The Association of Gamma-Glutamyl Transferase and Atrial Fibrillation

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Abstract

Background: Atrial fibrillation (AF) is the most commonly diagnosed cardiac arrhythmia in clinical practice and is related to significant morbidity and mortality. AF etiology and thus, predictive biomarkers are currently lacking. Liver enzymes have shown a correlation to cardiovascular disease. Gamma-glutamyl transferase (GGT) is a liver enzyme associated with oxidative stress that is postulated to have a link to AF occurrence. Researchers have recently placed emphasis on discovering a potential biomarker to predict AF. An elevation of systemic serum GGT and the association with the risk of AF development is the area of interest.

Methods: Exhaustive search of available medical literature was performed using MEDLINE-Ovid, MEDLINE-Pubmed, Web of Science, Google Scholar, and UpToDate. Articles were determined relevant based on keywords and eligibility criteria.

Results: Nine articles were reviewed and two were deemed relevant. Two observational studies were assessed for quality and critically reviewed. One study found that those in the highest quintile of GGT levels had a 40% increased risk of AF (HR 1.44, (95% CI 1.17-1.77). Another study found that there was a log-linear positive association of GGT with AF risk in analyses initially adjusted for age.

Conclusion: The two studies both indicated an elevation in GGT and may be associated as a biomarker for the development of AF. Further study of this correlation is indicated before this biomarker can be implemented in clinical practice as a screening tool for AF.

Keywords: Atrial fibrillation, arrhythmias, liver enzymes, gamma-glutamyl transferase

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Biography
[Redacted for privacy]
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Table 1: Quality Assessment of Reviewed Studies

List of Abbreviations

AF Atrial fibrillation
GGT Gamma-glutamyl transferase
EKG Electrocardiogram
CVD Cardiovascular Disease
AST Aspartate aminotransferase
ALT Alanine aminotransferase
The Association of Gamma-Glutamyl Transferase and Atrial Fibriallation

BACKGROUND
Atrial fibrillation (AF) is the most common chronic cardiac arrhythmia that affects approximately 9% of individuals over the age of 80, and it is projected that 5.6 million US adults will have AF by the year 2050.\(^1\)\(^2\) AF incidence increases with age and importance of detection of this arrhythmia proves to be of increased interest with the aging population. Those with AF are at increased risk for stroke and significant morbidity and mortality, due to the increased susceptibility of thrombus formation as a result of atrial stasis.\(^1\) Due to its prevalence, extensive knowledge of AF is vitally important to clinicians and researchers alike.

The mechanism of AF is poorly understood; however, the association of biochemical systemic inflammation and the development of AF has gained attention by researchers. In the past, the biomarkers that have been studied for AF prediction include platelet markers and liver enzymes, such as aspartate aminotransferase (AST), alanine aminotransferase (AST), and gamma-glutamyl transferase (GGT). An elevation of liver enzymes has been shown to be associated with increased risk of cardiovascular disease, thus prompting researchers to investigate the association with other cardiac abnormalities.\(^3\) An area of focus has also been placed on specific enzymes rather than a generalized group that has shown a potential correlation.

Recently, GGT has gained particular interest in the research community for its potential to predict the risk of AF development. GGT has been used as an indicator of hepatic or biliary disease and has been linked with increased oxidative stress.\(^4\) These particular liver enzymes are used in clinical practice to detect liver cell damage or bile
flow interference. The goal of this study is to investigate if an elevation in serum GGT is an appropriate predictor of the development of AF when compared to populations with a low to normal serum GGT.

METHODS
An exhaustive search of available literature was conducted in June 2016 using the following research platforms: MEDLINE-Ovid, MEDLINE-Pubmed, Web of Science, Google Scholar, and UpToDate. Literature eligibility was determined based on keywords and eligibility criteria. Keywords included: gamma-glutamyl transferase, liver enzymes, atrial fibrillation, and arrhythmias. Studies were included if sampling from the general population and comparing outcomes to those with atrial fibrillation. The intervention assessed was a comparison to those with an elevated serum GGT to low to normal GGT. The outcome was AF. Animal studies and non-English language studies were excluded. Relevant articles were deemed reputable using Grading of Recommendation Assessment, Development and Evaluation (GRADE) working group guidelines.

RESULTS
The initial literature search produced 9 articles. Titles and abstracts were screened for eligibility based on keywords and eligibility criteria. Two articles were chosen that fit the eligibility criteria. The 2 articles examined adult populations initially free of atrial fibrillation. The level of serum GGT prior to AF development was evaluated and compared to those who did not develop AF in the study. One study evaluated men and women, while the other study evaluated Finnish men. Both studies evaluated the populations retrospectively.

Alonso et al
This community-based cohort study\textsuperscript{6} evaluated the association between circulation liver enzymes and AF incidence. The study included 9333 men and women, age 53-75 free of AF participating in Atherosclerosis Risk in Communities (ARIC) Study. The ARIC is aimed to study CVD and its risk factors. There were 15 792 men and women who were recruited from 4 communities in the US: Forsyth Co, NC; Jackson, MS; northwest suburbs of Minneapolis, MN; and Washington County, MD. A majority of participants in Washington County and Minneapolis sites were white. Jackson participants were black. Forsyth County were white and black. The study followed individuals from 1996-2010.\textsuperscript{6}

Baseline exams were conducted in 1987-89. Additional exams were conducted in 1990-92 (visit 2), 1993-95 (visit 3), 1996-98 (visit 4), and 2011-2013 (visit 5). Liver enzymes were measured in plasma samples collected during visit 4, thus only participants that attended visit 4 were included in the analysis (n=11 656). Additional exclusion of participants were: participants with unavailable data on liver enzymes or other covariates, race other than white or black, non-whites in Minneapolis and Washington County field centers, prevalent AF at visit 4, missing or unreadable electrocardiogram (EKG) 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. Following exclusion, 9333 participants were eligible.\textsuperscript{6}

ALT, AST, and GGT samples were collected in 1996-1998 and were stored at -70°C. The samples were measured in 2010-2011 from visit 4 plasma samples using an Olympus AU400e automated chemistry analyzer in accordance to the manufacturer’s
protocol. AF diagnoses were collected from EKGs performed during study exams, hospital discharge diagnoses, and death certificates. A standard supine 12-lead resting EKG was recorded with a MAC PC Personal Cardiograph and transmitted to the ARIC EKG reading center for automatic coding at each study exam. All detected AF cases were visually reviewed by a cardiologist.  

Statistical analysis was completed using Cox proportional hazard models to estimate liver enzyme with incident AF association, with adjustment for confounding variables. Initially, liver enzymes were modeled using restricted cubic splines to investigate the dose-response shape and liver enzymes were considered untransformed. A base 2 log-transformation was used to facilitate interpretation of coefficients that showed after transformation, hazard ratios (HR) can be interpreted as the relative increase in risk of AF associated with doubling of the level of serum liver enzyme. The dose-response analysis suggested a linear association between GGT and AF, but non-linear for ALT and AST. Enzymes were categorized in quintiles using the lowest risk quintile as reference. Those in the highest quintile of GGT levels 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), when comparing to those in the bottom quintile of GGT levels. The HR (95%CI) for log₂(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.  

Kunutsor et al.

The goal of this cross-sectional study was to assess the associations of baseline and long-term GGT activity with the risk of development of AF, heart failure, and/or
ventricular arrhythmias. The study involved 1780 Finnish men in the Kuopio Ischaemic Heart Disease (KIHD) study. The mean of participants was 53 (SD:5) years. Baseline characteristics were obtained using a questionnaire that assessed age, alcohol consumption, smoking status, left ventricular hypertrophy, history of diabetes, history of hypertension, history of coronary heart disease, use of antihypertensives, and use of medication for dyslipidemia. Physical baseline measurements included body mass index, systolic blood pressure, diastolic blood pressure, and resting heart rate. Lipid markers included total cholesterol, high-density lipoprotein cholesterol, and triglycerides. Metabolic, inflammatory, and renal markers included fasting plasma glucose, serum creatinine, C-reactive protein, and estimated glomerular filtration rate.

Baseline GGT was taken and then repeat measurements were taken at 4 and 11 years after baseline. The baseline \( \log_e \) GGT (U/L) mean in standard deviation or percent was 3.11 (0.63). The repeat measurements were available in a random sample 624 men, yielding a total of 1143 repeat measurements of GGT. There were 336 incident AF events (annual rate 8.93/1000 person-years at risk; 95% CI: 8.03-9.94). Baseline GGT values were higher in men with diabetes compared to men without diabetes, higher in men with a history of hypertension compared to men without a history of hypertension and higher in current smokers compared to non-smokers. There was a log-linear positive association of GGT with AF risk in analyses initially adjusted for age. The regression dilution ratio of \( \log_e \) GGT was 0.68 (95% CI: 0.61-0.74). After correction for within person variability, HR for AF was 1.06 (0.88-1.27).
DISCUSSION

Finding a predictive biomarker for AF is important for clinical practice due to the morbidity and mortality resulting from AF complications. The two reviewed articles\textsuperscript{6,7} suggest an elevation in serum GGT may predict the development of AF. Although the true magnitude of that risk is unknown as there is a lack of precision with the Kunutsor et al study\textsuperscript{7} and some inconsistency with the results as demonstrated by the HR in the Alonso et al study\textsuperscript{6} being significant (HR 1.44, 95% CI 1.17-1.77) while the other study\textsuperscript{7} had a less significant HR (1.06, 95% CI 0.88-1.27). Additionally, Alonso et al\textsuperscript{6} included participants of the Atherosclerosis Risk in Communities (ARIC) cohort, which potentiates selection bias. In their investigation of AF, the population was exclusive to whites and blacks, and excluded any other ethnic groups. The KIHD study by Kunutsor et al\textsuperscript{7}, was exclusive to middle-aged Finnish men. The exclusion of other ethnic groups and women shows a selection bias and fails to allow the results to be applied across various populations. Although the KIHD study has little loss to follow-up, the sample size of 1780 participants was small. The retrospective nature of both of these studies may have underestimated AF cases due to numerous initial AF events having the ability to spontaneously resolve within the first 24 hours of onset.\textsuperscript{1} Specifically, the Kunutsor et al study\textsuperscript{7} did not delineate if AF was paroxysmal or treated by cardioversion due to data being obtained from hospital records. Due to these limitations, more studies would be warranted in order to solidify this correlation.

The relation of AF and increased GGT level remains an area of further research. Tekin et al\textsuperscript{9} took interest in the correlation of both AF and GGT having an association
with systemic inflammation and oxidative stress and their study has shown that patients
with chronic AF have an increase in serum GGT activity when compared to those without
AF. The logistic regression analysis of this study portrayed that serum GGT activity was
significantly and independently associated with AF. Additionally, GGT shows to be a
possible marker to identify patients at risk for AF recurrence after catheter ablation.\(^\text{10}\)
This biomarker would prove helpful in identifying which individuals would be more
likely to maintain normal sinus rhythm post-ablation. The link of elevated systemic GGT
and AF remains an area where further studies area indicated.

**CONCLUSION**

AF remains an important medical condition due to its prevalence and the
increasing incidence with the aging population. The studies reviewed suggest serum GGT
as a potential biomarker to predict the risk of AF development. The importance is
exemplified due to the significant morbidity and mortality experienced by complications
of individuals affected with AF. Further studies of the association of AF and serum GGT
are advised. With insight of AF predictability, it could potentially guide researchers in the
direction to better understand the etiology of AF, which remains currently undiscovered.
This discovery is likely to dramatically decrease the high costs associated with the
hospitalization of AF, AF-related complications, and maintenance therapy. Knowledge of
the cause of AF could prove to be a monumental discovery in medicine and the
improvement of the morbidity of those at risk for AF.
References


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\(^a\) Limited participant inclusion criteria to the exclusion of other races beyond white and black  
\(^b\) Only included middle-aged Finnish men from eastern Finland  
\(^c\) Small sample size