

## Original Research Article

# The relation of serum GGT level in patients with non valvular atrial fibrillation and normal sinus rhythm

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**Received:** 26 February 2018

**Accepted:** 09 March 2018

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### ABSTRACT

**Background:** The primary objective of the study was to assess and compare the relation of serum GGT level in patients with non valvular atrial fibrillation and normal sinus rhythm. The fundamental mechanisms underlying AF remains poorly understood. Oxidative stress is hypothesized to induce and maintain nonvalvular atrial fibrillation particularly in elderly patients. GGT levels are increased in patients with chronic inflammation. Increased serum levels of GGT are found in chronic nonvalvular atrial fibrillation (AF) patients as compared with patients in sinus rhythm.

**Methods:** We included 75 patients of nonvalvular atrial fibrillation and 75 patients of sinus rhythm after applying exclusion criteria. Serum level of gamma glutamyl transrerase (GGT) of both the groups was compared.

**Results:** Presence of coronary artery disease, hypertension, gender, hyperlipidemia, diabetes mellitus and smoking status were comparable between the 2 groups ( $P > 0.05$  for all). Serum gamma glutamyl transferase activity in 75 cases was  $71.45 \pm 26.21$  with maximum being 147 IU/L more than the normal range for age, whereas in controls it was  $19.68 \pm 5.53$  i.e. much within the normal range for age.

**Conclusions:** At the end of the study we concluded that serum GGT levels were significantly higher in patients with chronic nonvalvular atrial fibrillation (AF) patients as compared with patients in sinus rhythm.

**Keywords:** Atrial Fibrillation (AF), Gamma Glutamyl Transferase (GGT)

## INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia. Prevalence in the general population ranges from 2 to 10% in different age groups.<sup>1</sup> It independently contributes to an increased risk of embolic stroke and heart failure.

Though it may remain asymptomatic in many cases there is loss of atrial appendage contractility and emptying leading to the risk of clot formation and subsequent thromboembolic events.<sup>1-3</sup> The fundamental mechanisms

underlying AF remains poorly understood. Many studies have related an increase in CRP and IL-6 in both PAF and persistent AF. Elevation of CRP and IL-6 might also contribute to generation and perpetuation of AF, as evidenced by marked inflammatory infiltrates, myocyte necrosis, and fibrosis found in atrial biopsies of patients with lone AF.<sup>4</sup>

The exact mechanism of inflammation leading to tissue remodeling in AF patients is unclear. Tissue injury due to chronic inflammation leads to membrane dysfunction by inhibiting the exchange of sodium and calcium ions in

sarcomeres. This can eventually lead to generation and the maintenance of AF.<sup>5,6</sup>

Markers of platelet activation as assessed by soluble P-selectin levels have been shown to be elevated within 12 hours in patients with PAF and return to normal upon resolution to normal sinus rhythm.<sup>7</sup> The development of accelerated platelet activity and hypercoagulability appears to be related to irregular atrial wall motion, which causes abnormal atrial blood flow and injury to the endothelium; and platelet aggregation and frequent collision of platelets, which leads to acceleration of platelet activity. Thus, as shown in Stroke Prevention in Atrial Fibrillation trials I and II, administration of antiplatelet drugs is important to prevent the occurrence of stroke induced by AF.<sup>8</sup>

Gamma Glutamyl Transferase (GGT) is an enzyme that is found in all cell membranes except erythrocytes. It is involved in extracellular glutathione catabolism and provides intracellular glutathione resynthesis in turn reduces oxidative stress. According to the Framingham Heart Study including 3451 participants, elevated serum GGT activity is associated with increased onset of metabolic syndrome and predicts cardiovascular disease. An epidemiological investigation including 163944 participants showed that GGT activity was independently associated with cardiovascular mortality.<sup>2,9,10</sup>

Recent studies also showed that increased serum GGT activity is associated with increased oxidative stress and activation of systemic inflammation in humans.<sup>11,12</sup> Therefore, both AF and GGT activities are associated with systemic inflammation and oxidative stress. Serum G-Glutamyl Transferase (GGT) activity is a frequently used test that is inexpensive, easily available, highly sensitive marker of hepatobiliary dysfunction, and alcohol consumption.<sup>13</sup> Also, there is an association between GGT activity and platelet hyperactivity. It is thought that human platelets contain isoenzyme GGT4 and continuous disruption of platelets can influence GGT activity.<sup>14</sup>

The AF is associated with a prothrombotic state related to endothelial dysfunction. Oxidative stress is associated with AF which in turn leads to increased synthesis of antioxidants like glutathione thereby increasing activity of gamma glutamyl transferase in serum.

## METHODS

The present study was conducted in the Department of General Medicine and Department of Cardiology, at a tertiary care medical college hospital in north india. Patients were enrolled into two groups after matching confounding factors like age, sex etc.

Applying inclusion and exclusion criteria 75 patients in each were categorised into Group A (patients with NVAF) and Group B (patients with NSR). All patients

and control individuals had echocardiographic examination to rule out valvular heart disease.

### *Inclusion criteria*

#### Group A

- Patients with chronic non valvular atrial fibrillation i.e.>1 week,
- Age > 18 years.

#### Group B

- Patients with normal sinus rhythm,
- Age > 18 years.

### *Exclusion criteria*

#### Patients with

- Acute coronary syndrome
- Recent MI i.e. <4weeks
- Heart failure
- Recent stroke history i.e. <4weeks
- Infections within past 4 weeks
- Hematological diseases like polycythemia vera, thrombophilia
- Chronic alcoholic
- Hepatobiliary diseases
- Chronic renal failure
- IConnective tissue inflammatory disease
- Active malignancies
- Acute AF and AF with valvular heart disease.

### *Statistical analysis*

Results are expressed as the mean±standard deviation and percentage. The differences between 2 groups were tested for significance by chi-square and independent samples t tests. Differences between 2 groups were considered significant at P value <0.05.

We investigated the association of different variables with AF using logistic regression analysis. Parameters namely, age, presence of hypertension, diabetes mellitus, GGT activity, and ejection fraction were included in regression analysis. Statistical analyses were performed using SPSS 15.0 Statistical Package Program for Windows.

## RESULTS

Baseline characteristics of patients and control individuals are presented in Table 1. Presence of coronary artery disease, hypertension, gender, hyperlipidemia, diabetes mellitus, smoking status was comparable between the 2 groups (P>0.05 for all). However, serum GGT activity was significantly higher in patients with AF compared with those without AF.

Table 2 shows Logistic regression analysis using variables age, HTN, DM, EF and GGT. It reveals that

serum GGT activity was significantly and independently associated with AF.

**Table 1: Comparison of patient with atrial fibrillation and control individuals.**

Variables	Cases (patients with NVAF)	Controls (patients with NSR)	P value
Age (yrs.)	67.52±7.72	69.76±8.05	0.0840
Sex (male)	39(52%)	39(52%)	1.00
Coronary artery disease	17 (22.67%)	14 (18.67%)	0.5432
Hypertension	23 (30.67%)	32 (42.67%)	0.1273
Diabetes mellitus	25 (33.33%)	23 (30.67%)	0.7263
Hyperlipidemia	4 (5.33%)	5 (6.67%)	0.7310
Smoking	56 (74.67%)	47 (62.67%)	0.1131
WBC count	7662.13±1287.06	7832.05±1346.31	0.4307
Blood glucose level	125.35 (45.45%)	125.76 (49.99%)	0.9578
Total cholesterol	159.23±42.86	166.47±48.96	0.3368
Triglycerides	138.41±46.92	122.91± 79.49	0.1478
LDL-C	101.83± 36.64	96.99± 37.74	0.4268
HDL-C	45.13±5.50	46.75±6.62	0.1068
GGT (IU/l)	71.45± 26.21	19.68± 5.53	0.0001
EF (%)	59.17± 5.88	59.33± 4.08	0.8468

**Table 2: Logistic regression analysis.**

Variables	Odds ratio	Confidence interval		P value
		Lower	Upper	
Age	1.021	0.929	1.121	0.67
Hypertension	0.564	0.126	2.519	0.45
DM	1.432	0.288	7.132	0.66
EF	1.036	0.879	1.220	0.68
GGT	0.830	0.756	0.911	0.001

**DISCUSSION**

Nonvalvular atrial fibrillation refers to atrial fibrillation in the absence of mitral stenosis or valvular prostheses. With the decline in prevalence of rheumatic heart disease, the relative prevalence of nonvalvular atrial fibrillation has increased markedly. As most of the patients with RHD associated AF belong to middle age group, patients with non valvular AF show increasing trends after the age of 55 to 60. Almost all the patients of NVAF in our study were beyond 50 years of age and majority were in the range of 50 to 80 years age group. Gulacan Tekin et al, reported mean age of 73±8 in their study while mean age was 67.52±7.72 in patients of NVAF in our study.<sup>2</sup>

We found 17 (22.33%) out of 75 cases were having history suggestive of coronary artery disease which was confirmed by ECG and echocardiography. Gulacan Tekin et al, reported 24 % of the cases having coronary artery disease. Hypertensive heart disease has been one of the common cause for atrial fibrillation. In our study 23

(30.67%) patients with non valvular AF were hypertensive. They were either being treated for HTN or newly diagnosed during hospital stay. Gulacan Tekin et al, in his observation found 74% cases having hypertension much more than what our study found. Additionally, 32 (42.67%) patients with normal sinus rhythm were hypertensive.

Diabetes mellitus a well-known disease for its micro and macrovascular complications has been leading cause of cardiovascular morbidity and mortality since centuries. Though no direct etiological relationship has been established with atrial fibrillation we found 25 (33.33%) cases being diabetic either on medication or recently diagnosed by ADA 2013 criteria. Gulacan et al, in his study found 15% diabetics in cases and 16% in controls whereas we got 23 (30.67%) controls having diabetes. Mean blood glucose level was 125.35±45.45mg/dl among 75 patients with non valvular AF and 125.76±49.99mg/dl among 75 patients with normal sinus rhythm. Gulacan Tekan et al, in his observation among 81 cases got mean blood glucose level 113±37mg/dl and among 210 controls 109±40mg/dl. Oxidative stress and chronic inflammation in diabetes mellitus may play a role in causation and perpetuation of chronic AF.<sup>11,15</sup>

Among 75 cases mean serum total cholesterol came out to be 159.23±42.86mg/dl and among 75 controls it was 166.47±48.96mg/dl. It was slightly less than the observations of the study by Gulacan. In his study, mean total cholesterol was 172±45mg/dl in 81 cases and 180±36mg/dl in 210 controls.

Early morning fasting triglyceride level was done and mean level in 75 cases and controls were 138.41±46.92mg/dl and 122.91±79.49mg/dl respectively. Gulacan et al reported lower levels i.e. 117±69mg/dl and 129±67mg/dl among cases and controls respectively.

Low density cholesterol mean value in 75 cases was 101.83±36.64mg/dl and in 75 controls was 96.99±37.74mg/dl. In a study by Gulacan et al, 81 cases had mean LDL-C was 108±32mg/dl and 210 controls had 114±28mg/dl. Whereas mean HDL-C was 45.13±5.50mg/dl and 46.75±6.62mg/dl among cases and controls respectively in our study and 37±9mg/dl and 37±10mg/dl in a study by Gulacan. Both LDL-C and HDL-C were statistically non-significant in cases and controls.

Serum gamma glutamyl transferase activity in 75 cases was 71.45±26.21 with maximum being 147IU/L more than the normal range for age, whereas in controls it was 19.68±5.53 i.e. much within the normal range for age. Gulacan tekin et al, in his observations reported serum GGT activity of 27±18IU/L in cases and 20±13IU/L in controls and similarly showed statistically significant difference.<sup>2</sup> GGT activity in serum is increased in oxidative stress and inflammation.<sup>13,14</sup>

All the patients were screened with 2D echocardiography. The results were; mean EF among cases was 59.17±5.88 and among controls was 59.33±4.08. Except few patients among both the groups most of them had normal EF. Gulacan et al, among 81 cases and 210 controls reported mean EF of 61±4 and 62±4 respectively.

Presence of coronary artery disease, hypertension, gender, hyperlipidemia, diabetes mellitus, smoking status was comparable between the 2 groups (P >0.05 for all). However, serum GGT activity was significantly higher in patients with AF compared with those without AF.

## CONCLUSION

In conclusion we found that serum GGT activity is independently and significantly associated with chronic non valvular AF. Larger studies are needed to improve the clinical utility of GGT activity and to better understand the role of inflammation in the pathogenesis of AF. Randomized controlled prospective studies are needed to evaluate the relationship between chronic AF and serum GGT activity.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: The study was approved by the Institutional Ethics Committee*

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**Cite this article as:** Nawal CL, Chejara RS, Panwar A, Agrawal MK, Singh A, Meena PD. The relation of serum GGT level in patients with non valvular atrial fibrillation and normal sinus rhythm. *Int J Res Med Sci* 2018;6:1174-8.