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Relationship between Serum Galectin-3 and Left Atrial Volume Index in Patients with Non-Valvular Atrial Fibrillation

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ABSTRACT

Background: Atrial fibrillation is considered as the most common cardiac arrhythmia. Inflammation is an important factor that has a role in the initiation, maintenance, and recurrence of atrial fibrillation. Both larger left atrial size and higher serum galectin-3 were found to be associated with increased recurrence of atrial fibrillation.

Aims: To study the relationship between serum galectin-3 and left atrial volume index in patients with non-valvular atrial fibrillation.

Methods: A case control study was conducted from January 2018 till January 2019 that enrolled 180 patients divided into three equal groups. Galectin-3 levels were measured by enzyme-linked immunosorbent assay.

Results: Serum Galectin-3 level was significantly higher in atrial fibrillation groups weather paroxysmal or persistent versus control. Likewise, left atrial volume index was significantly higher in patients with persistent compared to paroxysmal atrial fibrillation and both were significantly higher than the control group. The independent predictors of atrial fibrillation were serum Galectin-3 level (OR 1.166, 95% CI 1.039-1.309) and LAVI (OR 1.479, 95% CI 1.269-1.723). Multivariate linear regression analysis demonstrated that age, female gender, hypertension, left atrial volume index and age were independent predictors of higher serum Galectin-3 levels.

Conclusion: Patients with atrial fibrillation (whether persistent or paroxysmal) were significantly older, hypertensive and had higher left atrial volume index and galectin-3 levels than healthy population. galectin-3 level and left atrial volume index are independent predictors of atrial fibrillation.

Keywords: Atrial fibrillation; Left atrial volume index; Galectin-3

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INTRODUCTION

Atrial fibrillation (AF) is considered as the most common cardiac arrhythmia[1] that is known to be associated with electrical and structural changes in the atria known as atrial remodeling that is characterized by atrial dilatation and deterioration of atrial conduction[2]. Inflammation is an important factor that has a role in the initiation, maintenance, and recurrence of AF[3].

Galectin-3 (Gal-3) is considered as an α-galactoside-binding lectin. It is believed that Gal-3 plays multiple roles; a major role in the mediation of the cell-to-cell and cell-to-extracellular matrix interactions. Likewise, it acts as a novel chemo-attractant for monocytes and macrophages[4, 5].

In addition, it had an important role in several fibrotic conditions, including cardiac fibrosis[6]. Also, it's proposed that Gal-3 is an important factor in the cardiovascular inflammation and fibrosis that result in cardiac remodeling[6]. Although in multiple studies had claimed that there is an association between AF and atrial fibrosis[7, 8], the role of Gal-3 in the pathogenesis of these conditions has not yet been evaluated thoroughly. In recent studies, higher concentrations of circulating galectin-3 were found to be associated with increased risk for AF development[9, 10].

It has been theorized that there was relationship between the size of the left atrium (LA) with cardiovascular mortality, myocardial infarction (MI), cardiovascular stroke (CVS) and AF[11]. Moreover, the left atrial volume index (LAVI) was found to be stronger than the anteroposterior left atrial dimension in predicting the recurrence of the AF[12, 13].

In this study, we aimed to evaluate the relationship of Gal-3 with atrial structural remodeling, which would be interpreted by measuring the LAVI in non-valvular AF whether paroxysmal or persistent AF.

MATERIAL AND METHODS

Study Population

This study was a case-control study that recruited 120 patients aged >18 years and presented to Aswan University Hospital in the period from January 2018 to January 2019. Those patients were diagnosed as non-valvular AF either paroxysmal (Self-terminating, in most cases within 48 hours) or persistent AF that lasts longer than 7 days, including episodes that are terminated by cardioversion.

Sample Size Calculation

Sample size calculation was calculated G*Power 3 software. With a power of 90% and type I error of 5% (α=0.05 and β=90%), the minimum required sample was 160 patients (divided into three equal groups, persistent, paroxysmal AF and control groups) to detect an effect size of 10% in the mean level of gal-3. To avoid possible losses of samples (dropouts) during the study, the number of patients in each group was increased to 60 to be a total of 180 patients.

Ethical and Selection Criteria

The study was approved by the ethical committee of the Faculty of Medicine, Aswan University (IRB No. Aswu/253/6/18) and was adherent to the guidelines of the

declaration of Helsinki. The control group consisted of subjects without history of any disease who underwent routine screening visits in the outpatient clinics. Patients who were pregnant and those with history of valvular disease, congenital heart disease, abnormal thyroid function, coronary artery disease, kidney diseases and autoimmune disease were excluded from the study.

Data collection

Full history and examination data were reported. A standard 12-lead electrocardiogram (ECG) record was recorded at a paper speed of 25 mm/s and amplification of 10 mm/mV. Laboratory evaluation to blood urea by colorimetry or automated chemical analyzer, serum creatinine by Jaffe reaction, thyroid function tests (TSH, free T3, and free T4) by Enzyme Linked Fluorescent Assay (ELFA), electrolytes (sodium, potassium, ionized calcium). Sodium and potassium by atomic absorption spectrometer, ionized calcium by Ion Selective Electrodes and plasma concentrations of Gal-3 were detected by an enzyme-linked immunosorbent assay kit (SinoGeneClon Biotech Co.,Ltd).

Echocardiography examination was performed by using Philips IE 33 machine with simultaneous ECG tracing. Images were obtained by a single operator blinded to clinical and biochemical information. The LAVI was being achieved using the biplane area length method. The area in the apical four chamber view (A1) (not taking the initiation of pulmonary veins and left atrial appendage into account), two-chamber view (A2) (after detection of teapot sign for accuracy[12] and the smallest long axis length of the left atrium at ventricular end-systole were measured. Then the LAVI would be calculated by this formula: (0.85A1*A2)/L. The correction for BSA will be applied on LAVI.

Statistical Analysis

An Excel spreadsheet was established for the entry of data. We used validation checks on numerical variables and option-based data entry method for categorical variables to reduce potential errors. The analyses were carried with IBM-SPSS software (Statistical Package for the Social Sciences, version 21, SSPS Inc, Chicago, IL, USA). Numerical data were expressed as mean ± SD, median and interquartile range [IQR]. Frequency tables with percentages were used for categorical variables.

One-Way ANOVA was used to determine the mean difference between groups. Chi-square/Fisher-Exact tests were used to analyze categorical variables as appropriate. Spearman ranked correlation analysis was used for the relationship between serum gal-3 and predictor factors. Linear regression analysis was used to identify the univariate predictors of serum galectin-3 levels. Univariate predictors at p value < 0.1 were entered into a multivariate stepwise linear regression model to identify the independent predictors of galectin-3 levels. Binary logistic forward regression analysis was used to define the independent predictors of AF among variables that showed significant differences among studied groups. A p-value of < 0.05 was considered statistically significant.

RESULTS

The study was a case-control one included 180 participants (60 patients with paroxysmal AF, 60 with persistent AF and 60 control). The demographic data of the study groups were shown in table 1. Patients with persistent AF were significantly older (60.8 ± 11.3) compared with those with paroxysmal AF (54.5 ±15.8), and both AF groups were significantly older than the control group (40.14 ±12.8).

Regarding gender, female patients represented 40% of the persistent AF group, 60% of the paroxysmal AF group and about 29% of the control group and this relationship was statistically significant. Moreover, patients with paroxysmal AF were significantly more hypertensive (62%) than those with paroxysmal AF (47%).

Median serum Gal-3 level was significantly higher in AF groups either paroxysmal (21 ng/ml) or persistent (21.5 ng/ml) compared with control (5 ng/ml), p <0.0001 (Table 2 & Figure 1). Also, mean left atrial volume index (LAVI) was significantly higher in patients with persistent AF (38.9 ± 5.1 ml/m2) compared to paroxysmal AF (36.8 ± 5.3 ml/m2) and both were significantly higher than the control group (24.4 ± 4.8 ml/m2), p < 0.0001 (Table 2 & Figure 2).

Univariate correlation analysis was presented in table 3. There was significant positive moderate to high moderate correlation between serum gal-3 and female gender, patients age, presence of hypertension, diabetes, and LAVI (r=0.222 to 0.675, p < 0.05)

Multivariate regression analysis was illustrated in table 4. The R2 of the model was 0.664 i.e. the independent predictors included in the model represented 66.5% of the total predictors of the serum gal-3 level in the study sample.

The final linear regression model included four independent predictors of serum gal-3 level: hypertension, gender, LAVI and age. In other words, the intercept (serum gal-3 level) was 14.02 ng/ml (11.2–16.8) after adjusting for all correlates (p<0.001). Moreover, patients with hypertension had 2.79 ng/ml higher serum gal-3 level compared with those free from the disease (B-coefficient = 2.792, 95% CI: 0.751 - 4.833, p = 0.008). Furthermore, serum gal-3 level was 2.63 ng/ml higher in female patients compared with males (B-coefficient = 2.634, 95% CI: 1.144 - 4.124, p = 0.001).

Likewise, it was found that with every ml/m^2 increase in the LAVI there was 0.47 ng/ml increase in the level of serum gal-3 (B-coefficient=0.467, 95% CI: 0.328 - 0.605, p < 0.0001). Also, it was found that with every year increase in the patient's age there was 0.11 ng/ml increase in the level of serum gal-3 (B-coefficient = 0.111, 95% CI: 0.055 - 0.168, p < 0.0001).

All variables that were significantly different between AF and control groups were entered into a logistic regression model to define the independent predictors of the occurrence of AF. The independent predictors of AF were age, male gender, serum Gal-3 level, LAVI, EF% and k-level (Table 5).

DISCUSSION

In the present study, old age, male patients, the prevalence of diabetes and hypertension in AF patients were more than 50%. Patients' groups were more likely to be older, hypertensive or diabetic, although these risk factors (except age and sex) were not found to be independent predictors of

AF by logistic regression analysis. AF is a multifactorial condition. The risks of developing AF can be associated with demographic factors, lifestyle factors, cardiovascular conditions, and comorbid conditions/procedures[14].

Our findings were in agreement with Fumagalli et al., 2015 who utilized EORP-AF (EUR-Observational Research Program-Atrial Fibrillation) general pilot registry data to analyze the differences in presentation, co-morbidities, and treatment of AF according to age. In their study, one-third of patients was ≥ 75 years of age. Older patients were found to had frequent persistent or permanent AF compared with younger patients[15]. In line with these findings, Mashat et al., 2019 studied the risk factors and comorbidities of AF in Saudi Arabia through a retrospective review of cases in King Abdul-Aziz Hospital in Jeddah during the period from 2010 to 2017. A total of 167 patients were included in the analysis (43% were males). Hypertension was the most prevalent risk factor encountered about 73%, followed by valvular heart disease[16].

This study found that there were statistically significant differences between the study's groups in terms of LAVI. Patients with persistent or paroxysmal AF had significantly higher LAVI values than the control group. LAVI was significantly higher in persistent AF group compared to paroxysmal AF group. This was consistent with Habibi et al., 2016 who examined the association of LA volume and the function and incident AF in a multi-ethnic population free of clinical cardiovascular diseases. The baseline LA size and the function were compared between 197 participants with incident AF and 322 participants randomly selected from the whole Middle East Studies Association (MESA) cohort. In the multivariable analysis, they concluded that elevated LAVI was associated with incident AF[17].

Similarly, Farouk-Musa et al., 2018 performed a retrospective study to investigate the factors determining the occurrence of permanent AF. Four hundred and forty-two patients aged 46 ± 12 years, 190 men) were investigated. LAVI was found to be an independent predictor for the occurrence of AF. LAVI > 39 ml/m2 was the cut-off value for the best prediction of new-onset permanent AF (sensitivity 79%)[18].

In the present study, it was found that serum Gal-3 was significantly elevated in patients with AF compared to normal controls. The present study showed that the independent predictors of higher serum Gal-3 level were presence of hypertension, female gender, higher LAVI, and older age. In agreement with our findings, a prospective study was performed to determine whether serum Gal-3 levels were elevated in patients with AF and preserved left ventricular function[19]. Seventy-six patients with paroxysmal or persistent AF and preserved left ventricular systolic function and 75 age- and gender-matched control subjects were enrolled in this study. Serum Gal-3 and LAVI were significantly greater in patients with AF compared with the control group. Serum Gal-3 levels were also significantly higher in patients with persistent AF than those with paroxysmal AF. In addition, serum Gal-3 and LAVI were independent predictors of AF[18].

In agreement with our findings Clementy and colleagues[20] sought to study the accuracy of galectin-3 level in 71 predicting recurrences of AF after ablation. Serum concentrations of galectin-3 were determined in a consecutive series of patients addressed for AF ablation. Only higher galectin-3 level and larger left atrial diameter independently predicted recurrence. Patients with both galectin-3 level <15 ng/mL and left atrial diameter <40 millimeters had a 1-year arrhythmia-free survival rate - after a single procedure without anti-arrhythmic drug - of 91%, as compared with 41% in patients with galectin-3 ≥ 15 and left trial diameter ≥40[20].

Also, the relationship between serum Gal-3 levels and paroxysmal AF was examined[21]. Forty-six patients with paroxysmal AF and preserved left ventricular systolic function, and 38 age- and gender-matched control subjects, were involved in the study. Serum Gal-3 levels were significantly elevated in patients with paroxysmal AF compared with the control. Left atrial diameter was significantly higher in patients with paroxysmal AF. Left atrial diameter was found to be significantly correlated with serum Gal-3 levels in patients with paroxysmal AF[21].

The present study had some limitations; the study was a single-center experience and therefore the results cannot be generalized to the general population. Also, the cohorts chosen were not matched for comparison possibly limiting our drawn conclusions. Further studies are still needed to confirm our findings.

CONCLUSION

In conclusion: patients with AF (whether persistent or paroxysmal) had significantly older age, hypertensive and had higher LAVI and galectin-3 values than healthy population. Serum Gal-3 level and LAVI are independent predictors of AF. Hypertension, female gender, LAVI and age are independent predictors of serum galectin-3 level.

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DISCLOSURE

There were no conflicts of interest in this work.

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Table 1: Demographic characteristics of the included patients

Variables	Persistent AF (n = 60)	Paroxysmal AF (n = 60)	Control (n = 60)	P-value
Age in years				
• Mean ±SD	60.8 ±11.3*	54.5 ±15.8* ǂ	40.14 ±12.8	< 0.001
• Median (range)	63 (55 -68)	54.5 (45 -66)	38 (28 -46)	
Female, No (%)	24 (40%)	36 (60%) * ǂ	16 (29.3%)	= 0.001
Hypertension, No (%)	37 (61.7%)	28 (46.7%) ǂ	0	NA
DM, No (%)	21 (35%)	19 (31.6%)	0	NA
Vascular & Stroke, No (%)	0	1(1.7%)	0	NA

*Data are presented as mean ±SD, median (Range), or number (%). NA: not applicable, * P<0.001 compared to the control group, † p<0.05 compared to the control group, ǂ p<0.05 compared to the persistent group

Table 2: Galectin-3 level, LAVI and CHA_2D-VAS_2c Score of the included patients

Variables	Persistent AF (N =60)	Paroxysmal AF (N =60)	Normal (N =60)	P-value
Galectin-3 (ng/ml)				<0.001
• Mean ±SD	18.8 ± 5.7*	17.4 ± 7.6*	6.0 ± 3.4	
• Median (range)	21.5 (18.7-22.2)	20.9 (16.9 - 22.5)	5.1 (4.1 - 7.1)	
LAVI (ml/m²)				
• Mean ±SD	38.9 ± 5.1*	36.8 ± 5.3*ǂ	24.4 ± 4.8	<0.001
• Median (range)	39 (37 - 42)	37 (30 - 42)	24 (22 - 26)	
CHA2D-VAS2c Score				
• Mean ±SD	1.9 ± 1.3	1.8 ± 1.5	-	
• Median (range)	2 (1 - 3)	2 (0 - 3)		NS
Risk, No (%)				
• Low	15 (25%)	17 (28.3%)		NS
• Moderate	26 (43.3%)	21 (35%)	-	
• High	19 (31.6%)	21 (35%)		

*Data are presented as mean ± SD, median (Range), or number (%). * P < .001 compared to control group, † p<.05 compared to control group, ǂ p<.05 compared to persistent group. NS: non significance

Table 3: Univariate Correlation analysis for independent associates of serum Gal-3 levels

Variables	rho	P-value
• Study group	0.1	0.261
• Age	0.567	<0.001
• Female gender	0.402	<0.001
• Hypertension	0.457	<0.001
• Diabetes	0 .222	0.015
• Vascular disease or stroke	0.055	0.549
• LAVI	0.675	<0.001
• EF	- 0.166	0.07
• TSH	- 0.041	0.659
• Free T3	0.174	0.058
• Free T4	0.058	0.531

*Data are expressed as Spearman rank correlation coefficient (rho) and p-value. EF=ejection fraction; LAVI=left atrial volume index; TSH=thyroid stimulating hormone

Table 4: Multivariate stepwise linear regression analysis for identifying independent predictors of Gal-3 level

Variable	β (95% CI)	T-Statistics	P-value
• Constant	14.021 (11.2-16.8)	8.966	<0.001
• Hypertension	2.792 (0.751-4.833)	2.700	0.008
• Female gender	2.634 (1.144-4.124)	3.489	0.001
• LAVI	0.467 (0.328-0.605)	6.654	<0.001
• Age	0.111 (0.055-0.168)	3.881	< 0.001

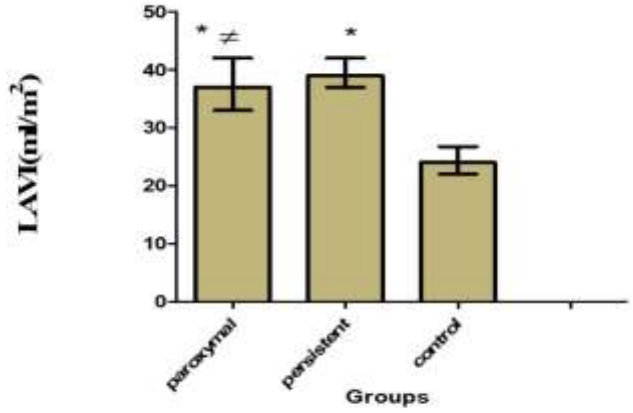
CI=confidence interval; LAVI=left atrial volume index, SE=standard error

Table 5: Independent Correlates of AF: Multivariable Logistic Regression

Factor	OR (95% CI) *	P-value
• Age/years	1.09 (1.06 – 1.12)	< 0.001
• Male Sex	2.75 (1.40 – 5.40)	= 0.018
• EF %	0.83 (0.77 – 0.89)	= 0.008
• K (mmol/l)	0.19 (0.06 – 0.57)	= 0.003
• Gal-3 (ng/ml)	1.29 (1.21 – 1.39)	< 0.001
• LAVI	1.55 (1.36 – 1.78)	< 0.001

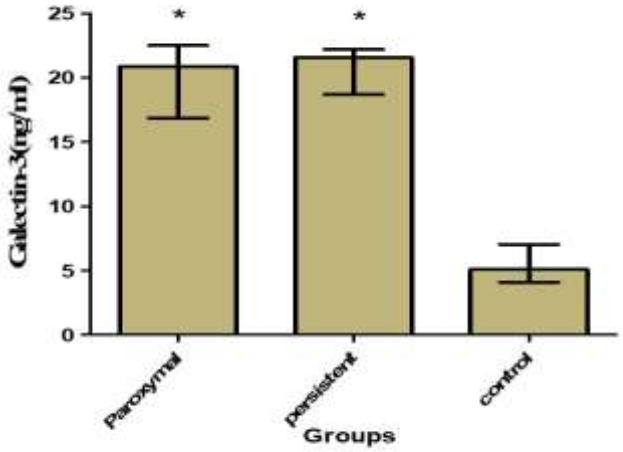
- *OR=Odds Ratio, CI= Confidence Interval

FIGURE LEGENDS



* P< .001 compared to control group, † p<.05 compared to control group, ‡ p<.05 compared to persistent group.

Figure 1: Galectin-3 level among studied groups



* P< .001 compared to control group, † p<.05 compared to control group, ‡ p<.05 compared to persistent group

Figure 2: LAVI of the included patient

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