Annals of Epidemiology 24 (2014) 817–821

Contents lists available at ScienceDirect

Annals of Epidemiology

journal homepage: www.annalsofepidemiology.org

Original article

Elevated hepatic enzymes and incidence of venous thromboembolism: a prospective study

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ARTICLE INFO

Article history:
Received 28 May 2014
Accepted 29 August 2014
Available online 8 September 2014

Keywords:
Venous thrombosis
Pulmonary embolus
Cohort study
Liver enzymes
Risk factors

ABSTRACT

Purpose: Approximately 10% of the general population has elevated blood concentrations of hepatic enzymes, which are linked to increased coagulation markers. We tested whether elevated hepatic enzymes are associated with increased risk of venous thromboembolism (VTE).
Methods: We followed 12,604 adults with measurements of alanine transaminase, aspartate aminotransferase (AST), and gamma-glutamyl transpeptidase (GGT) prospectively for VTE occurrence.
Results: AST and GGT above the laboratory normal values were associated over two decades of follow-up with increased risk of total (n = 532) and provoked VTE (n = 332), but with not unprovoked VTE (n = 200). In a model adjusted for age, race, sex, hormone replacement, alcohol intake, diabetes, body mass index, estimated glomerular filtration rate, and C-reactive protein, the hazard ratios (HR) (95% confidence interval) for high versus normal AST were 1.46 (1.00–2.11) for total VTE and 1.83 (1.21–2.79) for provoked VTE. For high GGT, the HR were 1.34 (1.06–1.69) for total VTE and 1.43 (1.07–1.91) for provoked VTE. When follow-up was limited to the first 10 years, associations were even stronger (HR ≈ 1.7 for total VTE).
Conclusions: Elevated concentrations of two hepatic enzymes (AST and GGT) in this general middle-aged population are associated with a modestly increased risk of VTE.

Introduction

Chronic liver disease has long been considered to carry a high risk of hemorrhage. However, recent evidence suggests that decreased plasma coagulation factors are accompanied by decreased anticoagulant factors to offset bleeding [1]. Case reports indicate that besides portal vein thromboses, cirrhosis patients often develop deep vein thrombosis (DVT) in leg and therefore may have a thrombogenic diathesis [2,3]. A large case-control administrative database study in Denmark showed a twofold elevated venous thromboembolism (VTE) risk for both cirrhosis and noncirrhotic liver disease [4]. Another administrative database study showed a modest increased risk of VTE in young cirrhosis patients (aged <45 years) compared with other young inpatients, but no increased risk of VTE in older cirrhosis patients [5]. In a nested case-control study in a general practice database, liver disease was associated with a 1.65-fold increase in VTE risk, but this result was not statistically significant [6]. In contrast with the several studies showing a positive association between liver disease and VTE, a population-based case-control study showed an inverse association between liver disease and VTE [7].

More modest hepatic dysfunction than frank liver disease may also relate to VTE risk, but solid epidemiologic data are lacking. A recent body mass index (BMI)-matched clinical case-control study linked nonalcoholic fatty liver disease with a twofold elevated odds of VTE [8]. Nonalcoholic fatty liver disease is associated with elevated levels of hepatic enzymes [9] and increased levels or

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http://dx.doi.org/10.1016/j.annepidem.2014.08.004

activity of several coagulation factor produced in the liver [10]. On the other hand, alcohol drinking, which can raise hepatic enzyme levels, generally has not been associated or was weakly inversely associated with VTE incidence [11]. Results from the National Health and Nutrition Examination Survey (NHANES 2005–2008) indicate that elevated hepatic enzymes are highly prevalent in the general population: that is, elevated alanine transaminase (ALT), 10%; aspartate aminotransferase (AST), 16%; and gamma-glutamyl transpeptidase (GGT), 9% [12]. Given findings to date and the high prevalence of hepatic dysfunction in the population, we prospectively assessed the association between hepatic enzyme levels and risk of VTE in the Atherosclerosis Risk in Communities (ARIC) Study.

Materials and methods

Study population

The ARIC study [13] and its methods for identification and classification of VTE have been described in detail elsewhere [14,15]. In brief, 15,792 men and women aged 45 to 64 years enrolled in the ARIC study in 1987 to 1989 and had subsequent examinations in 1990 to 1992, 1993 to 1995, and 1996 to 1998 and annual telephone contact. The present analysis used ARIC visit 2 as its start point for follow-up because baseline samples are now scarce. The institutional review committees at each study center approved the methods and staff obtained informed participant consent.

Measurement of hepatic enzymes and VTE risk factors

Participants were asked to fast for 12 hours before their morning visit 2 appointments, and serum and plasma samples were obtained and stored at −80°C. Soon after the visit, central laboratories measured serum creatinine by the Jaffe method and glucose by a hexokinase assay. In 2012 to 2013, a number of analytes, including hepatic enzymes, were measured on a previously unthawed visit 2 serum aliquot. Hepatic enzymes were measured on the Roche Modular P Chemistry analyzer using reagents from Roche Diagnostics (Indianapolis, IN). Using duplicate samples collected at visit 2 and stored, we calculated the coefficients of variation (CVs), which were 16% for ALT, 6% for AST, and 4% for GGT. This CV encompasses variability related to both sample processing and laboratory methods. High sensitivity C-reactive protein (hsCRP) was measured using a latex particle–enhanced immunoturbidimetric assay kit (Roche Diagnostics) and read on the Roche Modular P Chemistry analyzer (CV, 7%). Cystatin C was measured using Gentian Cystatin C reagent on the Roche Modular P Chemistry analyzer (CV, 3%).

Diabetes was defined as a fasting blood glucose of 126 mg/dL or higher, nonfasting blood glucose of 200 mg/dL or higher, a physician diagnosis of diabetes, or use of antidiabetic medication in the past 2 weeks. Alcohol intake was derived from the usual number of drinks of beer, wine, or liquor reported to be consumed per week. Hormone replacement therapy (HRT) included estrogen replacement with or without progesterone, identified from pill bottles brought to the examination. Glomerular filtration rate was estimated from cystatin C and creatinine using the Chronic Kidney Disease Collaboration algorithm [16]. BMI was calculated as weight (kilogram)/height (square meter). Factor VIII and activated partial thromboplastin time (aPTT) were available from the 1987-9 ARIC baseline visit [17,18].

VTE occurrence

ARIC participants were contacted annually by phone and asked about all hospitalizations in the previous year. Hospital records with discharge diagnoses for possible VTE events, based on a broad set of *International Classification of Diseases, Ninth Revision, Clinical Modification* discharge codes [14], were obtained from baseline through 2011. To validate the VTE events, two physicians (A.R.F. and M.C.) reviewed the records using standardized criteria [14]. A diagnosis of DVT or pulmonary embolism required positive imaging tests. We restricted DVTs for this analysis to those in the lower extremity or vena cava because the vast majority of upper extremity DVTs were the result of in-dwelling catheters. Cases were classified by the reviewers as unprovoked (no obvious cause) or provoked (associated with recent hospitalization, cancer, major trauma, surgery, or marked immobility, such as being bedridden or having a fixed orthopedic cast).

Statistical analysis

Of the 14,348 participants at ARIC visit 2, we successively excluded those who did not have any hepatic enzymes measured ($n = 975$), had a prior VTE ($n = 260$), were taking anticoagulants ($n = 95$), had heavy alcohol use (men >21 drinks/wk, women >14 drinks/wk) ($n = 374$), were not white or African American ($n = 37$), or had no follow-up after visit 2 ($n = 3$). (Those excluded for heavy alcohol use were 2–3 times as likely to have elevated hepatic enzyme concentrations.) This left 12,604 participants for the present analyses of incident VTE in relation to hepatic enzyme concentrations. Hepatic enzyme distributions were skewed and preliminary cubic spline graphs suggested nonlinearity in relation to VTE. The enzymes therefore were analyzed as categories: (a) five categories with cutpoints at 25, 50, 75, and 90th percentiles of the whole distribution, (b) high or low based on the sex-specific upper limit cutpoints (in units per liter) for normal ranges for the assays in our laboratory: ALT (women: 31 and men: 41), AST (women: 31 and men: 37), and GGT (women: 36 and men: 61). Time at risk for VTE was computed from the date of visit 2 to the earliest of the following: date of hospital discharge with incident VTE, date of death, date of last follow-up contact, or end of follow-up.

Our main hypothesis was that hepatic enzyme levels would be associated positively with VTE incidence. Cox proportional hazards models were used to calculate hazard ratios (HR) and 95% confidence intervals (CI) of incident VTE. We verified the proportional hazards assumption of the Cox models by inspection of ln(−ln) survival curves for hepatic enzyme categories. We selected possible confounding variables for regression models based on our previous prospective findings on VTE risk factors [15,17,18]. Model 1 adjusted for age (continuous), sex, and race (African American, white); Model 2 for age, race, sex/HRT (men, women using HRT, and women not using HRT), alcohol intake (continuous), diabetes status (yes or no), BMI, glomerular filtration rate, and CRP (all continuous). Model 3 included two potential mediators, factor VIII and aPTT (both continuous), from visit 1.

We also conducted three independent sensitivity analyses. First, we removed from analysis VTE cases in the first 3 years of follow-up, in case these early cases were unusual. Second, we removed from analyses participants with obesity (BMI $\geq$ 30 kg/m^2) at baseline because we considered obese participants most likely to have nonalcoholic fatty liver disease. Third, we truncated follow-up to 10 years because hepatic enzyme levels at baseline would become less relevant during late follow-up.

Results

Descriptive data

Among the 12,604 ARIC participants in this analysis, the median values (in units per liter) for ALT, AST, and GGT were 14, 20, and 21,