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A Case-Control Study assessing Serum Galectin 3 level in Atrial Fibrillation Patients

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Abstract

As a worldwide issue of concern, atrial fibrillation (AF) casts a huge burden on the health care system. Not only being an arrhythmia of high frequency and prevalence, but also due to the chronicity of some its types. It is imperative to increase the understanding of the pathophysiological basis behind atrial fibrillation or at least the processes that sub serves as a prerequisite for its development. Cardiac remodeling and fibrotic changes may derange the conductive properties of the myocardium and hence import an arrhythmogenic conditioning state. Galectin-3 (Gal-3) has a wide spectrum of biological activities. It can be utilized as a tool for screening many cardiac conditions especially those associated with fibrotic states.

Aim of study: this study was designated to explore the association between atrial fibrillation and serum galectin-3 levels. It was of a case-control type that comprised a cohort of 58 patients with atrial fibrillation, together with 30 controls without it. Patients were categorized into two categories depending upon whether they have a persistent or permanent atrial fibrillation. Serum galectin-3 was measured using ELISA technique, and the results were compared among the three groups.

Results: The Gal-3 was found to be higher in patients with permanent AF ($p < .0001$) where it recorded 19.27 ± 4.58 ng/ml. The rise in the marker concentration was statistically significant when compared to the 13.54 ± 4.9 ng/ml and 12.14 ± 4.69 ng/ml for the persistent AF and control groups, respectively. Likewise, patients with permanent AF had significantly higher values of left atrial diameter (LAD) ($p < .0001$) with a mean of 4.68 ± 0.37 cm, 4.09 ± 0.3, and 3.54 ± 0.32, for the permanent AF, persistent AF, and the control groups, respectively. Additionally, the LAD revealed a slight positive correlation with the Gal-3 level, $r\,(56) = 0.386$, $p < 0.003$, with an r^2 of 0.149. On the other hand, there was a significant reduction in the left ventricular ejection fraction (LVEF %) in patients with permanent AF, $p < 0.0001$. The LVEF%

was 53.27 ± 7.35 %, versus 62.13 ± 6.75 %, and 63.39 ± 5.77% for permanent AF, persistent AF, and control groups, respectively.
In conclusion, serum Gal-3 is elevated in conditions of both, long-standing AF as well as newly diagnosed AF. The marker correlated positively with the LAD and negatively with LVEF%. Furthermore, LVEF% revealed a moderate negative correlation with serum Gal-3 concentrations. The study concluded that as the left atrium increases in size, this will impose a deleterious effect on the left ventricle and will be reflected as an increasing level of the marker. Hence, Gal-3 can be used as a tool for evaluating fibrotic changes in patients with AF especially the chronic types.

Introduction

Atrial fibrillation (AF) is a prevalent type of supraventricular arrhythmias that has a significant impact on health resources by placing a heavy burden on the healthcare system, particularly in Western nations [1]. AF is characterized by a widespread and disordered atrial electrical activity which interferes with the normal function of the sinus node causing an inefficient mechanical atrial contraction [2]. It accounts for about one third of all hospitalizations linked to arrhythmias and is the most prevalent arrhythmia treated in emergency rooms [3]. It is common to classify AF into one of three forms; paroxysmal AF, which occurs intermittently and lasts for less than 7 days; persistent AF, which lasts longer than seven days and finally; permanent AF, which is similar to the persistent type, but lasts longer than a year [4].

Atrial fibrosis has been identified as one of the major contributors to the development of this type of arrhythmia, making it pivotal to understand the role of fibrosis in the pathophysiology of AF. Additionally, the degree of cardiac fibrosis has been proved to be a key player influencing the treatment approach, as demonstrated by the success rates of rhythm management [5].

In atrial fibrillation, the generation of focal myocardial fibrotic spots has a key role in the cardiac remodeling. This fibrotic process reflects the outcome of interaction among multifactorial processes that cause connective tissue redistribution within the myocardial tissue [6]. These tissue redistributive processes, in essence, are an adaptive response to a pathological condition. The cardiac fibrosis of AF at the translational level involves a versatile cellular and neurohormonal factors including cardiac fibroblast and myoblast [7], matrix metalloproteinases together with their inhibitors [8], collagen synthesis by transforming growth factor B1 signalling, inflammatory processes, and normal aging processes [9].

Despite the fact that cardiac fibroblasts are non-excitable cells but yet they have a dromotropic properties that are somewhat different from cardiomyocytes and are capable of current conduction using connexins [10]. This may produces uneven conduction of electric potentials, reduced refractory periods, and increased diastolic potential, and hence, resulting in a state of arrhythmogensity [11]. As a result, atrial fibrosis might be directly involved in the occurrence and perpetuation of focal and re-entry arrhythmic mechanisms.

Circulating biomarkers may be useful tools for assessing cardiac fibrosis [12]. Such cardiac biomarkers include galactin 3 (Gal-3) , relaxin-1 (RLN1) , corin [13,14], connective tissue growth factor (CTGF) [15], products of mesenchymal cell like α-smooth muscle actin (α-SMA), vimentin, and fibronectin [16]. Being one of the galectin family, galectin-3 (Gal-3) is lectin of cytosolic origin with a capability of binding β-galactoside and has a regulatory effect on the process of fibrogenesis. Various inflammatory cells express Gal-3 which after expression binds itself to glycoproteins outside the cell. After binding, it activates the production of collagen type I from the fibroblasts [17]. Lately, many studies pointed out that when Gal-3 expression is increased, the adverse cardiac events will increase as well, these include myocardial infarction, heart failure, and cardiomyopathy [18]. In this article, galectin

3 was used as a biomarker related to development of fibrosis, oxidative stress, and inflammation in cardiac tissue. This marker has garnered significant interest in cardiological illnesses.

Patients And Methods

The current study was carried out consonantly with the Declaration of Helsinki and after obtaining informed consent of all patients. The approval of medical ethics committees at Kerbela directorate of health was obtained as referenced by their permit with the number 23 issued at the 5th of June, 2020. The study was conducted on a group of 64 atrial fibrillation patients who were admitted to the causality department of Al-Hussein teaching hospital in Kerbela/ Iraq for the period between the 1st of July 2020 and 30th of September 2021. The study also involved 30 people as a control group who didn't have or had atrial fibrillation as far as they know.

Exclusion criteria were autoimmune disorders, cancer, acute inflammatory conditions (as sepsis and COPD in acute phase), severe heart failure (class III-IV NYHA), dilated cardiomyopathy, hypertrophic cardiomyopathy, and congenital cardiac pathologies [19]. Due to heart failure, three out of the 64 patients were excluded. Another two patients were ruled out after an acute exacerbation of COPD, and one for terminal illness. Each selected patient was designated into either of the following groups:

1. Group-A (a non-permanent AF group):

this group included those with newly diagnosed AF together with those suffering from persistent AF. It comprised 29 patients with a mean age of (54.36 ± 14.84) years, 9 (31.2%) of them were males.

2. Group-B (a permanent AF group): this group included those with permanent AF. This group involved a further 29 patients with a mean age of (59.07 ± 17.08) years, 10 (34.4%) of them were males.

3. Group-C (controls): this group had 30 participants with a sinus rhythm, and they hadn't have any fibrillation attack as far as they recall and as it wasn't documented in their records. Their mean age was (48.79 ± 17.08) years, 10 (34.4%) of them were males.

The assessment of AF type for each participant was based on clinical history and clinical data collected while at hospital stay. A battery of 12-lead ECG trace outs was conducted 3 times for each participant, whether at hospital stay or even after discharge when the patient returned at a scheduled date for rechecking. The first ECG was done at admission, the second and third ECGs were done at one week apart. If the AF was detected at all the three ECGs, then the patient was designated as having a permanent AF. If the AF was cleared at the following ECGs, then the patient was designated to have a non-permanent AF which might be of a paroxysmal or persistent type. The selection was scrutinized, when possible, to match the age and gender distribution among the groups.

The serum Gal-3 was measured using high sensitivity enzyme-linked immunosorbent assay (ELISA) provided by (Thermo Fisher Scientific, USA) with a within-run coefficient of 0.01 and a limit of detection of 0.29 ng/ ml and a coefficient of variance (CV) of 5.4%. The evaluation was done using COBAS 600 provided by Roche diagnostics Inc., Belgium. A cutoff level of 17.8 ng/ml was taken as a reference [20].

A transthoracic echocardiography was obtained for all participants to identify and assess the cardiac contractility using left ventricular ejection fraction (LVEF %) and atrial size using left atrial diameter (LAD). The left atrium's reference ranges were established in maximum diameter as follows: < 4.1 cm for adult males or < 3.9 cm for adult females. [21]

Statistic evaluation

Statistical analysis was performed utilizing SPSS 24.0 provided by IBM®. Age, gender ratio,

marker concentrations, LVEF, and LAD are continuous data that are reported as median and standard deviations. On the other hand, categorical data like the type of AF were presented as counts and percentages. The Pearson correlation has been used to assess the results' statistical significance for continuous and analysis of variance (ANOVA) for categorical data. The threshold for a result to be considered statistically significant has been set at *p*-value of 0.05.

Results

The overall average age of the 58 patients was 56.71 ± 13.52 (33-82) years. About 32.75% of them were females. As depicted in both table (1) and figure (1), patients with persistent AF group had an average serum galactin-3 level of 13.54 ± 4.9 ng/ml; those of the permanent AF group had an average marker level of 19.27 ± 4.58 ng/ml, and those of the control group had a mean level of 12.14 ± 4.69 ng/ml. The variation in the Gal-3 level among the three groups was significantly high, F (2, 85) = 20.08, $p<0.0001$. Subsequent analysis by Tukey`s HSD post hoc test showed that the marker was higher in those having permanent AF when in comparison to those with persistent AF, 95%CI= [2.72 - 8.74], $p=0.0001$ or controls 95% CI = [4.16-10.09], $p<0.0001$.

The left atrial size

One way analysis of variance (ANOVA) showed that the effect of left atrial (LA) size was significant, F (2, 85) = 48.39, $p<0.0001$. Scheffé post hoc criterion for significance indicated that the LA size was significantly higher in the permanent AF group (4.68 ± 0.37 cm) than in the other two groups combined where it was (4.09 ± 0.3), 95%CI = [0.34-0.76], and (3.54 ± 0.32), 95% CI = [0.93-1.35] for the persistent AF and the control groups, respectively. There was a moderate positive correlation between the marker level and the left atrial diameter, [r (54) = .386, p = .003], as shown by figure (1).

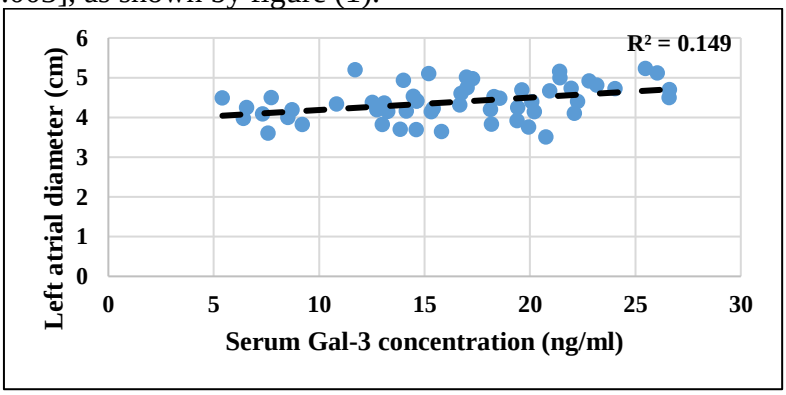

Figure 1: the slight positive correlation between the left atrial diameter (LAD) and the serum Gal-3 level.

The left ventricular ejection fraction

The results of ANOVA showed that there was statically significant difference among the three groups with respect to LVEF, F (2, 85) = 19.23, $p<0.0001$. Results indicated that the average LVEF was significantly lower in the permanent AF group (53.27 ± 7.35%) than were those in both the persistent AF group (62.13 ± 6.75%), F (2, 27) = 8.90, p =.011 and in the control group (63.39 ± 5.77), F (1, 27) = 10.22, p = .007. There was a moderate positive correlation between the marker level and the left atrial diameter, [r (54) = .331, p = .013], as shown by figure (2).

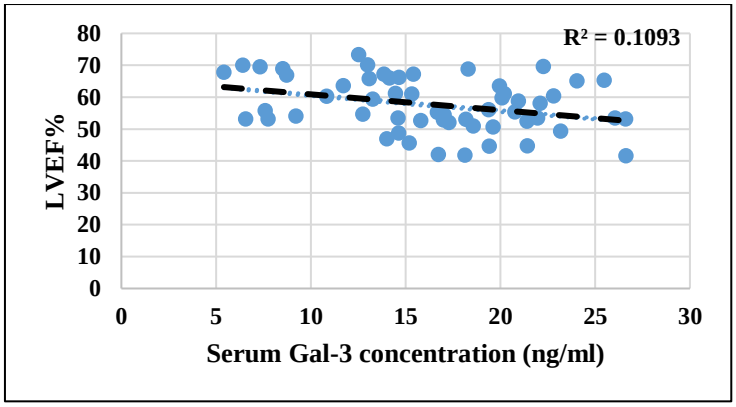

Figure 2: the slight negative correlation between the left ventricular ejection fraction (LVEF %) and the serum Gal-3 level.

Table 1: the anthropometric data and study parameters of the study participants. Nominal values are expressed as mean and standard deviation whereas categorical data are expressed as percentages. The level of significance was set at a p-value of <0.05.

Parameter	*Study groups*			*Intra-group p-value*	*Inter-groups p value*		
	Group-A	*Group-B*	*Controls*		*A vs. B*	*A vs. C*	*B vs. C*
Number	29	29	30	-	-	-	-
Males (n, %)	9 (32.14%)	10 [35.71%)	10 (35.71%)	0.561†	0.779†	0.779	1
Age (years)	54.36 ± 14.84	59.07 ± 11.87	48.79 ± 17.08	0.035*	0.46†	0.33†	0.026†
LAD (cm)	4.09 ± 0.3	4.68 ± 0.37	3.99 ± 0.12	<0.0001*	<0.0001*	<0.0001*	<0.0001*
LVEF (%)	62.13 ± 6.75	53.27 ± 7.35	63.39 ± 5.77	<0.0001*	<0.0001*	0.759†	<0.0001*
Galactin-3 (ng/ml)	13.54 ± 4.9	19.27 ± 4.58	12.14 ± 4.69	<0.0001*	<0.0001*	0.472†	<0.0001*
Hypertension	3	5	2	NA	-	-	-
Diabetes	2	0	0	NA	-	-	-
IHD	12	2	0	NA	-	-	-
BMI (kg/m²)	33.24 ± 7.21	31.16 ± 8.8	29.84 ± 6.33	0.08†	0.149†	0.561†	0.221†

* Significant statistical difference.
† Non-significant statistical difference.
LAD = left atrial diameter, LVEF% = percentage of left ventricular ejection fraction, IHD = ischemic heart disease, BMI = body mass index, kg = kilogram, m^2 = squared meter.

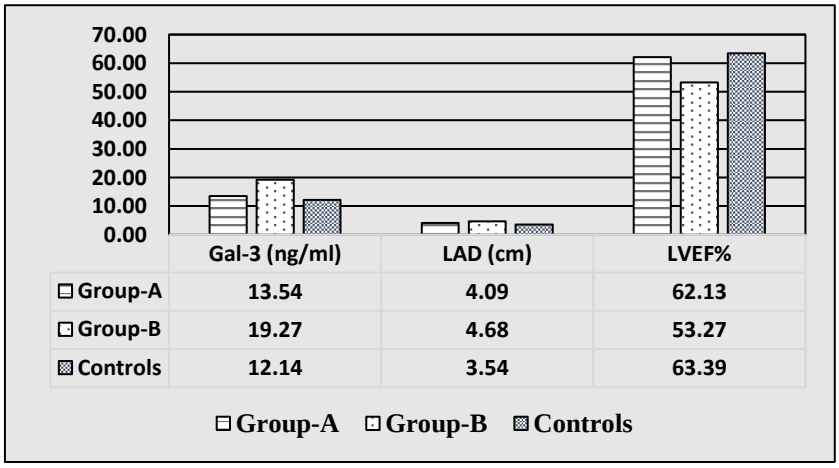

Figure 3: the serum Gal-3, left atrial size measured by (LAD), and cardiac contractility measured by (LVEF %) measured for the group-A (permanent AF group), group-B (persistent AF group), and group-C (control group). Values are expressed as means (Gal-3 = galactin-3, LAD = left atrial diameter, LVEF% = percentage of left ventricular ejection fraction).

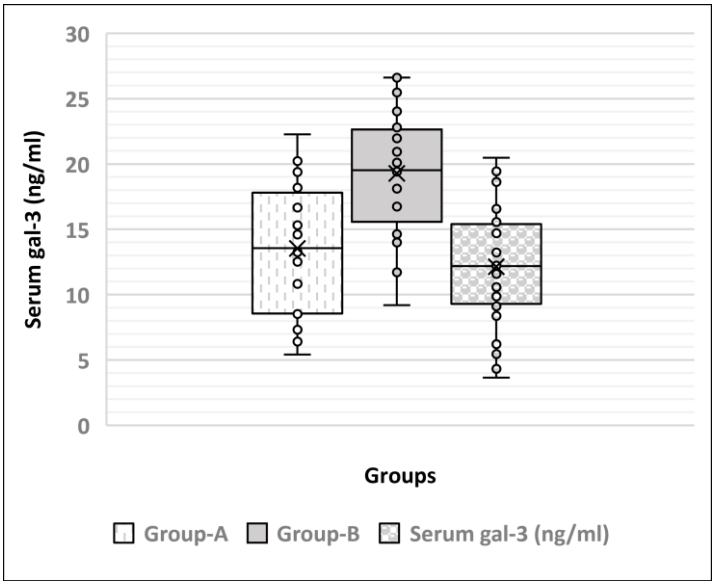

Figure 4: box plot of serum galectin 3 levels in measured the persistent AF, permanent AF, and control groups respectively. The medians and the interquartile ranges are shown as boxes whereas the 10th and 90th percentiles are shown as whiskers.

Discussion

The patient's age is the subject of the first discussion. The study observed that the median age for AF patients was noticeably high. None surprisingly, this result reflects the current trend of hospitalized participants being older and older [22]. It is critical to emphasize that in the near future, clinical management of the elderly patient with AF will become increasingly common and crucial. Adopting new data, such as that provided by biomarkers, can be helpful to customize the therapy and better recognize the distinctions between each individual patient. Additionally, the multi-pathology conditions and multiple therapies that are common in older patients provide a clinical context that makes treating AF more challenging.

The research data revealed that patients with permanent AF had a lower LVEF% and higher left atrial diameter with respect to other groups. These findings are compatible with those provided by several other studies in which a correlation between AF and reduced overall cardiac contractility was observed [23-25]. The aging process and the development of AF can both result in an irreversible structural cardiac adaptation that may be revealed as a left atrial dilation with various grades [26]. Finally, having a chronic heart condition, such as a permanent AF, is by itself can reduce the LVEF.

The median value recorded for serum Gal-3 level for the entire patients was 16.4 ± 5.52 ng/mL, this value was in concordance with other studies in which the serum Gal-3 level was 17.61 ± 6.84 ng/ml [27] and 16.1 ± 6.6 ng/ml. On the other hand, few reports assumed way lower values than those reported by this study where the biomarker recorded 9.6 ± 6 ng/ml and 6.83 ng/ml. The disparity among the figures might be attributed to the impact of the age. The current study involved a cohort with a greater mean of age compared to disparate studies.

Cardiac remodeling can occur after an insult to the heart so that the latter adapts to physiological or pathological stimuli [28]. For example, when the left ventricle is affected after an attack of myocardial infarction, it will undergo structural changes in terms of shape and size. The ventricle assumes a more globular form instead of the regular ellipsoid one after cross-section, and there will be thinning of the walls [29]. Mechanical stress is much known for causing cardiac remodeling. In general, mechanical load can be either pressure overload or volume-overload.

Atrial fibrillation can be both, a cause and consequent of mechanical stress. For instance, in heart failure and as a result of volume overload, the auricle will be stretched and thereby

contributing largely to the development of AF. Additionally, atrial dilation can impose deranged pathways for impulse conduction hence predisposing to re-entry phenomenon which is the key feature predisposing to AF.

Permanent AF patients expressed higher Gal-3 levels at 19.27 ± 4.58 ng/ml versus 13.54 ± 4.9 ng/ml and 12.14 ± 4.69 ng/ml for the persistent AF and the control group, respectively, $p<0.0001$. This is probably a mere reflection of their chronic condition. There are several causes of AF, but viewing the cause based upon the underlying pathophysiology would reveal that fibrotic myocardium is not the sole player. Longstanding AF causes an elevated left ventricular filling pressures, inducing dilation of the left atrium and myocardial fibrosis [30, 31]. This probably explains the prevailed rise of the biomarker in those having permanent AF compared to those with episodic attacks.

Our patients with paroxysmal AF had a Gal-3 level that is not as elevated as their counterparts with the permanent AF type, but nevertheless, they had higher than normal levels of the biomarker in general. Patients with paroxysmal AF had their 95th percentile of the Gal-3 at 20.57 ng/ml compared to the 17.61 ng/ml of the controls, as shown in figure (2). In such patients with somewhat newly diagnosed AF, the arrhythmia most probably initiated by a cardiac ischemic underground as might suggested by the higher number of IHD incidence in this group. Reduced cardiac blood flow is a crucial contributor for the development of AF. The cardiac ischemia will produce different conductive pathways with different speeds and refractoriness and thereby providing the substrate for AF development.

The pathophysiological basis behind ischemia induced AF are probably caused by the deranged action of the 3Na-2K ATPase pump with the consequent increased extracellular potassium and regional acidosis [32]. These factors will affect the imposed a negative bathmotropic effects reducing the excitability, increasing the time needed for recovery after excitation, and reduces the action potential duration [33].

Conclusion:

The biomarker was higher in permanent AF group compared to non-permanent and control groups. The results obtained by this study are amenable with the expectations of having more marker levels in conditions of long-standing AF since they have higher degrees of cardiac fibrosis. Additionally, those with newly diagnosed AF had their gal-3 levels higher than controls reflecting fibrotic adaptation of the myocardium to the cardiac insult that, by itself, triggered the AF attack.

The results revealed a moderate positive correlation between the atrial size and the marker level, as was proven by the echocardiographic evaluation of the patients. Furthermore, the left ventricular ejection fraction showed a moderate negative correlation with marker levels. We concluded that as the left atrium increases in size, this will impose a deleterious effect of the left ventricle and will be reflected as an increasing level of the marker. Hence, the Gal-3 can be used as a tool for evaluating fibrotic changes in patients with AF especially the chronic types.

The limitation of this study is the Gla-3 specificity to fibrosis where many factors may induce the marker expression such as inflammation. Therefore, the increase in marker`s level may reflects a cardiac or even an extra-cardiac inflammatory process rather than cardiac fibrosis. Here, we believe that combining the marker survey with an additional heart specific peptides may resolve the issue in the future.

An additional drawback of this study is that the Gal-3 is recently introduced in the medical literature and data in consideration to its cutoff levels are conflicting. Also, the confounding factors are scarce and need to be addressed in the future to eliminate other causes of raised Gal-3. Last, but not least, the small sample size, of the current study may have affected the statistical analysis in one way or another.

Conflict of Interest Statement:
We declare that there is no conflict of interest.

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