which the risk ratio is based was normally distributed). In parallel analyses, risk estimates where appropriate, were also transformed and pooled to involve comparisons between the top third and bottom third of the baseline levels of GGT, ALT, AST and ALP. Standard errors of the log risk estimates were calculated using published confidence limits and were standardised in the same way (Appendix Supplement 5 provides details of the statistical methods used and Stata command used). Authors of studies that reported risk estimates that could not be transformed were contacted to provide standardized estimates. We calculated summary RRs by pooling study-specific estimates (Stata command –metan-) using random effects models that accounted for between-study heterogeneity. When studies published more than one estimate of the association according to subgroups (e.g., by sex), a within-study summary estimate was obtained using a fixed effect analysis. Where appropriate and possible, we estimated dose–response associations of these liver enzyme levels with risk of CVD. A 2-step generalized least-squares trend estimation (GLST) analysis (Stata command –glst-) as described by Greenland and Orsini [20,21] was used to compute study-specific slopes (linear trends) from the correlated natural logs