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Opposite associations between alanine aminotransferase and γ-glutamyl transferase levels and all-cause mortality in type 2 diabetes: Analysis of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study

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ABSTRACT

Aims. Reported associations between liver enzymes and mortality may not hold true in type 2 diabetes, owing to a high prevalence of non-alcoholic fatty liver disease, which has been linked to cardiovascular disease and mortality in its own right. Our study aimed to determine whether alanine aminotransferase (ALT) or γ-glutamyl transferase (GGT) levels predict mortality in type 2 diabetes, and to examine possible mechanisms.

Methods. Data from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study were analyzed to examine the relationship between liver enzymes and all-cause and cause-specific mortality over 5 years.

Results. Over 5 years, 679 (6.9%) individuals died. After adjustment, for every standard deviation increase in ALT (13.2 U/L), the HR for death on study was 0.85 (95% CI 0.78–0.93),

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; CI, confidence interval; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; ELISA, enzyme-linked immunosorbent assay; GGT, γ-glutamyl transferase; HDL-c, high-density lipoprotein cholesterol; HOMA IR, homeostatic model of insulin resistance; HR, hazard ratio; hsCRP, highly sensitive C reactive protein; IQR, interquartile range; LDL-c, low-density lipoprotein cholesterol; NAFLD, non-alcoholic fatty liver disease; SD, standard deviation; sICAM, soluble intercellular cell adhesion molecule; sVCAM, soluble vascular cell adhesion molecule; WHR, waist-hip ratio.

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$p < 0.001$. Conversely, GGT >70 U/L, compared with GGT ≤70 U/L, had HR 1.82 (1.48–2.24), $p < 0.001$. For cause-specific mortality, lower ALT was associated with a higher risk of cardiovascular death only, whereas GGT >70 U/L was associated with higher risks of death due to cardiovascular disease, cancer and non-cancer/non-cardiovascular causes. The relationship for ALT persisted after adjustment for indirect measures of frailty but was attenuated by elevated hsCRP.

Conclusions. As in the general population, ALT has a negative, and GGT a positive, correlation with mortality in type 2 diabetes when ALT is less than two times the upper limit of normal. The relationship for ALT appears specific for death due to cardiovascular disease. Links of low ALT with frailty, as a potential mechanism for relationships seen, were neither supported nor conclusively refuted by our analysis and other factors are also likely to be important in those with type 2 diabetes.

1. Introduction

The enzymes alanine aminotransferase (ALT) and γ-glutamyl transferase (GGT) are found within many tissues. Blood elevations of ALT and GGT are widely used in clinical practice as markers of hepatic dysfunction [1]. GGT, found in hepatocytes and biliary epithelial cells, is a sensitive marker of hepatobiliary disease, while blood ALT levels increase when the hepatocyte membrane is damaged, as an indicator of hepatocellular injury. Both ALT and GGT are recognized as surrogate markers of the metabolic syndrome, fatty liver and cardiovascular disease risk, while GGT is also a marker of oxidative stress and systemic inflammation [1–4]. Several recent publications report an inverse association between ALT and mortality [5,6]. While this would seem counterintuitive if lower ALT is to be considered a marker of liver health, this observation has been repeatedly noted in different populations, including in the elderly, the middle-aged and those with HIV infection [5–9]. Intriguingly, the relationship is opposite to that for GGT, which has a positive association with mortality [4,9–11].

While the mechanisms behind the positive association between GGT and mortality can easily be discerned through the known correlations of GGT with liver disease, oxidative stress, inflammation and comorbidities [1,12], those explaining the inverse relationship between ALT and mortality are elusive. Possible links between low ALT and sarcopenia, biological frailty and chronological age have been postulated [6,7].

This study aimed to determine whether the relationships between blood levels of ALT and GGT and mortality observed in the general population were similar in a community dwelling cohort with type 2 diabetes. We surmised that such relationships may not exist in type 2 diabetes as it is a condition associated with higher ALT and GGT, largely owing to the presence of non-alcoholic fatty liver disease (NAFLD), which is also associated with increased cardiovascular disease and mortality [13–15]. A secondary aim was to explore potential mechanisms behind any relationships found between ALT and GGT and mortality.

2. Patients and Methods

The study was a subsidiary analysis of the FIELD study—a double-blind, placebo-controlled trial done in 63 centers in Australia, New Zealand, and Finland [16]. In brief, 9795 participants aged 50–75 years with type 2 diabetes according to WHO criteria [17] were randomly allocated between 1998 and 2000 to once-daily micronized fenofibrate or placebo. Participants had an initial total-cholesterol concentration 3.0–6.5 mmol/L, plus either total-cholesterol/HDL-c ratio ≥ 4.0 or plasma triglyceride concentration 1.0–5.0 mmol/L, and were not on lipid-modifying therapy at study entry. Exclusion criteria included: blood creatinine >130 μmol/L, history of chronic liver disease, as determined by patient or doctor report, a cardiovascular event within 3 months of recruitment, ALT > two times the upper limit of normal (> 100 U/L) and a recent history of alcohol abuse, as defined by the medical history or at the discretion of the investigators. All deaths were adjudicated by an outcomes assessment committee. Total mortality and cause-specific mortality were predefined secondary outcomes [16].

2.1. *Baseline Characteristics*

A full clinical assessment was performed at baseline. A history of cardiovascular disease was defined as any self-reported history of myocardial infarction, angina, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, stroke, claudication, peripheral vascular disease, or peripheral revascularisation. Dyslipidemia was defined as low HDL-c (<1.03 mmol/L in men, <1.29 mmol/L in women) and high triglyceride concentration (>1.70 mmol/L). Nephropathy was defined as the presence of albuminuria [16]. Alcohol consumption was classified as none, infrequent (special occasion to once/week) or regular (≥2 times/week); data were lacking for grams taken per week. Grade of current exercise capacity using routine daily activities (very light, light, moderate, heavy and very heavy; see eTable 1 for more detail), in addition to the highest level of education obtained (primary school, some high school, completed high school,