HOSPITAL CHRONICLES 2012, 7(3): 156–161

ORIGINAL ARTICLE

# Elevated Levels Within the Normal Limits of Liver Enzymes in Patients With Atrial Fibrillation

Spyros Tsikrikas, MD,[1] Konstantinos P. Letsas, MD, FESC,[1] Panagiotis Korantzopoulos, MD, PhD,[2] Charalampos Charalampous, MD,[1] Charalampos Ntavelas, MD,[1] George Bakosis, MD,[1] Charalampos Kavvouras, MD,[1] Dimitrios Asvestas, MD,[1] Antonios Sideris, MD[1]

*[1]Second Department of Cardiology, Evagelismos General Hospital of Athens, Athens, Greece*
*[2]Department of Cardiology, University Hospital of Ioannina, Ioannina, Greece*

**KEY WORDS:** *atrial fibrillation; γ-glutamyltransferase; alanine transaminase; inflammation; oxidative stress*

**Abbreviations**
ACC = American College of Cardiology
AF = atrial fibrillation
AHA = American Heart Association
ALT = alanine transaminase
BMI = body mass index
γ-GT = gamma-glutamyltransferase
CAD = coronary artery disease
CI = confidence interval(s)
CRP = C-reactive protein
ESC = European Society of Cardiology
hs-CRP = high sensitivity-C-reactive protein
LA = left atrium
LAD = left atrial diameter
LVEF = left ventricular ejection fraction
LVEDD = left ventricular end-diastolic diameter
LVESD = left ventricular end-systolic diameter
NADPH = nicotinamide adenosine dinucleotide phosphate
PAF = paroxysmal atrial fibrillation
PersAF = persistent atrial fibrillation
ROS = reactive oxygen species
WBC = white blood cells

*Corresponding author:*
Konstantinos P. Letsas, MD, FESC
Second Department of Cardiology, Evagelismos Hospital, 10676, Athens, Greece
Fax: +30-210-6513317
e-mail: k.letsas@mail.gr

*Manuscript received February 12, 2012; Revised manuscript received April 26, 2012; Accepted June 1, 2012*

## ABSTRACT

**BACKGROUND:** Emerging evidence suggests that a strong link exists between certain liver enzymes such as γ-glutamyltransferase (γ-GT) and alanine transaminase (ALT) and cardiovascular diseases independently of alcohol intake. Elevated levels of γ-GT and ALT within normal values are considered as markers of inflammation and oxidative stress independent of the metabolic syndrome.

**OBJECTIVE:** This pilot observational study was conducted to evaluate serum levels of γ-GT and ALT within normal values in different atrial fibrillation (AF) populations.

**METHODS:** Consecutive patients with AF and healthy control subjects were screened. Clinical and echocardiographic characteristics were carefully recorded. In each participant, serum levels of γ-GT and ALT along with conventional inflammatory markers were determined. The final study population consisted of 81 patients with paroxysmal AF, 45 patients with persistent AF, and 39 control subjects.

**RESULTS:** Serum γ-GT levels within normal values were significantly elevated in patients with paroxysmal (30.40±12.34 U/L) and persistent AF (38.38±18.11 U/L) in relation to control population (24.03±11.73 U/L) ($p<0.001$). Of note, γ-GT concentration was significantly higher in patients with persistent AF compared to those with paroxysmal AF ($p = 0.010$). Serum ALT levels were significantly higher in patients with paroxysmal (27.51±10.23 U/L) and persistent AF (28.73±9.34 U/L) compared to controls (20.26±9.34 U/L) ($p<0.001$). In multinomial logistic regression analysis, the relative risk ratio of developing paroxysmal AF per 1 U/L increase in ALT was 1.08 (CI: 1.02-1.14, p: 0.011). The relative risk ratio of having persistent AF per 1 U/L increase in γ-GT was 1.06 (CI: 1.01-1.12, $p = 0.013$).

**CONCLUSION:** This study shows an association between increased levels within normal reference intervals of liver enzymes such as γ-GT and ALT and AF. Serum γ-GT levels may be related to AF burden. Larger studies are needed to examine this potential association.

Conflict of interest: none declared

## INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice and contributes to impaired quality of life and increased morbidity and mortality.[1-3] The pathogenesis of AF is associated with the development of an appropriate atrial substrate related to abnormalities in atrial architecture such as atrial dilatation, fibrosis, apoptotic phenomena, and tissue dedifferentiation.[4-6] Accumulating data suggest that inflammation and oxidative stress play a pivotal role in the genesis and perpetuation of AF.[7] Atrial biopsies taken from patients with AF have demonstrated evidence of inflammatory infiltrates compared with healthy individuals, a fact that strongly supports the hypothesis that ongoing inflammation may lead to structural remodeling of the atria, and thus to promote the perpetuation of AF.[8] In atrial myocardium during AF, there is substantial oxidative damage that may contribute to atrial remodeling. Oxidative stress results from excessive reactive oxygen species (ROS), which are involved in pathological processes such as DNA damage, apoptosis, and cellular hypertrophy as well as signal pathway modulation.[9] Increased oxidative stress also underlies the early electrophysiological remodeling associated with AF.[7] Elevated levels of several markers of the inflammatory cascade and oxidative stress have been reported in different AF populations.[10]

Emerging evidence suggests that a strong link exists between certain liver enzymes such as γ-glutamyltransferase (γ-GT) and alanine transaminase (ALT) and cardiovascular diseases, independently of alcohol intake.[11,12] Elevated serum levels of γ-GT and ALT within normal values are considered as markers of inflammation and oxidative stress independent of metabolic syndrome.[13] Serum levels of γ-GT and ALT have never been studied before in patients with AF. This pilot observational study was conducted to evaluate serum levels of γ-GT and ALT within normal values in different AF populations including patients with paroxysmal and persistent AF. Any relationship with known conventional markers of inflammation and oxidative stress including high sensitivity C-reactive protein (hs-CRP), white blood cell (WBC) count, fibrinogen and uric acid was also investigated.

## METHODS

### PATIENTS

In this cross-sectional study, we recruited consecutive patients with AF, either paroxysmal or persistent, who were seen at the emergency department or at the outpatient clinic of our hospital. The arrhythmia classification (paroxysmal and persistent AF) was based on the current AHA/ACC/ESC guidelines.[14] Paroxysmal AF was defined as a self-terminating arrhythmia lasting less than 7 days. An arrhythmic episode lasting longer than 7 days or requiring termination by cardioversion, either with drugs or by direct current cardioversion, was designated as persistent AF. All baseline demographic and clinical characteristics were carefully recorded. Patients with valvular heart diseases, thyroid dysfunction, renal failure, hepatic failure, active inflammation, malignancies, infections, alcohol or drug addiction and administration of drugs or supplements with anti-inflammatory or antioxidant action, apart from statins, were excluded from the study. Of note, all subjects included in this study displayed serum concentration of liver enzymes within normal values. Control patients were identified at the outpatient clinic during the same time period and recruited according to the same eligibility and ineligibility criteria, with the exception that control patients were free of current AF and any history of AF.

### ECHOCARDIOGRAPHIC STUDY

Comprehensive transthoracic M-mode, 2-D scans and Doppler recordings were obtained in parasternal and apical views in all patients and controls using the Vivid-7 system equipped with a 2.4 MHz transducer (GE Medical Systems, Milwaukee, WI, USA). Left ventricular ejection fraction (LVEF) was estimated using the Simpson's method (four-chamber apical view). Left ventricular end-diastolic (LVEDD) and end-systolic (LVESD) diameters as well as end-systolic anteroposterior left atrial (LA) diameter (LAD) were determined in parasternal long-axis view. All measurements were averaged for 3 cardiac cycles.

### BLOOD SAMPLES

Blood samples were obtained from all patients in the fasting state. The WBC count in the peripheral blood was determined by an automated cell counter (Sysmex NE 9000). Serum levels of CRP were measured using a high-sensitivity latex particle-enhanced immunoassay on a Hitachi 717 automated analyzer (Tina-quant CRP detection, Roche Diagnostics). The precision of the assay calculated by the intra-assay and inter-assay coefficient of variation was <7%, the sensitivity of the method was 0.1 mg/dl and the detection limit was 0.3 mg/dl. Plasma fibrinogen levels were determined by the modified Claus method using the Multifibren U reagent (BCS analyzer; Dade-Behring). Serum uric acid levels were determined through uricase enzymatic method (Roche Diagnostics). Serum ALT (normal values <45 U/L)[15] and γ-GT levels (normal values <50 U/L in men and <40 U/L in woman)[16] were measured using an enzymatic reaction with a Hitachi 717 automated analyzer (Roche Diagnostics).

### STATISTICAL ANALYSIS

Continuous variables are presented as mean values + SD, whereas categorical ones are presented as absolute and relative frequencies (percentages). Differences in quantitative characteristics between groups were evaluated using one-way

analysis of variance (ANOVA) or Student's t-test, depending on the number of the groups compared. Pearson's $\chi^2$ test was used in order to test for any associations between two categorical variables. Correlations among study parameters were sought using the Spearman's rho test. Forward model building procedure was used in order to select the model with the best predictive value during multinomial logistic regression analysis. The three categories of the dependent categorical variable were paroxysmal AF, persistent AF and controls. All reported p values are based on two-sided tests and compared to a significance level of 0.05. Data were analyzed using STATA™ statistical software (Version 9.0, Stata Corporation, College Station, TX, USA). The study was approved by the local review committee and patients gave their written informed consent to take part in the study.

## RESULTS

The final study population consisted of 81 patients with paroxysmal AF, 45 patients with persistent AF and 39 controls. Table 1 shows the clinical, echocardiographic and laboratory data of the study groups. There were no significant differences among study groups regarding age, sex, incidence of hypertension and coronary artery disease, statins use, WBC count, fibrinogen levels and hs-CRP levels ($p > 0.05$). Subjects with AF, either paroxysmal or persistent, displayed higher body mass index (BMI) ($p = 0.001$), increased LVEDD ($p = 0.002$) and LAD ($p < 0.001$), and increased levels of uric acid ($p = 0.002$), ALT ($p < 0.001$), and γ-GT ($p < 0.001$) compared with the control population. Furthermore, patients with persistent AF exhibited decreased LVEF ($p = 0.002$) and increased LVESD ($p = 0.004$) in relation to controls.

Serum γ-GT levels within normal values were significantly elevated in patients with paroxysmal AF (30.40±12.34 U/L) and persistent AF (38.38±18.11 U/L) in relation to control population (24.03±11.73 U/L) ($p < 0.001$). In particular, γ-GT concentration was significantly higher in patients with persistent AF compared to paroxysmal AF ($p = 0.010$). Serum γ-GT levels were significantly correlated with LVEDD (rho = 0.160, p = 0.040), LAD (rho = 0.166, p = 0.033), age (rho = 0.188, p = 0.016), BMI (rho = 0.249, p = 0.001), and

**TABLE 1.** Clinical, Echocardiographic, and Laboratory Characteristics of the Study Groups

| | Control (n=39) | PAF (n=81) | PersAF (n=45) | PAF vs. Control p Value | PersAF vs. Control p Value | PAF vs. PersAF p Value | Overall p Value |
|---|---|---|---|---|---|---|---|
| Age (years) | 52.51 ±10.69 | 55.42±9.01 | 54.42±9.23 | 0.122 | 0.382 | 0.556 | 0.294 |
| Sex (males) (%) | 13 (33.3) | 25 (30.9) | 12 (26.7) | 0.785 | 0.505 | 0.620 | 0.793 |
| CAD (%) | 0 (0) | 3 (2.5) | 2 (6.7) | 0.454 | 0.245 | 0.348 | 0.189 |
| Hypertension (%) | 10 (25.6) | 13 (16) | 8 (17.8) | 0.211 | 0.381 | 0.803 | 0.443 |
| AF duration (years) | - | 5.90±3.04 | 4.96 ±2.81 | - | - | 0.093 | 0.093 |
| BMI (Kg/m$^2$) | 24.31±3.73 | 25.98±3.41 | 27.15±2.81 | **0.016** | **<0.001** | 0.053 | **0.001** |
| Number of AADs (n) | - | 3.15±1.11 | 3.00±.90 | - | - | 0.430 | 0.430 |
| Statins (%) | 7 (17.9) | 15 (18.5) | 9 (20) | 0.940 | 0.811 | 0.839 | 0.968 |
| LVEF (mm) | 60.54±5.56 | 60.05±7.90 | 55.07±9.76 | 0.695 | **0.002** | **0.002** | 0.001 |
| LVEDD (mm) | 48.31±4.96 | 50.83±5.53 | 52.22±4.24 | **0.017** | **<0.001** | 0.145 | **0.002** |
| LVESD (mm) | 30.95±4.94 | 31.77±6.52 | 34.09±4.86 | 0.490 | **0.004** | **0.039** | **0.030** |
| LAD (mm) | 34.90±4.01 | 39.12±4.79 | 42.51±5.69 | **<0.001** | **<0.001** | **0.001** | **<0.001** |
| WBC (mm$^3$) | 6645.90±1173.50 | 6153.33±1362.89 | 6438.44±1428.50 | 0.055 | 0.473 | 0.271 | 0.150 |
| Fibrinogen (mg/dl) | 336.74±98.40 | 316.20±79.89 | 317.20±67.37 | 0.260 | 0.299 | 0.943 | 0.403 |
| Uric acid (mg/dl) | 4.72±1.17 | 5.65±1.38 | 5.49±1.42 | **<0.001** | **0.010** | 0.527 | **0.002** |
| hs-CRP (mg/dl) | 0.34±0.10 | 0.37±0.26 | 0.43±0.31 | 0.512 | 0.080 | 0.265 | 0.256 |
| ALT (U/L) | 20.26±9.34 | 27.51±10.23 | 28.73±9.34 | **<0.001** | **<0.001** | 0.509 | **<0.001** |
| γ-GT (U/L) | 24.03±11.73 | 30.40±12.34 | 38.38±18.11 | **0.008** | **<0.001** | **0.010** | **<0.001** |

AADs = antiarrhythmic drugs; ALT = alanine aminotransferase; BMI = body mass index; γ-GT = gamma-glutamyltransferase; CAD = coronary artery disease; hs-CRP = high sensitivity-C-reactive protein; LAD = left atrial diameter; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; PAF = paroxysmal atrial fibrillation; PersAF = persistent atrial fibrillation; WBC = white blood cells.

uric acid levels (rho = 0.201, p <0.0001). Serum ALT levels were also significantly higher in patients with paroxysmal AF (27.51±10.23 U/L) and persistent AF (28.73±9.34 U/L) compared to control subjects (20.26±9.34 U/L) (p <0.001). ALT was significantly correlated with LVEDD (rho = 0.174, p = 0.025), LAD (rho = 0.206, p = 0.008), and uric acid levels (rho = 0.20, p = 0.001).

As shown in Table 2, in multinomial logistic regression analysis, the relative risk ratio of having paroxysmal AF per 1 U/L increase in ALT was 1.08 (CI: 1.02-1.14, p = 0.011), after adjustment for the effect of age, sex, BMI, statin use, and LAD. The relative risk ratio of having persistent AF per 1 U/L increase in γ-GT was 1.06 (CI: 1.01-1.12, p = 0.013).

## DISCUSSION

The main findings of the present study include the following: i. serum γ-GT and ALT levels within the normal reference intervals are significantly elevated in patients with paroxysmal and persistent AF; ii. an increase in ALT levels was significantly associated with paroxysmal AF development; and iii. an increase in γ-GT levels was significantly associated with development of persistent AF.

Increased levels of the liver enzymes, γ-GT and ALT, have been found to be associated with diabetes, cardiovascular risk factors and components of the insulin resistance syndrome, even within normal reference intervals.[11,12,16] γ-GT is mainly produced in the liver. Serum levels of γ-GT are determined by several factors, such as alcohol intake, body fat content, plasma lipid/lipoproteins and glucose levels, and various medications.[17] γ-GT play a pivotal role in maintaining intracellular antioxidant defense systems through its mediation of extracellular glutathione transport into most types of cells. Free radical production leads to depletion of glutathione, induces the expression of γ-GT and subsequently elevates serum activity of γ-GT. An increase in γ-GT activity can basically be a response to oxidative stress, and increased serum concentrations of γ-GT may identify people with a low-grade yet persistent increase of oxidative and other cellular or systemic stresses.[18,19] Increasing data are available about the associations between γ-GT levels and markers of oxidative stress (directly with F2-isoprostanes, an oxidative damage product of arachidonic acid; inversely with serum and dietary antioxidant vitamins), suggesting that the strong associations between cardiovascular risk factors might be explained by some oxidative mechanism.[20-22]

**TABLE 2.** Multinomial Logistic Regression Analysis Showing the Relative Risk Ratio of AF Development Based on γ-GT and ALT Serum Levels

| Variable | Relative Risk Ratio (RRR) | 95% Confidence Intervals | p Value |
|---|---|---|---|
| PAF vs. Controls | | | |
| γ-GT (per 1 U/L increase) | 1.01 | 0.97-1.05 | 0.683 |
| ALT (per 1 U/L increase) | 1.08 | 1.02-1.14 | **0.011** |
| PersAF vs. Controls | | | |
| γ-GT (per 1 U/L increase) | 1.06 | 1.01-1.12 | **0.013** |
| ALT (per 1 U/L increase) | 1.02 | 0.96-1.09 | 0.514 |

Abbreviations as in Table 1.

Accumulating data links oxidative stress with the pathogenesis of electrophysiological and structural remodeling processes that perpetuate AF.[1] In a recent study, Kim et al measured nicotinamide adenosine dinucleotide phosphate (NADPH)-stimulated superoxide production in right atrial appendage samples from 170 consecutive patients undergoing coronary artery bypass surgery. These investigators found that patients who developed AF after surgery had a significant increase in atrial NADPH oxidase activity than patients who remained in sinus rhythm, and increased atrial NADPH oxidase activity was independently associated with an increased risk of post-operative AF.[23] More recently, clinical studies have shown that oxidative stress markers are increased in AF, and are associated with the presence of AF. In a cross-sectional case-control design study, Neuman et al showed that oxidative stress markers were significantly elevated in persistent AF patients, and oxidative stress but not inflammatory markers were associated with AF.[24] In addition, Ramlawi et al investigated oxidative stress markers in patients undergoing coronary artery bypass grafting or valve procedures. They found that patients with post-operative AF had significantly higher serum peroxide levels compared to patients in sinus rhythm 6 hours following the procedure.[25] Furthermore, drugs that have antioxidant properties such as steroids and vitamin C show beneficial effects on AF development.[26,27] In our study, γ-GT levels were significantly higher in patients with persistent AF compared with those with paroxysmal AF and the control population, an event possibly linked to the AF burden. For one unit increase in γ-GT levels, the relative risk of having persistent AF was increased 6%, after adjustment for the effect of several factors including BMI. In addition, γ-GT levels were significantly correlated with LAD, indicating a possible role in left atrial structural remodeling.

ALT has been less validated as a potential cardiovascular risk marker.[28] ALT is often used in epidemiological studies as a surrogate marker for non-alcoholic fatty liver disease. In addition, recent prospective epidemiological studies have demonstrated that ALT is associated with future risk of type 2 diabetes mellitus and the metabolic syndrome.[29] A meta-analysis that examined the association of ALT with incident cardiovascular events found a hazard ratio of 1.18 (95% CI:

0.99, 1.41) for coronary heart disease and a hazard ratio of 1.10 (95% CI: 0.89, 1.36) for coronary artery disease or stroke (combined).[11] Yamada et al have shown that elevated serum ALT levels were related to increased plasma levels of CRP and lipid peroxides.[13] We showed that serum ALT levels were significantly elevated in patients with paroxysmal and persistent AF compared to controls. ALT was also significantly correlated with LAD. For one unit increase in ALT levels, the relative risk of having paroxysmal AF was increased 8%, after adjustment for the effect of several factors.

### LIMITATIONS

Our study has some potential limitations. First, the number of participants was relative small. Second, the observational design of the study identifies only an association and not causality. Moreover, due to the observational design, only single measurements were available. Third, data regarding angiotensin converting enzyme inhibitor or angiotensin II receptor blocker use that may display anti-inflammatory effects are missing. Finally, we have to acknowledge that paroxysmal AF patients are a quite heterogeneous group in terms of symptoms and arrhythmia burden, and thus the relative impact on γ-GT and ALT levels may be different.

### CLINICAL IMPLICATIONS

Several issues regarding the role of oxidative stress in AF remain to be elucidated. Up to now, it is not clear whether oxidative stress is a primary pathogenetic event or a consequence of AF. However, there is a possibility that both processes feeding each other leading to a vicious cycle. Even though recent studies point to enzymatic sources of ROS and to molecular targets of oxidative damage, the exact pathophysiologic mechanisms have not been adequately investigated. The implementation of interventions targeting selectively at these specific pathways would be the ideal mode of studying these phenomena leading to the development of effective therapeutic strategies. Factors that reduce oxidative stress in cardiovascular diseases have not yet been tested in the setting of AF. These include xanthine oxidase inhibitors such as allopurinol, thiol-containing compounds such as N-acetylcysteine and α-lipoic acid, selective NAD(P)H oxidase inhibitors (experimental agents), as well as experimental gene transfer strategies aiming at overexpression of edogenous antioxidant enzymes.

## CONCLUSION

This observational study shows for the first time an association between increased levels within normal reference intervals of γ-GT and of ALT and AF. Serum γ-GT levels may be additionally related to the burden of AF. Larger studies are needed to validate our findings.

## REFERENCES


1. Cheng TO. Global epidemic of atrial fibrillation including China. *Int J Cardiol* 2007;122:160.
2. Aldhoon B, Melenovský V, Peichl P, Kautzner J. New insights into mechanisms of atrial fibrillation. *Physiol Res* 2010;59:1-12.
3. Patel P, Dokainish H, Tsai P, Lakkis N. Update on the Association of Inflammation and Atrial Fibrillation *J Cardiovasc Electrophysiol* 2010;21:1064-1070.
4. Allessie M, Ausma J, Schotten U. Electrical, contracticle and structural remodeling during atrial fibrillation. *Cardiovasc Res* 2002;54:230-246.
5. Shiroshita-Takeshita A, Bianca BJJM, Nattel S. Atrial fibrillation: basic mechanisms, remodeling and triggers. *J Interv Card Electrophysiol* 2005;13:181-193.
6. Nattel S. Therapeutic implications of atrial fibrillation mechanisms: can mechanistic insights be used to improve AF management? *Cardiovasc Res* 2002;54:347-360.
7. Van Wagoner DR. Oxidative stress and inflammation in atrial fibrillation: role in pathogenesis and potential as a therapeutic target. *J Cardiovasc Pharmacol* 2008;52:306-313.
8. Frustaci A, Chimente C, Bellocci F, Morgante E, Russo MA, Maseri A. Histological substrate of atrial biopsies in patients with lone atrial fibrillation. *Circulation* 1997;96:1180-1184.
9. Huang CX, Liu Y, Xia WF, Tang YH, Huang H. Oxidative stress: a possible pathogenesis of atrial fibrillation. *Med Hypotheses* 2009;72:466-467.
10. Issac TT, Dokainish H, Lakkis NM. Role of inflammation in initiation and perpetuation of atrial fibrillation: a systematic review of the published data. *J Am Coll Cardiol* 2007;50:2021-2018.
11. Fraser A, Harris R, Sattar N, Ebrahim S, Smith GD, Lawlor DA. Gamma-glutamyltransferase is associated with incident vascular events independently of alcohol intake: analysis of the British Women's Heart and Health Study and Meta-Analysis. *Arterioscler Thromb Vasc Biol* 2007;27:2729-2735.
12. Fraser A, Harris R, Sattar N, Ebrahim S, Davey Smith G, Lawlor DA. Alanine aminotransferase, gamma-glutamyltransferase, and incident diabetes: the British Women's Heart and Health Study and meta-analysis. *Diabetes Care* 2009;32:741-750.
13. Yamada J, Tomiyama H, Yambe M, et al. Elevated serum levels of alanine aminotransferase and gamma glutamyltransferase are markers of inflammation and oxidative stress independent of the metabolic syndrome. *Atherosclerosis* 2006; 189:198-205.
14. Fuster V, Rydén LE, Cannom DS, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2011;123:e269-367.
15. Kaplan MM. Alanine aminotransferase levels: what's normal? *Ann Intern Med* 2002;137:49-51.
16. Lee DH, Silventoinen K, Jacobs DR Jr, Jousilahti P, Tuomileto J. Gamma-glutamyltransferase, obesity, and the risk of type-2 diabetes: observational cohort study among 20 158 middle-aged

men and women. *J Clin Endocrinol Metab* 2004;89:5410-5414.
17. Whitfield JB. Gamma glutamyl transferase. *Crit Rev Clin Lab Sci* 2001;38:263-355.
18. Schulze PC, Lee RT. Oxidative stress and atherosclerosis. *Curr Atheroscler Rep* 2005;7:242-248.
19. Lee DH, Blomhoff R, Jacobs DR. Is serum gamma glutamyltransferase a marker of oxidative stress? *Free Radic Res* 2004;38:535-539.
20. Lee DH, Gross MD, Jacobs DR Jr. Association of serum carotenoids and tocopherols with gamma-glutamyltransferase: the Cardiovascular Risk Development in Young Adults (CARDIA) Study. *Clin Chem* 2004;50:582-588.
21. Lee DH, Steffen LM, Jacobs DR Jr. Association between serum gamma-glutamyltransferase and dietary factors: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Clin Nutr* 2004;79:600-605.
22. Lim JS, Yang JH, Chun BY, Kam S, Jacobs DR Jr, Lee DH. Is serum gamma-glutamyltransferase inversely associated with serum antioxidants as a marker of oxidative stress? *Free Radic Biol Med* 2004;37:1018-1023.
23. Kim YM, Kattach H, Ratnatunga C, et al. Association of atrial nicotinamide adenine dinucleotide phosphate oxidase activity with the development of atrial fibrillation after cardiac surgery. *J Am Coll Cardiol* 2008;51:68-74.
24. Neuman RB, Bloom HL, Shukrullah I, et al. Oxidative stress markers are associated with persistent atrial fibrillation. *Clin Chem* 2007;53:1652-1657.
25. Ramlawi B, Otu H, Mieno S, et al. Oxidative stress and atrial fibrillation after cardiac surgery: a case-control study. *Ann Thorac Surg* 2007;84:1166-1172.
26. Prasongsukarn K, Abel JG, Jamieson WR, et al. The effects of steroids on the occurrence of postoperative atrial fibrillation after coronary artery bypass grafting surgery: a prospective randomized trial. *J Thorac Cardiovasc Surg* 2005;130:93-98.
27. Korantzopoulos P, Kolettis TM, Kountouris E, et al. Oral vitamin C administration reduces early recurrence rates after electrical cardioversion of persistent atrial fibrillation and attenuates associated inflammation. *Int J Cardiol* 2005;102:321-326.
28. Mikhailidis DP, Lioudaki E, Ganotakis ES. Liver enzymes: potential cardiovascular risk markers? *Curr Pharm Des* 2011; 17:3632-3643.
29. Schindhelm RK, Diamant M, Dekker JM, Tushuizen ME, Teerlink T, Heine RJ. Alanine aminotransferase as a marker of non-alcoholic fatty liver disease in relation to type 2 diabetes mellitus and cardiovascular disease. *Diabetes Metab Res Rev* 2006;22:437-443.