TLAR 1947

Arch Rheumatol 2015;30(1):1-5
doi: 10.5606/ArchRheumatol.2015.5061

ORIGINAL ARTICLE

Serum Fetuin-A Level in Patients With Ankylosing Spondylitis and its Relationship With Clinical Parameters

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ABSTRACT

Objectives: This study aims to investigate the association of serum fetuin-A levels with disease activation and clinical parameters in ankylosing spondylitis (AS) patients.

Patients and methods: Forty-seven AS patients (30 males, 17 females; mean age 39.7±11.1 years; range 20 to 69 years) and 30 healthy controls (14 males, 16 females; mean age 42.0±11.5 years; range 19 to 63 years) were included in the study. Erythrocyte sedimentation rate, C-reactive protein, Bath Ankylosing Spondylitis Disease Activity Index, Bath Ankylosing Spondylitis Functional Index, Bath Ankylosing Spondylitis Radiology Index, and Bath Ankylosing Spondylitis Metrology Index were used in the assessment of AS. Serum fetuin-A levels were measured using ELISA.

Results: Mean serum fetuin-A values in AS patients (984±203 ng/mL) were significantly lower compared to controls (1156±218 ng/mL) (p=0.001). While a statistically significant negative correlation was detected in AS patients between fetuin-A values and C-reactive protein (p=0.009, r=-0.377), no significant correlation was detected between erythrocyte sedimentation rate, Bath Ankylosing Spondylitis Disease Activity Index, Bath Ankylosing Spondylitis Metrology Index, Bath Ankylosing Spondylitis Functional Index or Bath Ankylosing Spondylitis Radiology Index parameters and fetuin-A.

Conclusion: Serum fetuin-A levels in AS patients were lower than the control group. However, further research is required to establish the role of serum fetuin-A levels as a surrogate marker of disease activity.

Keywords: Acute phase reactants; ankylosing spondylitis; fetuin-A.

Ankylosing spondylitis (AS) is a chronic inflammatory disease of the axial skeleton of uncertain etiology characterized by backache and morning stiffness.[1] Several acute phase proteins, particularly erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are used in AS as markers of disease activity to detect prognosis and evaluate treatment response.[2] These proteins are synthesized from the liver in response to cytokines that increase during inflammation. Another inflammation marker known as fetuin-A, which is largely secreted from the liver in adults, has recently been described. Fetuin-A protein has a molecular weight of 59 kD and is present at a serum concentration of 0.5-1 g/L.[3] Some authors have argued that fetuin-A is a negative acute phase protein.[4] Since serum levels decrease together with albumin in acute inflammation, it is thought to be a negative acute phase reactant.[4] Serum fetuin-A levels have been reported to decrease by 20-30% in diseases such as rheumatoid arthritis (RA), pancreatitis and

Received: May 27, 2014 ***Accepted:*** August 15, 2014 ***Published online:*** February 05, 2015

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chronic kidney failure.[5-7] Previous studies have also reported fetuin-A to be inversely correlated with levels of the proinflammatory cytokines interleukin-1 β, interleukin-6, and tumor necrosis factor-α.[8,9] However, others claimed that fetuin-A is a positive acute phase reactant although this hypothesis was supported by only one study. That study demonstrated that fetuin-A levels were elevated in AS patients.[10] It is therefore unclear whether fetuin-A is a negative or positive acute phase reactant.

In this study, we aimed to investigate the association of serum fetuin-A levels with disease activation and clinical parameters in AS patients.

PATIENTS AND METHODS

This study was carried out at the Canakkale Onsekiz Mart University Medical Faculty Hospital between June 2013 and February 2014. Forty-seven AS patients (30 males, 17 females; mean age 39.7±11.1 years; range 20 to 69 years) who were under observation and 30 controls (14 males, 16 females; mean age 42.0±11.5 years; range 19 to 63 years) were included. Patients were asked about their age, sex, duration of disease, cigarette and alcohol consumption and any drugs they were still using. Patients with diabetes, hypertension, hyperlipidemia, chronic kidney disease, or chronic liver disease were excluded. The study was approved by Çanakkale Onsekiz Mart University Medical Faculty Hospital ethical committee and written consents were obtained from all patients.

Patients were evaluated with Bath Ankylosing Spondylitis Disease Activity Index (BASDAI),[11] Bath Ankylosing Spondylitis Functional Index (BASFI),[12] Bath Ankylosing Spondylitis Radiology Index (BASRI),[13] and Bath Ankylosing Spondylitis Metrology Index (BASMI).[14]

Venous blood specimens were collected between 08:00 and 09:00 hours after 12-hour fasting and placed into vacuum tubes to detect fetuin-A levels in the patient and control groups. After specimens were kept for 30 minutes at room temperature, sera were separated by centrifugation at 4000 rpm for 10 minutes and then stored at -80 °C until the day of the study. Fetuin-A levels in serum were measured using a commercial kit based on the quantitative sandwich ELISA technique (Catalog No. EK0757, Boster Biological Technology Co. Ltd., China). Results were read on an ELX 808 IU model ELISA reader.

Statistical analysis

Data analysis was performed with SPSS for Windows version 15.0 software program (SPSS Inc., Chicago, IL, USA). Variable conformity with normal distribution was investigated using the Kolmogorov-Smirnov/Shapiro-Wilk tests. Mean, standard deviation, median, minimum, maximum, frequency and percentage values were used to express descriptive data. The Student's t test was used to compare normally distributed variables between groups, and the Mann-Whitney U test for non-normally distributed variables. Chi-square test was used for comparison of the categorical variables. Correlations between constant variables in the patient group were examined using Spearman's correlation test. Significance was set at $p<0.05$.

RESULTS

There was no significant difference between the patient and control groups in terms of age, sex, body mass index, and alcohol or cigarette use ($p>0.05$, Table 1).

Mean duration of disease among AS patients was 5.4±7.3 years. Forty-three patients were using nonsteroidal anti-inflammatory drugs and four patients were receiving anti-tumor necrosis factor therapy. Patients' mean BASDAI, BASFI, BASMI, BASRI-spine and total BASRI values were 3.2±1.8, 2.7±2, 3.7±1.9, 4±1.5 and 3.3±1.8, respectively. Mean ESR and CRP values in AS patients were statistically higher than the control group ($p<0.001$, Table 1).

Mean serum fetuin-A concentration in AS patients was significantly lower than the control group ($p=0.001$, Figure 1). Mean fetuin-A value in AS patient group was 984±203 ng/mL compared to 1156±218 ng/mL in the control group. We observed a negative correlation between fetuin-A and CRP ($r=-0.377$, $p=0.009$), but there was no significant correlation between fetuin-A and ESR, BASDAI, BASMI, BASFI or BASRI.

Table 1. Sociodemographic and clinical characteristics of patient and control groups

Variables	Patients (n=47)			Controls (n=30)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			39.7±11.1			42±11.5	0.380
Sex							0.138
Female	17			16			
Male	30			14			
Body mass index (kg/m^2)			27.3±5.4			28.8±4.3	0.220
Cigarette use		44.7			50		0.558
Alcohol use		25.5			15		0.545
Erythrocyte sedimentation rate (mm/hour)			30.7±19.71			10.6±7.7	<0.001
C-reactive protein (mg/dL)			1.17±1.16			0.28±0.24	<0.001
Fetuin-A (ng/mL)			984±203			1156±218	0.001

SD: Standard deviation.

DISCUSSION

Fetuin-A behaves as a negative acute phase reactant, the levels of which decrease in acute and chronic inflammation. Lebreton et al.[4] showed that fetuin-A concentrations decrease throughout inflammation and trauma. Furthermore, their results showed that fetuin-A had a negative correlation with acute-phase reactants alpha 1 antitrypsin and haptoglobin and a positive correlation with albumin. These findings indicate that fetuin-A is a negative acute-phase reactant. In a study on peritoneal dialysis patients, Wang et al.[15] demonstrated a reverse correlation between fetuin-A and inflammation and malnutrition. Serum fetuin-A was highest among patients without inflammation and malnutrition and lowest among those with both inflammation and malnutrition. In a study of patients with chronic kidney failure, Oikawa et al.[16] investigated levels of serum fetuin-A in hemodialysis patients and showed them to be significantly lower than in healthy controls. Furthermore, they identified a negative correlation between serum fetuin-A levels and high-sensitivity CRP and a positive association with serum albumin. These data suggest that low fetuin-A level is a useful predictor of inflammation.

There is limited number of studies in the literature concerning fetuin-A in inflammatory rheumatic diseases. Oncu et al.[17] studied 67 familial Mediterranean fever (FMF) patients. The authors measured fetuin-A three times: during the attack-free period, 12 hours after an attack and seven days after an attack, and discovered significantly decreased fetuin-A compared to the twelve-hour attack period. In the same study, they also observed a significant negative correlation between fetuin-A and ESR, CRP, cerulopasmin, fibrinogen, and white blood cell count. The results of this study indicate that fetuin-A can be a novel indicator of disease activity in FMF patients and used as an additional marker to differentiate FMF attacks.

Sato et al.[5] studied 102 RA patients and a 155-member control group and reported low fetuin-A in RA patients. Fetuin-A was negatively correlated with ESR and CRP, while a positive correlation was identified with albumin, hemoglobin and total cholesterol. However, no association was shown between fetuin-A and age, sex, serum creatinine levels, calcium levels

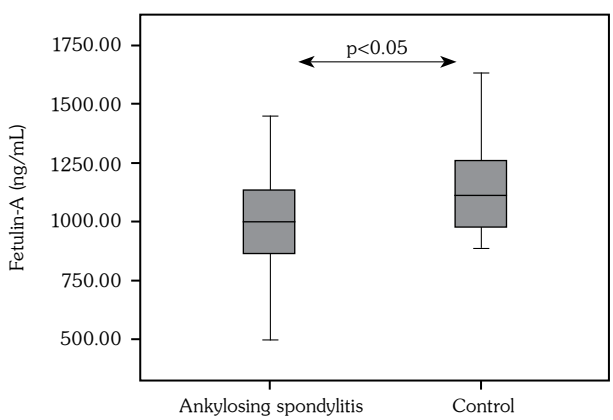

Figure 1. Comparison of fetuin-A (ng/mL) levels in patients with ankylosing spondylitis and control subjects.

or aortic calcification. Similarly, in a study of 35 RA patients and 30 healthy controls, Saroha et al.[18] reported lower serum fetuin-A levels in patients compared to controls. They concluded that the low serum fetuin-A concentrations in RA patients might be due to chronic inflammation developing in association with malnutrition and inflammatory activity.[5] However, no correlation was detected with clinical parameters such as ESR, BASDAI, BASFI or BASMI. Additionally, in the same study, a comparison of fetuin-A levels of patients using biological agents with high disease activity score and peripheral joint involvement revealed no significant difference. Sarı et al.[10] suggested that the elevated fetuin-A might be attributed to the disease itself, independently of clinical markers. In our study, we detected lower serum fetuin-A levels in the AS patient group compared to the control group (p=0.001). We also identified a negative correlation between patient fetuin-A levels and CRP. However, we found no correlation between fetuin-A and disease markers such as ESR, BASDAI, BASFI or BASMI. In contrast to Sarı et al.,[10] we also assessed patient BASRI indices. However, we did not detect any correlation between BASRI and fetuin-A. In contrast to previous studies reporting high fetuin-A levels in AS patients,[10] we found low fetuin-A levels similar to studies in RA and FMF patients.[5,17,18] In addition, the negative correlation we showed between CRP and fetuin-A, and the negative correlation with ESR and CRP demonstrated in studies involving chronic kidney failure, cardiovascular disease, and rheumatic diseases indicate that fetuin-A may be a negative acute phase reactant.[5,16-19]

In conclusion, we demonstrated that fetuin-A levels in AS patients were lower than in control subjects. We also showed that fetuin-A is negatively correlated with CRP. We suggest that fetuin-A in AS patients may be a novel indicator of disease activity. Furthermore, the negative correlation between fetuin-A and CRP may be indicative of an inflammation related decrease of fetuin-A in patients with AS.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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