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ORIGINAL ARTICLE

Increased Circulating Fetuin-A Levels in Patients with Atrial Fibrillation

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Abstract

Background: Biomarkers related to the pathogenesis of atrial fibrillation (AF) have attracted the attention of experts. One of these recently studied biomarkers is Fetuin-A.

Objectives: This study aimed to evaluate the relationship between serum Fetuin-A levels and AF.

Methods: This study used the convenience sampling method, based on inclusion criteria and consent to participate in the study. The Shapiro-Wilk test was used to confirm the normal distribution of all continuous variables. Categorical variables were presented using absolute and relative frequencies. Both groups (48 patients with AF and 47 controls) were compared in terms of biochemical, hematological, and echocardiographic findings and Fetuin-A. the Chi-square or Fisher's exact test were used to compare groups concerning categorical variables. Continuous variables were compared using the independent samples t-test. P<0.05 was considered statistically significant.

Results: Serum Fetuin-A values increased in AF patients when compared to the controls (544±49 μg/mL versus 484±46 μg/mL, p=0.001). Moreover, Fetuin-A level was independently associated with AF — AOR = 0.978, 95%; confidence interval (CI) 0.969-988, p < 0.001. The cut-off values in Fetuin-A levels in patients with AF were >511.80 μg/mL with a sensitivity of 75% and a specificity of 73% — area under the curve (AUC) = 0.804, 95% CI = 0.715 - 0.892.

Conclusions: According to this study, there was a relationship between serum Fetuin-A levels and AF, regardless of conventional cardiovascular risk factors. Therefore, Fetuin-A may play a role in the pathophysiology of AF. Prospectively designed cohort studies are necessary to assess whether or not the results can be generalized for other populations.

Keywords: alfa-2-Glicoproteína-HS; Atrial fibrillation; Inflammation.

Introduction

Atrial fibrillation (AF) is one of the most prevalent arrhythmias in the world and the main cause of cardiac-related morbidity and mortality.[1] Its frequency increases with age. AF development in chronic cardiovascular diseases, such as coronary artery disease (CAD), hypertension, and heart failure, worsens the clinical disease and is an important cause of hospitalization due to arrhythmia. Although it is associated with many conditions, there is no specific cause of AF. In approximately ten percent of all AF cases, no underlying heart problem is found. AF, in these cases, may be associated with other factors, such as excessive caffeine use, stress, alcohol or certain drugs, as well as electrolyte or metabolic imbalances[2,3] However, in some cases of AF, no cause can be found. The relationship between inflammation, calcification, aging, and AF is a well-known theme and has been reported in previous studies.[3,4]

Fetuin-A was first discovered in fetal serum, excreted by many different kinds of tissues, such as adipose tissue, placenta, and tongue, but primarily generated and secreted by the liver. Fetuin-A participates in many functions in human growth and development, the pathophysiology of inflammation and calcification, and in the course of many chronic diseases, such as cardiovascular disease, diabetes, metabolic syndrome, and kidney disease.[5-11] Because of the opposing

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Central Illustration: Increased Circulating Fetuin-A Levels in Patients with Atrial Fibrillation

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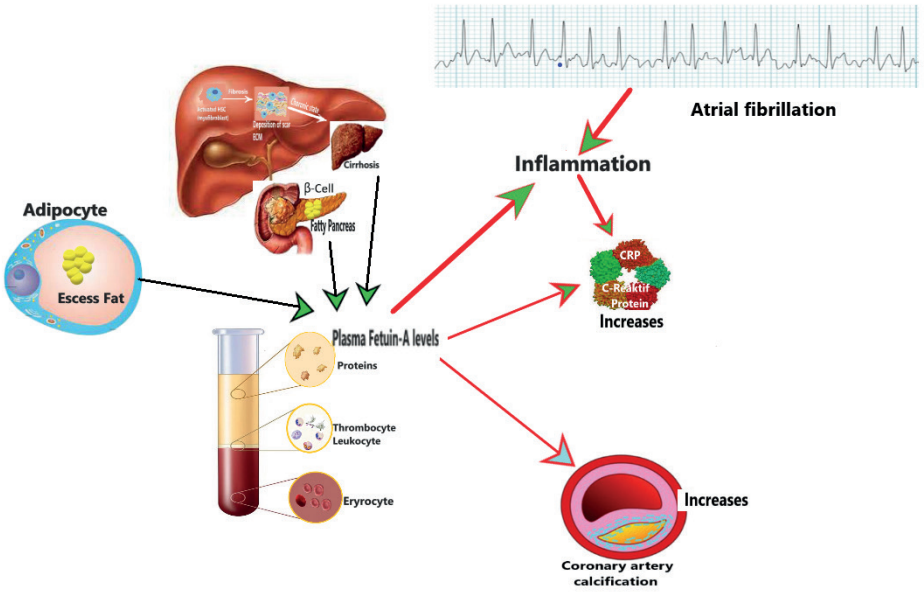

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pathways, previous studies have failed to provide consistent results concerning the relationship between circulating Fetuin-A and the risk of cardiovascular diseases. Nevertheless, lower Fetuin-A levels have predicted increased cardiovascular mortality in end-stage renal disease patients, dialysis patients, and the general population, which indicates a potential connection between calcification levels and higher cardiovascular events and mortality.[12-14] However, other studies have reported that increased Fetuin-A levels in patients with type 2 diabetes mellitus were independently and positively correlated with the presence of cardiovascular events. The aforementioned results suggested that different pathways of the regulation of Fetuin-A in various diseases could influence the results.[8]

To the best of our knowledge, the potential association between Fetuin-A and AF has not been studied to date. Therefore, the present study aimed to investigate the circulating Fetuin-A levels in AF patients.

Materials and Methods

Study design and setting

The prospective case control study recruited 95 consecutive patients (48 patients with AF, 47 patients with normal sinus rhythm) who were attending the Cardiology Department of Sivas Cumhuriyet University Hospital. Convenience sampling was used, based on inclusion criteria and consent to participate in the study. Each AF patient was matched with a normal sinus rhythm patient regarding age, gender, hypertension, and diabetes. The study protocol was approved by the institutional ethics committee for human research and an informed consent form was signed by each patient and/or legal guardian.

Inclusion criteria for the patient's were: must be older than 18 years of age, have normal ejection fraction tested by echocardiography (>50), and show a normalAF rhythm, whereas normal sinus rhythm was the critera for the control group .

Patients with the following medical conditions were excluded from this study: prior weight management strategies, such as calorie restrictions and bariatric surgery; reduced ejection fraction tested by echocardiography (<50); acute coronary syndrome; acute/chronic heart failure; moderate-to-severe valvular heart disease; the presence of a pacemaker; hepatic or renal insufficiency (alanine aminotransferase and aspartate aminotransferase levels of >2-fold normal; serum creatinine levels of >1.5 mg/dL); hypothyroidism or hyperthyroidism; a current acute or chronic infection; malignancy ; connective tissue disease; a

medical history of strokes; alcohol use; and hematological, respiratory, immunological, and inflammatory disorders.

The presence of hypertension was defined as patients using antihypertensive drugs or at least two blood pressure measurements of 140/90 mmHg or above. Diabetes mellitus was defined as patients using antidiabetic drugs, patients whose blood sugar was controlled by dieting, or patients whose blood sugar, after eight hours of fasting, was 126 mg/dl. Hypercholesterolemia was defined as patients who have been treated for hypercholesterolemia, or serum cholesterol concentrations higher than 200 mg/dL, with either fasting or nonfasting. CAD was defined as the presence of a clinical history of CAD, abnormal stress test results with evidence of ischemia, segmental left ventricular akinesia or dyskinesia tested by echocardiography, pathologic Q waves tested by electrocardiography, or a >50% luminal narrowing of any epicardial coronary arteries observed in a prior coronary angiogram. Smoking was defined as smokers who are currently smoking or who have quit within the past year.

The blood samples were drawn under appropriate conditions after 8 hours of fasting. The biochemical test was measured by means of a Beckman Coulter Synchron LX20 (Brea, CA, USA) autoanalyzer, using original kits.

Transthoracic echocardiographic examinations were evaluated using the Vivid 7 cardiac ultrasonography system **(GE** Healthcare**, Medical Systems)** by experienced echocardiographers, along with 2.5-MHz to 5-MHz probes. The modified Simpson method was used to calculate the left ventricular ejection fraction (LVEF) and chamber sizes according to recent guidelines.[10]

The group with and without AF were evaluated in terms of demographic, echocardiographic, hematological, and biochemical laboratory data.

Immunoassay analysis

Plasma Fetuin-A levels were measured from peripheral venous blood samples collected from patients. After receiving venous blood samples, the tubes were centrifuged at 4000 rpm for 4-5 minutes. Samples were stored at -80°C. Plasma Fetuin-A levels were measured using a human Fetuin-A enzyme-linked immunosorbent assay. Measurements using an ELISA kit were performed in duplicate for each sample (Cat no: EK-067-52, lot no: 603894; Phoenix Pharmaceuticals, Belmont, CA, USA).

Statistical analyses

Statistical analysis was performed using the SPSS 22.0 packet computer program (IBM corp. New-York, USA); the value of $P<0.05$ was considered statistically significant. The Shapiro-Wilk test was used to confirm the normal distribution of all continuous variables, which were presented as mean and standard deviation. Categorical variables were presented using absolute and relative frequencies. The chi-square and/or Fisher's exact test were used to compare the groups (with AF and without AF) to determine the categorical variables. Continuous variables were compared using the independent samples t-test. Multiple logistic regression analysis was then performed to explore which variables were independently associated with AF, taking into account the potential covariate effects, including participant's sex, age, and BMI, using odds ratios (OR) and 95% confidence intervals (CI). Fetuin-A and C reactive protein were included in the model as independent variables. Receiver operator characteristic (ROC) curve analysis was performed to identify the optimal cut-off value for Fetuin-A (which sensitivity and specificity level would be the maximum) to predict AF. The area under the curve (AUC) with a 95% CI was estimated when predicting AF. The optimal cut-off value of Fetuin-A was identified as the value parallel to the highest sum of sensitivity and specificity-1.

Results

A total of 95 patients were included in the study and compared, in which 48 patients (23 males, 25 females; mean age 75±8 years) were AF and 47 patients (21 males, 26 females; mean age 76±8 years) presented a normal sinus rhythm. The demographic characteristics, and biochemical and echocardiographic values of the patients are shown in Table 1. No statistically significant difference was found between the two groups in terms of age, gender, the presence of diabetes mellitus, hypertension, CAD, and smoking status. There was also no statistically significant difference between the groups in terms of biochemical tests, including glucose, blood urea nitrogen, creatinine, total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, aspartate aminotransferase, and alanine aminotransferase.

No statistically significant difference was observed between the groups in terms of ejection fractions; however, the left atrial diameter was significantly higher in the AF group (Table 1).

Table 1 – Characteristics of the patients with and without AF

Variables	Patients With Normal Sinus Rhythm (n:47)	Patients With Atrial Fibrillation (n:48)	P-value
Mean age (years)	76.0±8.0	75.0±8.0	0.39
Gender, male, n (%)	21 (44.7)	23 (47.9)	0.75*
Hypertension, n (%)	46 (97.9)	45 (93.8)	0.32*
Diabetes mellitus, n (%)	18 (38.3)	20 (41.7)	0.74*
Hyperlipidemia, n (%)	34 (72.3)	27 (56.3)	0.10*
CAD, n (%)	26 (55.3)	21 (43.8)	0.26*
Current smoking, n (%)	9 (19.1)	8 (16.7)	0.75*
White blood cell, (x 10^3/μL)	6.9±1.1	7.2±1.4	0.26
Hemoglobin (g/dl)	12.0±1.6	12.3±1.6	0.32
Platelet (10^3/mL)	239.9±60.9	235.2±58.8	0.70
Glucose (mg/dL)	106.3±22.4	110.3±20.2	0.36
Blood urea nitrogen (mg/dL)	22.9±11.0	22.7±9.5	0.94
Creatinine (mg/dl)	1.02±0.2	1.00±0.2	0.72
Total cholesterol (mg/dL)	185.7±44.1	196.7±35.9	0.18
Triglyceride (mg/dL)	157.2±54.2	155.9±40.8	0.89
HDL-cholesterol (mg/dL)	43.5±13.0	41.8±5.2	0.42
LDL-cholesterol (mg/dL)	108.7±27.9	114.7±19.5	0.22
AST (IU/L)	22.4±8.4	23.6±8.7	0.49
ALT (IU/l)	23.8±9.6	35.4±14.7	0.27
Left ventricle ejection fraction (%)	55.0±2.0	53.0±3.0	0.57
Left atrial diameter, mm	36.0±2.0	45.0±4.0	<0.001
C reactive protein (mg/dL)	2.9±0.6	3.3±1.0	0.016
Fetuin-A (μg/mL)	484.0±46.0	544.0±49.0	0.001
Body mass index	32.0±5.0	31.0±5.0	0.40

** χ2 test; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transferase; LVEDD: Left ventricular end diastolic diameter. CAD: Coronary artery disease.*

As shown in Table 2, the Fetuin-A level was independently associated with AF. In the ROC analysis, the optimal cut-off value for Fetuin-A in patients with AF was >511.80 μg/mL, with a sensitivity of 75% and a specificity of 73% (AUC = 0.804, 95% CI = 0.715 - 0.892) (Figure 1, Table 3).

Discussion

The present study demonstrated that higher plasma Fetuin-A levels were associated with patients with AF after adjustment for confounding factors.

Fetuin-A is a glycoprotein that is primarily synthesized by the hepatocytes and which acts systemically in the blood.[15] Fetuin-A is considered to be involved in many normal and pathological processes, such as the response

Table 2 – Multiple logistic regression analyses of variables associated with AF (n = 95)

Independent Variables	Adjusted OR*	95% CI	P-value
C reactive protein	0.570	0.313 -1.041	0.067
Fetuin-A	0.978	0.969 -0.988	<0.001

** Adjusted for age, sex, and BMI; OR: odds ratio; CI: confidence interval.*

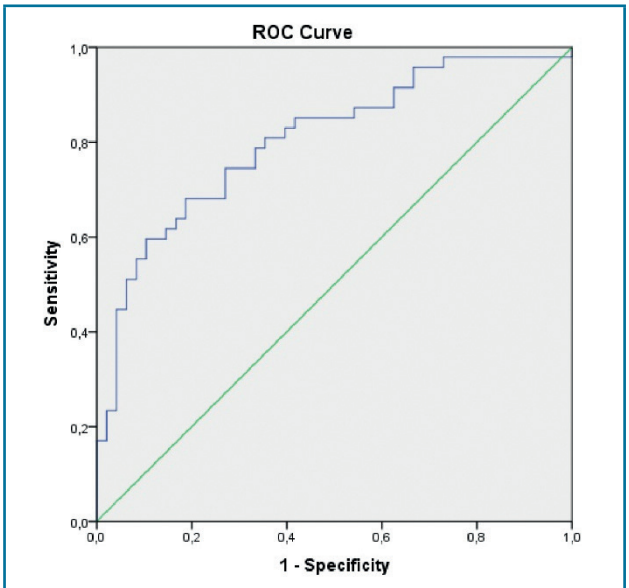

Figure 1 – ROC curve of fetuin-A levels in patients with atrial fibrillation.

Table 3 – Cut-off value, sensitivity and specificity of serum Fetuin-A levels in predicting AF.

	Fetuin-A level
Cut-off value	511.80
Sensitivity	0.75
Specificity	0.73
AUC (95% CI)*	0.804 (0.715-0.892)

**AUC: area under the curve; CI: confidence interval; AF: atrial fibrillation*

to systemic inflammation, hepatocyte-growth-factor activity, the regulation of insulin activity, the inhibition of unwanted mineralization, osteogenesis, and bone resorption.[15,16] However, in some cases, the effect of the circulating Fetuin-A is not fully known, and AF is one of these unknown factors. Since AF is an inflammatory condition, some biomarkers may appear or change as a result of the disease, while some may be pre-existing or altered, causing disease or disease progression. The role of Fetuin-A, which plays an important role in the process of inflammation and calcification, may be interesting in AF, a pathology in which the same processes play an important role in the pathogenesis (Central Figure). The relationship between serum Fetuin-A levels and emerging AF and the prognosis of the disease has not been studied in previous works.

Although there is evidence that Fetuin-A participates in many functions in the pathophysiology of inflammation and calcification, and thus in the course of many chronic diseases, its role is still unclear as to whether or not Fetuin-A protects against or actually exacerbates vascular disorders.[5-11] The published literature suggests that Fetuin-A has a biphasic effect on atherosclerosis by acting as a protective factor through the inhibition of calcification or as an atherogenic factor via the induction of insulin resistance.[17,18] Furthermore, some studies have demonstrated that high serum Fetuin-A levels are associated with CADs and their comorbidity conditions, such as diabetes, insulin resistance, dyslipidemia, or fatty liver disease.[4,10,18-21] Our study found that a high Fetuin-A level was independently associated with AF. Another study, however, found no association between insulin resistance and Fetuin-A levels in patients with diabetes mellitus.

It has been shown in previous studies that low serum Fetuin-A levels are associated with myocardial calcification, cardiac fibrosis, diastolic dysfunction, impaired tolerance to ischemia, and catecholamine resistance in a Fetuin-A knock-out mouse model.[11] In a recent meta-analysis of four prospective CAD studies, all causes of mortality proved to be low in patients with high serum Fetuin-A levels.[5] Low serum Fetuin-A levels in dialysis patients were associated with uremic vascular calcification and cardiovascular mortality in a cross-sectional study.[12] In the French Registry of Acute ST-Elevation Non-ST-Elevation Myocardial Infarction (FAST-MI), including in 754 patients, decreased serum Fetuin-A values, combined with a high CRP level, were associated with one-year cardiovascular mortality in patients with acute coronary syndromes.[22] Low Fetuin-A was reported as a predictor of mortality in ST-elevation myocardial infarction patients at 6 months, regardless of NT-proBNP, CRP, and CADILLAC risk scores, but there was no association with peak cardiac troponin values in patients with ST-elevation myocardial infarction.[23] One prospective study, including 1,620 patients with CAD, during a follow-up of approximately 6 years, showed that low plasma Fetuin-A levels were associated with an increased risk of CVD mortality and all causes, regardless of traditional CVD risk factors.[24] In a seven-study meta-analysis of 2,283 patients with aortic valve stenosis and 1,549 controls, circulating Fetuin-A levels were lower in patients with end-stage aortic valve stenosis than in healthy subjects.[25] Bortnick et al. declared that Fetuin-A was negatively associated with mitral annular calcium in their study with 5,888 enrolled participants.[26] Ix et al. concluded that low circulating serum Fetuin-A levels were associated with mitral annular calcium and reported that low circulating serum Fetuin-A levels were associated with aortic stenosis in participants without diabetes.[27] The results of another study support these data, showing that Fetuin-A is associated with a major adverse clinical event in the progression of aortic valve disease, regardless of renal function and inflammation.[28]

The calcification-inhibiting effect of Fetuin-A is well-known, but there are conflicting studies in this area. Decreased serum Fetuin-A proved to be associated with calcification, especially in cases of chronic kidney failure, where calcium and phosphate balance were impaired; however, the inhibitory effect of Fetuin-A on calcification was not fully understood when electrolyte balance was not impaired.[29-31] Even with normal renal functions, it is known that high serum phosphorus levels

are associated with atherosclerosis.[32] In one prospective cohort, including 296 patients with aortic valve stenosis, the serum Fetuin-A value was not related to disease or the severity of the disease. Furthermore, the serum Fetuin-A value was not associated with disease progression during 3 years of follow-up. Although calcification plays an important role in the pathophysiology of aortic valve stenosis, and Fetuin-A has a known calcification inhibitory effect, the results of the study showed that there was no relationship between aortic valve stenosis and Fetuin-A.[33] No association was observed between Fetuin-A and cardiovascular events and mortality in the 6-year follow-up of 833 patients with CAD and without end-stage renal disease.[21]

Fetuin-A is an effective hepatokine on circulating calcium and phosphorus balance. Fetuin-A has been studied in CVDs, but there is no study in AF patients. Hence, this is the first study to evaluate Fetuin-A levels in AF patients. According to our study's results for patients with AF, which show high mortality and morbidity events, especially among the elderly, Fetuin-A may well be a new and effective biomarker.

Study Strengths and Limitations

The strength of this case-control study lies in the fact that it is the first to evaluate Fetuin-A levels in AF and was designed prospectively. However, the current study has some limitations. First, the number of patients included was small and all patients were recruited from a single center. Second, we cannot infer whether the Fetuin-A elevation is the cause or the result. AF may be developed when Fetuin-A is elevated, or Fetuin-A may be elevated because AF develops. To clarify this issue, it is necessary to plan prospective, large-scale studies that begin before AF develops. Third, this study does not show the relationship between Fetuin-A and AF, not does it define if it is a true link or merely a relationship. Therefore, the results of this current study should be interpreted with caution.

Conclusion

This case-control study showed that serum Fetuin-A levels were associated with AF. Although CVD risk factors were adjusted, the relationship between Fetuin-A plasma levels and AF was interesting. Nonetheless, large prospective studies are needed to confirm the results of this study and to allow for its use in daily practices. According to our research, this is the first study of its kind to evaluate the relationship between AF and Fetuin-A.

Author Contributions

Conception and design of the research, acquisition of data, obtaining financing and writing of the manuscript: Tekin G; analysis and interpretation of the data: Tekin G, Tekin YK, Aydın H; statistical analysis: Tekin G, Nur N; critical revision of the manuscript for intellectual content: Tekin G, Tekin YK, Aydın H, Nur N.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Sivas Cumhuriyet University under the protocol number 2018-09/01. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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