Published in final edited form as:

Am J Cardiol. 2013 January 15; 111(2): 219–224. doi:10.1016/j.amjcard.2012.09.021.

Relation of Circulating Liver Transaminase Concentrations to Risk of New-onset Atrial Fibrillation

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Abstract

Heart failure, a strong risk factor for atrial fibrillation (AF), often is accompanied by elevated liver transaminases. We hypothesized that elevated transaminases are associated with the risk of incident AF in the community. We studied 3,744 participants (mean age 65 ± 10 years, 56.8% women) of the Framingham Heart Study Original and Offspring cohorts, free of clinical heart failure. We examined Cox proportional hazards models adjusted for standard AF risk factors (age, sex, body mass index, systolic blood pressure, electrocardiographic PR interval, anti-hypertensive treatment, smoking, diabetes, valvular heart disease, alcohol consumption) to investigate associations between baseline serum transaminase levels [alanine transaminase (ALT), aspartate transaminase (AST)] and incidence of AF in up to 10 years (29,099 person years) follow-up. During follow-up, 383 individuals developed AF. Both transaminases were significantly associated with greater risk of incident AF (hazard ratio expressed per standard deviation of natural logarithmically transformed biomarker: ALT hazard ratio 1.19, 95% confidence interval 1.07 to 1.32, $p = 0.002$; AST hazard ratio 1.12, 95% confidence interval 1.01 to 1.24, $p = 0.03$). The associations between transaminases and AF remained consistent after exclusion of participants

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with moderate-to-severe alcohol consumption. However, when added to known risk factors for AF, ALT and AST only subtly improved the prediction of AF. In conclusion, elevated transaminase concentrations are associated with increased AF incidence. The mechanisms by which higher mean transaminase concentrations are associated with incident AF remain to be determined.

Keywords

atrial fibrillation; biomarker; risk factors; liver function tests

Heart failure is one of the strongest risk factors for atrial fibrillation (AF),¹ and commonly goes along with an elevation of liver transaminases.² We hypothesized that elevation of liver transaminases also may be a marker of subclinical heart failure, and thus an indirect marker of AF risk. In addition, the current guidelines for the management of patients with AF by the American College of Cardiology, the American Heart Association and the European Society of Cardiology recommend the assessment of liver function tests for the evaluation of patients with an initial, incident diagnosis of AF, at least if their heart rate is difficult to control.³ Since many drugs prescribed in the context of AF management are metabolized hepatically or affect liver function,⁴ presumably, the guidelines recommend the assessment of liver function for pharmacodynamic reasons. With the present study we therefore sought to assess whether transaminases are associated with risk of new-onset AF in a community-based sample.

Methods

The Framingham Heart Study was founded in 1948 by enrolling 5,209 individuals who were followed regularly every 2 years.⁵ For the present study, we examined 1,401 participants who attended the 20th examination cycle (1986 to 1990). Starting in 1971, the offspring of the Original cohort and their spouses were enrolled in the Framingham Offspring Study (n = 5,124), and were followed every 4 to 8 years. Offspring participants who attended the 7th examination cycle (1998 to 2001) were eligible (n = 3,539). We combined participants from both the Original and the Offspring cohorts and excluded 1,196 participants for the following indications (detailed in Supplemental Table 1 [online only]): age <45 years at examination (since the incidence of AF below this threshold is very low, and to make the age distribution of the 2 cohorts more comparable); did not attend the examination on site; incomplete or missing follow-up; incomplete covariate information; prevalent AF or heart failure; and transaminases exceeding 3 times the upper limit of the normal (>120 U/l) [suggestive of prevalent liver disease; values $\geq$ 120 U/l are considered only mildly elevated⁶]. The Boston University Medical Center Institutional Review Board approved the study protocols, and participants provided written informed consent at each examination.

We studied AF risk over up to 10 years follow up from the baseline examinations (cohort 20th (1986 to 1990) and Offspring 7th (1998 to 2001) examination). An AF diagnosis was based on atrial fibrillation or atrial flutter on electrocardiograms, or medical record information from routinely collected Framingham Heart Study examinations and in- or outpatient medical visits. Health history updates during examination visits and between examinations also contained a routine question regarding AF. If any cardiovascular, cancer or orthopedic diagnosis or AF was indicated, all available medical records to substantiate diagnoses were reviewed. All incident AF electrocardiograms were individually reviewed by at least 2 Framingham cardiologists.⁷

Clinical covariates were routinely ascertained during the Framingham Heart Study examination visits. Physicians performed interviews, physical examinations, and collected data on self-reported medication use (e.g. hypertension and statins), smoking status and alcohol consumption. Participants were considered current smokers if they reported smoking cigarettes during the preceding year. Alcohol consumption was categorized as light, or moderate / heavy drinking for men, if they consumed 1 to 14 or >14 drinks per week, respectively, and for women, if they consumed 1 to 7 or >7 drinks per week, respectively. Systolic blood pressure was assessed as the average of 2 seated measurements. A systolic murmur of grade 3 or more on a scale of 6, or any diastolic murmur was considered a clinically significant heart murmur. A dedicated end-point committee adjudicated all diagnoses of heart failure based on criteria published elsewhere.⁸

Fasting blood samples were drawn and processed immediately for storage at -70°C during the examination visits. Liver function tests assessed at the baseline examination included alanine transaminase (ALT, previously referred to as alanine aminotransferase, glutamic pyruvic transaminase or SGPT) and aspartate transaminase (AST, previously referred to as aspartate aminotransferase, glutamic oxaloacetic transaminase or SGOT). In the Original cohort, ALT and AST were measured by a Cobas Mira Analyzer using Roche Diagnostics reagents (Roche Diagnostics Corporation, Indianapolis, Indiana). In the Offspring cohort, ALT and AST were determined enzymatically using a Roche Hitachi 911 analyzer (Roche Diagnostics Corporation, Indianapolis, Indiana). For ALT, the intra- and inter-assay coefficients of variation were 3.8% and 4.4%, respectively. For AST, the intra- and inter-assay coefficients of variation were 3.1% and 4.5%, respectively. Details on the distribution of ALT and AST are provided in Supplemental Table 2 and Supplemental Figure 1 (online only). Both assays had comparable detection ranges. C-reactive protein (CRP) was available only in the Offspring cohort and was determined using the Dade Behring BN 100 high sensitivity CRP reagent kit. Intra- and inter-assay coefficients of variation were 3.2% and 5.3%, respectively.

All discrete variables are expressed as frequencies and percentages. Untransformed biomarkers are summarized with medians and 25th/75th percentiles; all other continuous variables including natural logarithmically transformed ALT, AST and CRP are summarized with means $\pm$ standard deviation. Log-transformed ALT and AST were standardized to mean = 0 and standard deviation = 1.

Interaction testing did not suggest effect modification by sex, so Cox models are sex-pooled. We used Cox proportional hazards models to assess the relations between ALT and AST, and incidence of AF. The follow up time was up to 10 years; participants were followed from their baseline examination until the development of AF. Censoring occurred at the time of death or at the end of follow-up. All models adjusted for age, sex and cohort. Further multivariable models additionally adjusted for baseline risk factors included in the Framingham AF risk prediction model: body mass index, systolic blood pressure, electrocardiographic PR interval, anti-hypertensive treatment, smoking, diabetes, and valvular heart disease.⁷ To account for its potential involvement in liver pathology, we also incorporated alcohol consumption into the model. We assessed the assumption of proportional hazards by calculating a supremum test based on the cumulative sums of Martingale-based residuals.⁹ Correlation between the clinically related transaminases was assessed by Pearson correlation; models including both transaminases were not assessed due to potential collinearity. Instead, we forced inclusion of previously established AF risk factors and used stepwise, automated selection process with $p = 0.05$ to determine which transaminase would be selected. Effect estimates and confidence intervals for ALT and AST are shown for a 1 standard deviation increase in the log-transformed biomarker values. For graphical presentation, we used cumulative hazard plots, and spline plots with 3 knots

around the untransformed median biomarker values of 18.0 U/l for ALT and 21.0 U/l for AST.

In secondary analyses, we assessed whether inflammation as measured by CRP might partially mediate the risk associated with elevated transaminases. As sensitivity analyses, we restricted our association analysis to individuals at the baseline examination with transaminases within the reference range (transaminase values ≤ 40 U/l), and we excluded participants with moderate / heavy alcohol consumption. We also adjusted for the competing risk of death during follow up. Further analyses additionally adjusted for the interim occurrence of heart failure and myocardial infarction, respectively.

In supplemental analyses, we assessed the ability of the transaminases to improve risk prediction of AF. To ensure complete follow up for all individuals, we calculated all prediction analyses restricted to 8-year risk of AF. We calculated C-statistics and the difference in the C-statistic between the model with and without the respective transaminase (delta-C).¹⁰ To assess calibration, we calculated a Hosmer-Lemeshow statistic adapted for survival analyses.¹¹ In addition, we investigated the integrated discrimination improvement (IDI) and the relative IDI for each transaminase.¹² Reclassification of AF cases based on the risk score including transaminases versus the score without the biomarkers was determined by both a continuous and a user defined net reclassification improvement (NRI) analysis.¹² Eight-year risk categories for NRI were selected as 5%, 5 to 10%, and 10%. Confidence intervals for prediction analyses were calculated using bootstrapping and 1000 times re-sampling.

Results

Our overall study consisted of 3,744 participants, 875 of whom were derived from the Original cohort and 2,869 from the Offspring cohort. Clinical characteristics and the distributions of biomarkers are provided in Table 1. The mean follow-up duration was 7.77 ± 2 years (minimum 0.04 years, maximum 10.00 years) in 29,099 person-years of observation. During follow-up, 383 participants developed AF (Table 2). The mean age at the time of AF diagnosis was 76 years. At baseline, participants who subsequently developed AF were on average 6.8 years older than those who remained AF-free.

In an age-, sex- and cohort-adjusted model, ALT was significantly associated with incident AF; AST slightly missed statistical significance. In the multivariable-adjusted model, both ALT and AST were significantly associated with incident AF (Table 3, upper part). Cumulative hazard curves illustrate the incidence of AF for individuals with baseline transaminases levels within reference limits (≤ 40 U/l) versus those with elevated levels (>40 U/l) (Figure 1, Left Panel, ALT and Right Panel, AST). Spline plots illustrate the increased risk of AF by increased transaminase values (Supplemental Figure 2 [online only], Left Panel, ALT and Right Panel, AST). For ALT, a hazard ratio of 2 is reached at untransformed values around 80 U/l, a hazard ratio of 3 at around 120 U/l, and a hazard ratio of 4 at around 150 U/l. ALT and AST were highly correlated ($r = 0.73$). In the Offspring cohort, neither of the transaminases was significantly correlated with CRP ($r = -0.07$ ALT and $r = 0.05$ AST). By stepwise regression, ALT, but not AST reached statistical significance for risk of AF once established risk factors were considered.

Secondary analyses are presented in bottom of Table 3. We additionally adjusted our model for CRP (available in Offspring cohort only); the effect estimates minimally changed, and ALT remained significantly associated with new-onset AF, but AST did not. Consideration of death as a competing risk did not affect the associations. The incorporation of interim heart failure into the multivariable adjusted model did not change the association of

transaminases with AF risk. After inclusion of interim myocardial infarction during follow up, hazard ratios were slightly diminished; ALT remained significantly associated, but AST was not statistically significantly associated with AF. Restricting our analyses to individuals who presented with transaminases within normal limits at baseline, the effect estimates for both ALT and AST remained in the same direction, but failed to reach statistical significance. Finally, we excluded participants with moderate to severe alcohol consumption, and both assessed transaminases remained significantly associated with incident AF after multivariable adjustment.

We assessed the ability of transaminases to improve AF risk prediction after 8 years of follow up as supplemental analyses (Supplemental Tables 3 and 4 [online only]). Models showed good calibration for both ALT and AST. The predictive ability of both ALT and AST, determined by an increase in the C-statistic, the absolute and relative integrated discrimination improvement, and the user defined net reclassification improvement, failed to reach significance. Only the continuous net reclassification improvement metric suggested modest significant prediction improvement (17.8% for ALT, 16.3% for AST).

Discussion

In our study we found evidence that impaired liver function as assessed by elevation of transaminases was significantly associated with incident AF over a 10-year follow-up period with multivariable adjustment for risk factors from a widely validated AF risk score. We further report that ALT and AST only subtly improved the prediction of AF when added to risk factors from an established AF risk score.

To date, numerous risk factors for AF have been described,¹ but the literature on AF and liver function is sparse. Only 1 case report describes a relation between the occurrence of AF in the context of manifest liver disease.¹³ Another study reported that almost 28% of outpatients with AF presented with transaminase elevation >40 U/L; however, no suggestion was made regarding the causality or temporality of this observation.¹⁴

We found that transaminase elevation is associated with a moderate increased risk in incident AF. However, we are uncertain why ALT appeared to be more consistently associated with AF than AST. ALT is highly liver-specific and localized in the cytosol,¹⁵ whereas AST is present also in the mitochondria of various organs.¹⁶ Both biomarkers indicate disintegration of liver cells, but ALT may be released more readily and thus occur more frequently.

Whereas we found an association between transaminases and AF, the underlying pathophysiological pathways remain unclear and there are several plausible possibilities. The association might be due to preclinical heart failure. Heart failure and AF are closely related and share the burden of risk factors. Transaminase elevation is common in heart failure², particularly in advanced stages.¹⁷ We excluded individuals with clinical heart failure at baseline. Also, adjustment for clinically relevant interim heart failure, during follow up did not change our effect estimates for ALT or AST. Yet we hypothesize, but cannot prove, that alterations in hepatic function presage heart failure. Regarding other potentially involved pathways, several investigations consistently found increased concentrations of transaminases in the context of the metabolic syndrome,^{18–20} oxidative stress and inflammation, and non-alcoholic fatty liver disease has been reported to be the most common cause.²¹ When we adjusted for CRP, marking oxidative stress and inflammation,²² the significance of the association with AF diminished for ALT and vanished for AST. Other factors possibly linking non-alcoholic fatty liver disease, oxidative

stress / inflammation and AF are a deranged adipokine profile, hypercoagulability, endothelial dysfunction, and accelerated progression of atherosclerosis.²³

Alcohol consumption, leading to transaminase elevation,²⁴ was a last mechanism we considered to explain the relation between transaminase elevation and AF risk. To reflect the importance of alcohol, all of our multivariable models incorporated adjustment for alcohol consumption. Our sensitivity analysis excluded all participants with moderate or heavy alcohol intake, and the associations between transaminases and AF risk remained largely unchanged. Yet, it is possible that the true extent of alcohol use was misclassified due to participants' non-disclosure of their true drinking habits.

Overall, the association between transaminases and AF is likely to be multifactorial. We acknowledge that residual confounding may partially or completely explain the association. For instance, natriuretic peptides (which were unavailable at the index examination) are a valuable diagnostic and predictive marker of cardiac dysfunction,²⁵ are correlated with degree of liver dysfunction,²⁶ and also are strongly associated with AF.^{27,28}

We were also interested in the association between transaminases and AF because of guideline-based recommendation to assess liver function in patients with incident, first episode of AF.³ We note that the recommendation is undoubtedly for pharmacodynamic reasons. Almost all antiarrhythmic and anticoagulant drugs are at least partly eliminated hepatically, and their half-life and clearance are affected in the setting of impaired liver function.⁴ Impaired liver function constitutes an increased risk for bleeding complications, a circumstance that led to the incorporation of liver function into clinical scores like HAS-BLED to assess the risk of bleeding.²⁹

In our supplemental analysis, we also aimed to identify the potential of transaminases to contribute to AF risk prediction. Both ALT and AST subtly improved the prediction of AF beyond previously established factors. The discrepancy between a transaminase–AF association, yet weak predictive abilities, requires careful interpretation. One might be that transaminases only are an imperfect marker of a truly underlying condition.

Our study results benefit from a well-phenotyped sample with highly systematic follow up and detailed outcome ascertainment. However, a number of limitations need to be considered. Our sample is predominantly of European descent. We thus cannot comment on individuals of different ethnic/racial backgrounds. Despite careful assessment of each AF event, the arrhythmia is often asymptomatic and might thus have been missed during case ascertainment. Further, different subtypes of AF exist. We investigated overall AF only and therefore cannot comment on the association of transaminases depending on AF type (e.g., paroxysmal, permanent atrial fibrillation or flutter). Also, we cannot comment on whether transaminase levels influence the progression of AF from a paroxysmal to a permanent type. Our study was limited by a fixed sample size, the lack of a validation sample, and availability of CRP in the Offspring cohort only. Liver function in its entirety is only partly reflected by transaminases. Other liver related biomarkers, in particular bilirubin, alkaline phosphate, and gamma-glutamyltransferase, were not consistently available in the investigated examination cycles. Also, transaminases were assessed at baseline only; we could not investigate the relation of variation in transaminases over time to incident AF risk. Further, complete 10-year follow up was not available for all participants; we thus had to restrict our risk prediction analysis to 8 years of follow up. We cannot exclude residual confounding.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the National Institutes of Health, Bethesda, Maryland [grant numbers N01-HC25195, 6R01-NS17950, grant number 1R01HL092577 to Dr. Benjamin and Dr. Ellinor, grant number N01HC25195 to Dr. Benjamin and Dr. Vasan, grant numbers 1R01HL101056, 1R01HL102214, 1R01AG028321 to Dr. Benjamin, grant numbers 5R21DA027021, 1R01HL104156, 1K24HL105780 to Dr. Ellinor, and grant number 1K08DK090150-01 to Dr. Calderwood], by the German Heart Foundation, Frankfurt/Main, Germany to Dr. Sinner, by the American Heart Association, Dallas, Texas [grant number 09FTF2190028 to Dr. Magnani], and partially by the Evans Center for Interdisciplinary Biomedical Research (<http://www.bumc.bu.edu/evanscenteribr/>) ARC on Atrial Fibrillation at Boston University, Boston, Massachusetts (to Dr. Benjamin and Dr. Magnani)

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Figure 1. Cumulative hazard curves for the incidence of atrial fibrillation (AF) are depicted by transaminase values ≤40 U/l vs. >40 U/l; p-values are derived from log-rank tests. Left Panel: ALT – alanine aminotransferase; Right Panel: AST – aspartate aminotransferase.

Table 1

Baseline characteristics of the study sample

Variable	Total sample (n = 3,744)
Clinical	
Age (years)	65 ± 10
Women	2127 (56.8%)
Current smoker	454 (12.1%)
Light alcohol drinker	1769 (47.3%)
Moderate / heavy alcohol drinker	636 (17.0%)
Body mass index (kg/m ²)	27.8 ± 5.2
Systolic blood pressure (mm Hg)	132 ± 21
Diastolic blood pressure (mm Hg)	75 ± 10
Heart rate (beats / minute)	66 ± 11
PR interval (ms)	168 ± 28
Diabetes mellitus	360 (9.6%)
Antihypertensive treatment	1408 (37.6%)
Statin medication use	532 (14.2%)
Significant cardiac murmur	120 (3.2%)
Biomarkers	
Alanine transaminase (U/l)	19 (14–25)
Log _e alanine transaminase	3.0 ± 0.4
Aspartate transaminase (U/l)	21 (18–25)
Log _e aspartate transaminase	3.1 ± 0.3
C-reactive protein (mg/l)	2.2 (1.0–5.2)
Log _e C-reactive protein	0.8 ± 1.1

Untransformed Biomarkers expressed as median (25th–75th percentile), all other continuous variables expressed as mean ± SD; categorical variables are n (%). C-reactive protein available in the Offspring cohort only.

Table 2

Incidence of atrial fibrillation

	n event	n total	Person-years	AF incidence / 1000 person years
Total sample	383	3744	29,099	13.2
40U/l both markers	348	3744	27,204	12.8
>40 U/l either marker	35	252	1894	18.5

Table 3

Cox proportional hazard models relating transaminases to incidence of atrial fibrillation

Adjustments	ALT		AST	
	HR (95% CI)	P	HR (95% CI)	P
Primary models				
Age and sex	1.21 (1.09–1.34)	<0.001	1.11 (1.00–1.23)	0.05
Multivariable	1.19 (1.07–1.32)	0.002	1.12 (1.01–1.24)	0.03
Secondary models				
Multivariable model with additional adjustments				
C-reactive protein	1.18 (1.04–1.35)	0.01	1.10 (0.98–1.24)	0.12
Competing risk of death during follow up	1.21 (1.08–1.35)	<0.001	1.12 (1.01–1.25)	0.03
Interim heart failure	1.19 (1.06–1.32)	0.002	1.12 (1.01–1.24)	0.03
Interim myocardial infarction	1.20 (1.07–1.34)	0.002	1.10 (0.99–1.22)	0.08
Restricting to transaminases < 40U/l	1.14 (0.99–1.32)	0.07	1.06 (0.93–1.22)	0.39
Excluding moderate/heavy alcohol consumption	1.28 (1.10–1.39)	<0.001	1.18 (1.05–1.32)	0.005

Multivariable adjustment included age, sex, body mass index, alcohol consumption, smoking status, diabetes mellitus, antihypertensive treatment, cardiac murmur, PR interval and systolic blood pressure. HRs expressed per 1 SD of log_e ALT or log_e AST.

ALT – alanine transaminase; AST – aspartate transaminase; HR – hazard ratio.