

CLINICAL ADVANCES IN LIVER, PANCREAS, AND BILIARY TRACT

Elevated Serum Alanine Aminotransferase and γ -Glutamyltransferase and Mortality in the United States Population

CONSTANCE E. RUHL* and JAMES E. EVERHART†

*Social & Scientific Systems, Inc, Silver Spring, Maryland; and †National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland

Background & Aims: Elevated serum alanine aminotransferase (ALT) and γ -glutamyltransferase (GGT) activities are markers of liver injury, but may also be associated with other diseases and death. In a prospective, national, population-based sample, we examined whether elevated ALT and GGT were associated with increased risk of all-cause and disease-specific mortality. **Methods:** Death certificate–based 12-year mortality was analyzed among 14,950 adult participants in the third US National Health and Nutrition Examination Survey, 1988–1994, who were negative for markers of viral hepatitis B and C. Abnormal ALT was defined as >30 U/L in men or >19 U/L in women, and abnormal GGT as >51 U/L in men or >33 U/L in women. **Results:** Cumulative mortality was 13.9% from all causes, including 4.2% from cardiovascular disease, 4.2% from neoplasms, 0.44% from diabetes, and 0.13% from liver disease. In multivariate-adjusted analyses, elevated ALT was not associated with all-cause mortality (hazard ratio [HR], 1.2; 95% confidence interval [CI], 0.88–1.6). ALT elevation was associated with deaths from liver disease (HR, 8.2; 95% CI, 2.1–31.9), but not from cardiovascular disease (HR, 0.90; 95% CI, 0.56–1.4), neoplasms (HR, 1.0; 95% CI, 0.65–1.5), or diabetes (HR, 2.4; 95% CI, 0.65–9.1). All-cause mortality increased with elevated GGT (HR, 1.5; 95% CI, 1.2–1.8), as did mortality from liver disease (HR, 13.0; 95% CI, 2.4–71.5), neoplasms (HR, 1.5; 95% CI, 1.01–2.2), and diabetes (HR, 3.3; 95% CI, 1.4–7.6), but not from cardiovascular disease (HR, 1.3; 95% CI, 0.80–2.0). **Conclusions:** In the US population, elevated GGT was associated with mortality from all causes, liver disease, cancer, and diabetes, while ALT was associated only with liver disease mortality.

The most commonly used marker for chronic liver disease is elevated alanine aminotransferase (ALT) activity. Although produced by other organs, it is found

predominantly in hepatocytes and is considered a specific marker for liver injury. Few studies have investigated the relationship of abnormal ALT with mortality. Higher ALT was associated with mortality from all causes in some studies,^{1–3} but not others.^{4,5} Data on mortality from specific causes are even more limited.¹ To our knowledge, the relationship of ALT with mortality outcomes has not been established in the general US population. Elevated γ -glutamyltransferase (GGT) results from fatty liver disease, both alcoholic and nonalcoholic, cholestatic liver disease, and induction by drugs such as phenytoin. Although detection and diagnosis of liver disease is its primary clinical use, GGT is a nearly ubiquitous epithelial enzyme that is responsible for catabolism of extracellular glutathione. In addition to liver disease, GGT has been associated with high all-cause mortality, cardiovascular disease (CVD) incidence and death, diabetes, and cancer incidence and death.^{4,6–20}

Using death certificate data from the third National Health and Nutrition Examination Study (NHANES III), a prospective, population-based sample, we examined whether elevated ALT and GGT were associated with increased mortality overall and from specific causes. The multitude of other variables collected in NHANES III allowed evaluation of potential confounders for mortality.

Methods

NHANES III was conducted in the United States from 1988 through 1994 by the National Center for Health Statistics (NCHS) of the Centers for Disease Con-

Abbreviations used in this paper: ALT, alanine aminotransferase; BMI, body mass index; CDC, Centers for Disease Control and Prevention; CI, confidence interval; CVD, cardiovascular disease; GGT, γ -glutamyltransferase; HDL, high-density lipoprotein; HR, hazard ratio; ICD, International Classification of Diseases; NCHS, National Center for Health Statistics; NHANES, National Health and Nutrition Examination Survey.

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0016-5085/09/\$36.00
doi:10.1053/j.gastro.2008.10.052

trol and Prevention (CDC).²¹ It consisted of interview, examination, and laboratory data collected from a complex multistage, stratified, clustered probability sample of the civilian, noninstitutionalized population aged 2 months and older, with oversampling of the elderly, non-Hispanic blacks, and Mexican Americans. The study was approved by the CDC Institutional Review Board, and all participants provided written consent to participate. Of 23,258 sampled persons aged 20 years and older, 16,573 (71%) attended an examination at a mobile examination center. For the primary analyses, we excluded participants with hepatitis B (positive serum hepatitis B surface antigen) or hepatitis C (positive serum hepatitis C antibody) ($n = 453$). We excluded persons with missing data on hepatitis B or hepatitis C ($n = 1047$), serum ALT ($n = 112$), or mortality status ($n = 11$). The sample for analysis of ALT, therefore, consisted of 14,950 participants. An additional 3320 participants were surveyed before GGT was added to the protocol and, therefore, were excluded from analyses of GGT, resulting in an analysis sample of 11,630. A serum sample was collected and shipped weekly at -20°C . Serum ALT and GGT concentrations were assayed by using a Hitachi 737 Analyzer (Boehringer-Mannheim Diagnostics, Indianapolis, IN) at the White Sands Research Center, Alamogordo, New Mexico.²² Abnormal liver enzymes were defined based on recommended cutoffs as a serum concentration of >30 U/L for men and >19 U/L for women for ALT,²³ and of >51 U/L for men and >33 U/L for women for GGT.²²

Participants were passively followed up for mortality through December 31, 2000, using a probabilistic match that linked NHANES III participants with National Death Index records to ascertain vital status and cause of death. This matching methodology is well established and has been described in detail.²⁴ The accuracy of the NHANES III-National Death Index matching methodology was high in a validation study that applied it to the NHANES I Epidemiologic Follow-up Study (96.1% of decedents and 99.4% of living participants were classified correctly).²⁵ Persons not matched to a death record were considered to be alive through the end of follow-up and were administratively censored on December 31, 2000. Mortality outcomes were based on death certificate underlying cause of death coded according to the *International Classification of Diseases, Ninth Revision* (ICD-9) for deaths occurring between 1988 and 1998, and according to the *International Classification of Diseases, Tenth Revision* (ICD-10) for deaths occurring between 1999 and 2000.²⁴ Outcomes consisted of all-cause mortality and the following cause-specific mortality: CVD (ICD-9 codes: 410–414, 428, 429.2, 433–435, 437.0–437.1, 440, and 444; ICD-10 codes: G45, I20–I25, I50, I63, I65–I66, I67.2, I67.8, I69.3, I70, and I74), diabetes (ICD-9 code: 250; ICD-10 codes: E10–E14), liver disease (ICD-9 codes: 70.2–70.9, 275.0–275.1, and 570–573; ICD-10 codes: B16–B19, E83.0–E83.1, and K70–K77), neoplasms (ICD-9

codes: 140–239; ICD-10 codes: C00–D48), and all other mortality. Deaths with liver cancer coded as underlying cause of death ($n = 13$) were included with neoplasms.

Data were collected at baseline, as previously described, on factors known or thought to be related to elevated liver enzymes or mortality and included as covariates in multivariate analyses: age (years), sex, ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, other), education (years: <12 , 12, >12), cigarette smoking (never, former, <1 pack/day, ≥ 1 pack/day), alcohol drinking (never, former, <1 drink/day, 1–2 drinks/day, or >2 drinks/day), doctor-diagnosed diabetes, physical activity, caffeinated beverage consumption, body mass index (BMI; weight [kg]/height [m^2]), waist and hip circumferences, blood pressure, hemoglobin A_{1C}, serum total and high-density lipoprotein (HDL) cholesterol concentrations, and serum transferrin saturation.^{22,26–32} C-reactive protein was assayed using a Behring Nephelometric Analyzer (Behring Diagnostics Inc, Somerville, NJ) and categorized as 0–0.3 and >0.3 .²²

Statistical Analysis

Separate analyses were conducted for ALT and GGT. Baseline characteristics were compared by liver enzyme status using a t test for continuous variables or a χ^2 test for categorical variables. Cumulative mortality during follow-up among persons with and without liver enzyme elevation was calculated using Kaplan–Meier analysis. Hazard rate ratio (HR) estimates (relative risk) for mortality outcomes were calculated by Cox proportional hazard regression analysis (SUDAAN, PROC SURVIVAL, SUDAAN User's Manual, Release 8.0, 2001; Research Triangle Institute, Research Triangle Park, NC) to control for effects of potential risk factors while taking into consideration varying lengths of follow-up. Time at risk was from the date of the NHANES III examination to the date of death or to December 31, 2000. For analyses of cause-specific mortality, participants who died of other causes were censored at the date of death. All factors met the proportional hazard assumption of a relatively constant risk ratio through examination of $-\log(-\log)$ plots of survival versus time by categories.³³ Multivariate analyses excluded persons with missing values for any risk factor included in the model. A P value of $<.05$ was considered to indicate statistical significance. All analyses utilized sample weights that accounted for unequal selection probabilities and nonresponse. All variance calculations accounted for the design effects of the survey using Taylor series linearization.³⁴

Results

ALT

The prevalence ($\pm$ SE) of elevated ALT was 13.5% ($\pm 0.77\%$). Compared with participants with normal ALT, those with ALT elevation were younger and more likely to be Mexican American, obese, diabetic, lighter smokers,

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