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Circulating levels of liver enzymes and incidence of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) cohort

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Abstract

Background—Elevated levels of circulating liver enzymes have been associated with increased risk of cardiovascular disease. Their possible association with atrial fibrillation (AF) has received little attention.

Methods—We studied 9333 men and women, age 53–75, free of AF participating in the Atherosclerosis Risk in Communities Study followed up from 1996 to 2010. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma glutamyl transpeptidase (GGT) were measured in stored plasma samples. Incident AF was ascertained from hospitalizations and death certificates. Associations between liver enzymes and AF incidence were assessed using multivariable Cox proportional hazards models.

Results—During a mean follow-up of 12 years, 1021 incident AF events were identified. Levels of AST, and to a lesser extent of ALT, showed a U-shaped association with AF risk, with higher AF risk among individuals in the two extremes of the distribution in minimally adjusted models. The associations were weakened after adjustment for potential confounders. In contrast, GGT,

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modeled as log base 2, was linearly associated with AF risk after multivariable adjustment: a doubling of GGT levels was associated with a 20% increased risk of AF (95% confidence interval, 10–30%). Additional adjustment for inflammatory markers did not appreciably affect the results. Associations were not different in men and women, in whites and blacks, among never drinkers of alcohol, and among those without prevalent heart failure.

Conclusions—In this community-based prospective study, higher levels of liver enzymes, mainly GGT, were associated with an increased risk of AF. The mechanisms underlying this association deserve further scrutiny.

Keywords

atrial fibrillation; liver disease; epidemiology; liver enzymes; cohort

Introduction

Atrial fibrillation (AF) is the most commonly diagnosed cardiac arrhythmia in clinical practice. It affects >2 million people in the United States, and this figure is projected to double by 2050 [1]. Individuals with AF are at a substantially increased risk of stroke and overall mortality [2]. Therefore, considerable interest exists in identifying risk factors and biomarkers of AF risk. To date, numerous studies have shown that multiple variables contribute to an elevated risk for AF, including major cardiovascular risk factors and biomarkers involved in diverse pathways [3, 4, 5, 6].

Liver enzymes could be a potentially novel biomarker of AF risk. Circulating liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are indicative of hepatocellular homeostasis and injury, and gamma glutamyl transpeptidase (GGT) reflects both liver injury and oxidative stress. Prior epidemiologic evidence suggests that circulating levels of liver enzymes, even in individuals without overt hepatic disease, might be associated with an increased risk of cardiovascular disease (CVD) [7], potentially due to their role as markers of nonalcoholic fatty liver disease (NAFLD) [8].

A recently published analysis from the Framingham Heart Study showed that higher levels of both ALT and AST were associated with an increased risk of AF, independently of alcohol consumption, among individuals free of clinical heart failure (HF) [9]. This association, however, needs to be replicated in large, independent prospective studies conducted in diverse populations. Also, no previous studies have assessed the association of GGT with AF incidence. Therefore, our objective was to assess the association of circulating liver enzymes (ALT, AST, GGT) with AF incidence in the Atherosclerosis Risk in Communities (ARIC) study, a large predominantly bi-racial community-based cohort.

Methods

Study population

The ARIC study is a prospective community-based study of CVD and its risk factors. At baseline (1987–89), 15,792 men and women age 45–64 were recruited from 4 communities in the US: Forsyth Co, NC; Jackson, MS; northwest suburbs of Minneapolis, MN; and

Washington County, MD. Additional exams were conducted in 1990–92 (Visit 2), 1993–95 (Visit 3), 1996–98 (Visit 4), and 2011–2013 (Visit 5). Participants were mostly white in the Washington County and Minneapolis sites, exclusively black in Jackson, and mostly white and black in Forsyth County [10].

Liver enzymes were measured in plasma samples collected during Visit 4. Therefore, only individuals attending Visit 4 were included in this analysis (n=11,656). We excluded participants with unavailable data on liver enzymes or other covariates, race other than white or black, non-whites in the Minneapolis and Washington County field centers, prevalent AF at Visit 4, missing or unreadable electrocardiogram (ECG) at baseline, individuals with excessive alcohol intake (≥ 28 g/day in men and ≥ 14 g/day in women), and those with abnormal liver enzyme levels (ALT or AST ≥ 40 U/L or GGT ≥ 110 U/L), to avoid including individuals with liver disease. Numbers of excluded individuals are presented in Figure 1. After exclusions, 9,333 participants were eligible for the analysis. Institutional Review Boards at participating institutions approved the study protocol. All participants provided written informed consent.

Measurement of liver enzymes

ALT, AST, and GGT were measured in 2010–2011 from Visit 4 plasma samples (stored at -70°C since collection in 1996–1998) using an Olympus AU400e automated chemistry analyzer (Center Valley, PA) according to the manufacturer's protocol. Inter-assay coefficients of variation were 11.1% for ALT, 8.5% for AST and 9.3% for GGT.

Ascertainment of AF

In the ARIC study, AF diagnoses have been collected through 3 different approaches: ECGs done during the study exams, hospital discharge diagnoses, and death certificates [11, 12]. At each study exam, a standard supine 12-lead resting ECG was recorded with a MAC PC Personal Cardiograph (Marquette Electronics Inc, Milwaukee, WI) and transmitted to the ARIC ECG reading center for automatic coding. All AF cases automatically detected from the study ECG were visually checked by a cardiologist [13]. Information on hospitalizations during follow-up is obtained from annual follow-up calls and surveillance of local hospitals, with hospital discharge diagnoses codes collected by trained abstractors [14]. AF during follow-up was defined if International Classification of Disease (ICD) 9th edition Clinical Modification (ICD-9-CM) 427.31 or 427.32 diagnosis codes were present in any position; AF diagnoses recorded in the same hospitalization as open cardiac surgery were not included. Finally, AF was considered present if a death certificate included the ICD-9 code 427.3 or ICD-10 code I48. We have previously shown that validity of AF ascertainment from hospital discharge codes is adequate.[11] For the present analysis, only cases ascertained from hospitalization discharge codes and death certificates after Visit 4 were included as incident cases, while study ECG-based cases and hospitalizations before Visit 4 were used to define prevalent AF at Visit 4.

Assessment of other covariates

Information on other covariates was collected during Visit 4 from questionnaires and a physical examination, with the exception of education level, which was collected at Visit 1.

Smoking status, alcohol intake, and use of antihypertensive medication were self-reported. Weight and height were obtained with the participant wearing light clothing. Body mass index (BMI) was calculated as the weight in kilograms divided by height in meters squared. Blood pressure was measured with a random-zero sphygmomanometer after 5 minutes of rest in the sitting position and was defined as the average of 2 measurements taken. Diabetes was defined as fasting glucose ≥ 126 mg/dL, nonfasting glucose ≥ 200 mg/dL, treatment for diabetes, or a self-reported diagnosis of diabetes. Plasma N-terminal prohormone of brain natriuretic peptide (NT-proBNP) was measured on a Cobas e411 analyzer using the Elecsys proBNP II immunoassay (Roche Diagnostics), and high-sensitivity C-reactive protein was measured with an immunonephelometric assay (Siemens Healthcare Diagnostics). Prevalent coronary heart disease (CHD) and HF at Visit 4 were defined as previously described [15].

Statistical analysis

We used Cox proportional hazards models to estimate the association of liver enzymes with incident AF with adjustment for potentially confounding variables. Time of follow-up was defined as the number of days between Visit 4 and AF ascertainment, death, lost to follow-up, or December 31, 2010, whichever occurred earlier. In initial analyses, liver enzymes were modeled using restricted cubic splines to explore their dose-response shape. In separate models, liver enzymes were considered untransformed and after a logarithmic transformation; because log-transformed values provided better fit to the data, analyses were conducted with transformed liver enzymes. A base 2 log-transformation was used to facilitate interpretation of the coefficients: after this transformation, hazard ratios (HR) can be interpreted as the relative increase in the hazard of AF associated with a doubling of the level of the biomarker. The dose-response analysis suggested a linear association between GGT and AF, but non-linear associations for ALT and AST. Therefore, enzymes were categorized in quintiles, using the lowest risk quintile as the reference, which was the 3rd quintile for a U-shaped association with ALT and AST, and the 1st quintile for the linear association with GGT. Finally, because the AST/ALT ratio is considered a marker of liver injury due to alcohol, we conducted an additional analysis with this variable as the main exposure.

We compared several models. Model 1 included age, sex, race, and study center. Model 2 included all variables in Model 1 plus BMI, diabetes mellitus, education level, ethanol intake, height, NT-proBNP, smoking, systolic blood pressure, use of antihypertensive medications, prevalent CHD, and prevalent HF as potential confounders of the association between liver enzymes and AF risk. Covariates for models 1 and 2 were selected based on a priori knowledge of risk factors for AF, as recommended elsewhere [16]. Finally, Model 3 included all variables in Model 2 plus incident CHD and HF after Visit 4 modeled as time-dependent covariates.

Several sensitivity analyses were conducted to evaluate the robustness of our results. First, we repeated the analysis excluding individuals with prevalent HF at Visit 4. Second, we conducted additional analyses adjusting for C-reactive protein, a biomarker of inflammation. Third, we assessed the association only among never drinkers. And, fourth, we conducted an analysis including individuals with elevated ALT or AST levels between 40 and 120 U/L,

and with elevated GGT levels between 110 U/L and 300 U/L. Finally, we tested the proportional hazards assumption including interaction terms between time and liver enzyme in the models, and exploring log(-log) survival curves. Interactions of age, sex, and race with liver enzyme levels were tested including multiplicative terms in the models.

Results

Among 9333 eligible participants free of AF at Visit 4, 1021 incident AF cases were identified during a mean of 12 years of follow-up. Table 1 and Supplementary Tables A1 and A2 show characteristics of study participants according to baseline categories of the different liver enzymes. Overall, those with higher ALT and AST were more likely to be male, white, with higher alcohol intake, taller, and had lower levels of NT-proBNP, while those with higher GGT were more likely to be male, black, diabetic, with higher BMI and alcohol intake, higher systolic blood pressure and prevalent CVD, but lower NT-proBNP.

The association of log-transformed liver enzymes, modeled as restricted cubic splines, with the incidence of AF is presented in Figure 2. Both AST and ALT showed non-linear associations with AF incidence, while the association of GGT with AF was roughly linear. Table 2 provides HR and 95% confidence intervals (95%CI) of AF by quintiles of liver enzymes. Minimally adjusted models (Model 1) supported the presence of a U-shaped association of ALT and AST with AF incidence. After adjustment for potential covariates (Model 2), however, those with low ALT or AST levels did not have a higher risk compared to individuals with average levels, and a slightly elevated risk of AF was present only in those with high AST: in Model 2, the HR (95%CI) of AF among those in the highest quintile of ALT, compared to those in the middle quintile, was 1.11 (0.91–1.36), while the corresponding figure for AST was 1.28 (1.04–1.57) (Table 2, Model 2). Compared to those in the bottom quintile of GGT levels, those in the highest quintile had a 40% increased risk of AF (HR 1.44, 95%CI 1.17–1.77), with a clear linear dose-response association (p for trend = 0.0001). The HR (95%CI) for $\log_2(\text{GGT})$ as a continuous variable in the model was 1.27 (1.17–1.38) after adjustment for age, sex, race and field center, and 1.20 (1.10–1.30) after additional adjustment for multiple confounders. No association was found between the AST/ALT ratio and AF risk (Supplementary Table A3).

In sensitivity analyses excluding 437 individuals with prevalent HF or after additionally adjusting for C-reactive protein, to reduce potential residual confounding, the results remained virtually unchanged (Supplementary Table A4), while restricting the analysis to the 2085 participants (221 AF events) that reported to be never drinkers, associations became slightly stronger, particularly for ALT and AST (supplementary table A5). We also conducted an additional analysis including 371 individuals (46 AF events) with elevated enzyme levels (between 40 and 120 U/L for ALT or AST, and between 110 and 300 U/L for GGT). The overall associations remained the same, with no strong evidence of a disproportionally elevated risk of AF among individuals in the highest group (supplementary table A6).

No significant interactions between race, sex, or age and quintiles of liver enzyme levels were observed. Finally, we did not find evidence of violation of the proportional hazards assumption.

Discussion

In this community-based prospective cohort, we found moderately strong associations between circulating levels of liver enzymes and the incidence of AF. Levels of AST, and to a lesser extent of ALT, showed a U-shaped association with AF risk, while the association between GGT and AF risk was linear: a doubling of GGT levels was associated with a 20% increased risk of AF after adjustment for potential confounders. Exclusion of individuals with HF or adjustment for C-reactive protein, a marker of systemic inflammation, did not affect the results. The associations were similar in men and women, whites and blacks, and were observed even in individuals reporting no alcohol intake.

Different pathophysiological mechanisms can explain the association between liver enzymes and AF incidence. Excessive alcohol intake leads to elevated liver enzymes, particularly GGT [17], and could also increase risk of AF [18]. Nonetheless, no association was found between the AST/ALT ratio, a marker of liver injury due to alcohol use, and AF risk. Similarly, restricting the analysis to never drinkers did not alter the results, suggesting the existence of alternative mechanisms. Also, modest elevations of liver enzymes could be present in patients with hepatic congestion derived from right-sided HF [19]. However, the reported associations were evident even after adjustment for NT-proBNP and in individuals without HF. Liver enzymes are also elevated in the presence of NAFLD [20]. This hepatic condition is common and has been associated with an increased risk of CVD through several potential pathways [8]. For example, individuals with NAFLD are more likely to have insulin resistance, increased overall visceral adiposity, and be diagnosed with the metabolic syndrome [21]. Moreover, NAFLD is associated with low-grade inflammation and increased levels of oxidative stress [22, 23]. All these factors—metabolic syndrome, inflammation, oxidative stress—have been shown to be associated with an increased risk of AF, potentially explaining the observed associations [12, 24, 25]. Consistent with this hypothesized pathway, a recent cross-sectional study among type 2 diabetics found that presence of NAFLD, assessed by ultrasonography, was associated with the prevalence of AF, even after adjustment for confounders [26]. In our analysis, liver enzymes—as possible markers of NAFLD—were also associated with AF incidence even after adjustment for cardiometabolic risk factors and markers of inflammation. However, the weak, non-linear association of AF risk with ALT and AST, and the stronger association with GGT, a marker of systemic processes such as oxidative stress, argues that our observations may be more related to systemic rather than hepatic processes. Consistent with our results, some previous studies have found GGT to be more strongly associated with incident CVD than ALT or AST [7, 27].

The published evidence on the association of circulating liver enzymes with AF is limited. An analysis including 3744 participants from the Framingham Study found that higher levels of ALT and AST were associated with an increased risk of AF in a linear fashion [9], but GGT was not evaluated. In contrast to our primary analysis, the Framingham Study

analysis included individuals with ALT or AST levels between 40 and 120 U/L. In our analysis, inclusion of individuals with levels between 40 and 120 did not change the overall shape of the association. Discrepancies between the Framingham Study analysis and our results could be due to differences in case ascertainment, the populations under study, or methods of covariate measurement. More recently, Targher and colleagues showed that GGT, but not ALT or AST, was associated with increased prevalence of AF among individuals with type 2 diabetes [26]. This association was attenuated after adjustment for ultrasonographically-defined NAFLD. To our knowledge, no other prospective studies have explored the association between circulating liver enzymes and AF risk.

Strengths and limitations

We should highlight some strengths of the present study. Our analysis included a large number of individuals from a diverse community-based cohort, with an adequate number of events to identify moderate associations. High-quality information on potential confounders was available and included in multivariable analyses. Also, losses to follow-up were kept to a minimum, reducing the risk of selection bias. Nonetheless, some limitations are evident. First, AF ascertainment relied mostly on hospitalization discharge codes, potentially missing asymptomatic cases and those managed exclusively in an outpatient setting. Previous studies, however, have showed adequate validity of this approach for epidemiologic studies [11, 28]. Second, circulating liver enzymes were only assessed once, which might lead to exposure misclassification due to within person-variability and the inability to investigate the impact of changes in these enzymes on AF risk. Third, we did not have information on the presence of valvular disease and, therefore, could not differentiate between valvular versus non-valvular AF. Finally, we focused on the study of associations, and not risk prediction. Given the only moderate strength of the observed associations (e.g. HR of 1.20 per doubling of GGT), it is unlikely that circulating liver enzymes will make significant contributions to the predictive ability of existing risk prediction models for AF [29].

In conclusion, we found that circulating liver enzymes, particularly GGT, are associated with the incidence of AF independently of cardiometabolic factors and biomarkers of inflammation. The mechanisms underlying this association and the implications for primary prevention of AF, such as the potential impact of NAFLD treatment through lifestyle interventions or medications on AF risk, deserve further scrutiny.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key questions

- What is already known about this subject?
 - Numerous studies have identified possible biomarkers for the risk of atrial fibrillation (AF) risk. Elevated levels of circulating liver enzymes have been previously associated with cardiovascular disease, but their role as biomarkers of AF risk is not well defined.
- What does this study add?
 - In a large, diverse community-based prospective study, we show that higher levels of gamma glutamyl transpeptidase, even at in the normal range, were associated with a higher risk of AF independently of other risk factors for, while the aspartate aminotransferase and alanine aminotransferase with AF risk was U-shaped.
- How might this impact on clinical practice?
 - Our results provide additional rationale to explore in more depth the role of liver dysfunction in the development of AF and the potential of gamma glutamyl transpeptidase as a biomarker of systemic processes related to AF.

Figure 1.
Flowchart of study participants, ARIC study, 1996–1998

Figure 2.

Association of blood liver enzymes with incidence of atrial fibrillation presented as hazard ratio (solid line) and 95% confidence intervals (shaded area). Results from enzyme-specific Cox proportional hazards model with $\log_2(\text{liver enzymes})$ modeled using restricted cubic splines, adjusted for age, sex, and race. Median value of the liver enzyme was considered the reference ($HR=1$). The histograms represent the frequency distribution of the liver enzymes in the study sample.

Table 1

Characteristics of study participants at Visit 4 by levels of liver enzymes, median cutoff, ARIC 1996–1998

	ALT [†]		AST [†]		GGT [†]	
	13 U/L	>13 U/L	18 U/L	>18 U/L	21 U/L	>21 U/L
N	5281	4052	5326	4007	4892	4441
Age, years	63.1 (5.7)	62.4 (5.6)	62.7 (5.7)	62.9 (5.6)	62.9 (5.7)	62.7 (5.6)
Female, %	67.1	45.5	63.3	50.4	67.1	47.4
Black, %	25.7	17.6	24.5	19.2	16.7	28.2
BMI, kg/m ²	28.4 (5.8)	29.5 (5.3)	29.0 (5.8)	28.6 (5.3)	27.8 (5.4)	30.0 (5.7)
Current smoker, %	16.7	9.7	17.3	8.8	13.8	13.4
Diabetes, %	13.6	19.4	17.7	14.0	9.4	23.5
Ethanol intake, g/day	1.9 (4.5)	2.7 (5.5)	1.9 (4.5)	2.7 (5.4)	1.9 (4.2)	2.7 (5.6)
Height, cm	165.9 (8.9)	169.1 (9.5)	166.6 (9.1)	168.3 (9.4)	166.1 (9.0)	168.7 (9.4)
High school graduate, %	42.6	42.3	43.2	41.5	43.8	41.0
Systolic BP, mmHg	127.2 (19.6)	127.2 (18.2)	127.1 (19.3)	127.4 (18.6)	125.7 (19.1)	128.9 (18.7)
Antihypertensive medication, %	42.3	43.2	43.1	42.2	36.6	49.5
NT-proBNP, pg/mL*	75.9 (105.8)	49.4 (77.0)	65.8 (97.7)	59.5 (90.5)	74.7 (99.0)	52.2 (84.9)
Prevalent CHD, %	7.6	8.0	7.4	8.3	6.3	9.3
Prevalent HF, %	4.9	4.5	4.9	4.4	3.6	5.9
ALT, U/L	9.7 (2.4)	19.1 (5.1)	11.1 (3.9)	17.4 (6.4)	11.9 (4.7)	15.9 (6.6)
AST, U/L	16.3 (3.6)	21.3 (4.9)	15.2 (2.2)	22.8 (4.0)	17.5 (4.3)	19.6 (5.2)
GGT, U/L	21.3 (12.9)	30.2 (17.2)	22.6 (13.6)	28.6 (17.2)	15.1 (3.9)	36.3 (16.0)

Values correspond to means (standard deviation) or percentage, unless otherwise noted. ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; BP: blood pressure; CHD: coronary heart disease; GGT: gamma glutamyl transpeptidase; HF: heart failure

* Geometric mean and interquartile range.

[†] All baseline characteristics have p-values <0.05 for between-group comparison except for systolic BP, antihypertensive medications, prevalent CHD, and prevalent HF in ALT and AST and age in AST and GGT.

Table 2

Hazard ratios (95% confidence intervals) of atrial fibrillation by quintiles of blood liver enzymes, ARIC 1996–2010

ALT	Q1	Q2	Q3	Q4	Q5	p-for trend*
Range, U/L	1–9	10–11	12–14	15–18	19–39	
N	2299	1524	2051	1773	1686	
AF Cases	261	159	216	191	194	
Person-years	26,446	17,916	24,578	21,265	20,341	
Model 1	1.21 (1.01–1.45)	1.05 (0.86–1.29)	1.00 (Reference)	1.02 (0.84–1.23)	1.12 (0.92–1.37)	0.29
Model 2	0.98 (0.82–1.18)	0.94 (0.77–1.16)	1.00 (Reference)	0.98 (0.81–1.19)	1.11 (0.91–1.36)	0.27
Model 3	0.96 (0.80–1.16)	0.94 (0.77–1.16)	1.00 (Reference)	0.92 (0.76–1.12)	1.05 (0.86–1.27)	0.60
AST	Q1	Q2	Q3	Q4	Q5	p-for trend*
Range, U/L	5–15	16–17	18–19	20–22	23–39	
N	2661	1786	1645	1612	1629	
AF Cases	299	194	166	162	200	
Person-years	31,033	21,146	19,934	19,220	19,213	
Model 1	1.28 (1.06–1.55)	1.11 (0.90–1.36)	1.00 (Reference)	0.98 (0.79–1.22)	1.24 (1.01–1.52)	0.24
Model 2	1.06 (0.87–1.28)	1.09 (0.89–1.34)	1.00 (Reference)	1.01 (0.81–1.25)	1.28 (1.04–1.57)	0.19
Model 3	1.10 (0.90–1.33)	1.18 (0.96–1.45)	1.00 (Reference)	1.02 (0.82–1.27)	1.28 (1.04–1.58)	0.44
GGT	Q1	Q2	Q3	Q4	Q5	p-for trend*
Range, U/L	2–14	15–18	19–24	25–33	34–109	
N	2109	1649	2005	1743	1827	
AF Cases	177	164	233	212	235	
Person-years	25,731	19,617	23,823	20,314	21,060	
Model 1	1.00 (Reference)	1.12 (0.90–1.38)	1.27 (1.04–1.56)	1.44 (1.17–1.76)	1.60 (1.31–1.95)	<0.0001
Model 2	1.00 (Reference)	1.13 (0.91–1.40)	1.21 (0.99–1.48)	1.40 (1.14–1.73)	1.44 (1.17–1.77)	0.0001
Model 3	1.00 (Reference)	1.11 (0.90–1.38)	1.16 (0.95–1.42)	1.29 (1.04–1.59)	1.30 (1.06–1.60)	0.01

Model 1: Cox proportional hazards model adjusted for age, sex, race, and study site

Model 2: Cox proportional hazards model adjusted for Model 1 variables with additional adjustment for body mass index, diabetes mellitus, education level, ethanol intake, height, N-terminal proBNP, smoking, systolic blood pressure, use of antihypertensive medications, prevalent coronary artery disease, and prevalent heart failure

Model 3: Cox proportional hazards model adjusted for Model 2 variables with additional adjustment for incident coronary artery disease or heart failure as time-dependent covariates

* P-value for linear trend in quintile number