Northwestern Med J. 2023;3(2):115-121
doi: 10.54307/NWMJ.2023.35119

Original Article

Serum 14-3-3 ETA levels in ankylosing spondylitis with pure axial involvement: Could it be a potential biomarker to assess disease activity?

Saf aksiyel tutulumlu ankilozan spondilitte serum 14-3-3 ETA seviyeleri: Hastalık aktivitesini değerlendirmek için potansiyel bir biyobelirteç olabilir mi?

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Atıf/Cite as: Atalar E, Kor A, Fırat Oğuz E, et al. Serum 14-3-3 ETA levels in ankylosing spondylitis with pure axial involvement: could it be a potential biomarker to assess disease activity? Northwestern Med J. 2023;3(2):115-121.

ABSTRACT

Aim: The 14-3-3η (eta) protein has been associated with the severity of the disease and joint destruction in patients with rheumatoid arthritis (RA). It has also been shown to be likely to be effective in inflammatory events. We aimed to investigate whether eta levels could be a potential biomarker in the diagnosis of ankylosing spondylitis (AS) and in the determination of disease activity in patients with AS.
Methods: This study included 51 patients diagnosed with AS and 49 healthy controls aged 20-65 years. The routine hemogram, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels were measured and the neutrophil/lymphocyte ratio (NLR) was calculated in the patients. The serum eta levels were also measured in the patient and healthy control groups. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Disease Activity Score (ASDAS) were used to assess disease activity. Sacroiliac joint radiographs of the patients were evaluated and the sacroiliitis was graded.
Results: There was no statistically significant correlation between the degree of sacroiliitis, disease activity indices, and eta levels. There was no statistically significant correlation between eta levels and hematological parameters except for CRP. There was a negative, weak, and statistically significant relationship between the patients' eta levels and CRP (r=-0.277; p=0.049). We could not find any correlation between the degree of sacroiliitis, disease activity indexes, and serum eta levels in AS patients.
Conclusion: Serum eta levels are not a good biomarker for detecting disease activity in patients with ankylosing spondylitis. The 14-3-3η protein may play a more active role in rheumatic diseases where peripheral joint involvement is prominent.

Keywords: 14-3-3 proteins, ankylosing spondylitis, biomarkers, mediators of inflammation

ÖZ

Amaç: 14-3-3η (eta) proteininin, romatoid artritli hastalarda hastalığın şiddeti ve eklem yıkımı ile ilişkili olduğu gösterilmiştir. Ayrıca diğer iltihaplı olaylarda da etkili olma ihtimalinin yüksek olduğu gösterilmiştir. Ankilozan spondilitli (AS) hastalarda eta düzeylerinin AS tanısında ve hastalık aktivitesini belirlemede potansiyel bir biyobelirteç olup olamayacağını araştırmayı amaçladık.
Yöntem: Bu çalışmaya yaşları 20-65 arasında olan, AS tanılı 51 hasta ve 49 sağlıklı kontrol alındı. Hastaların rutin hemogram, eritrosit sedimantasyon hızı (ESR), C-reaktif protein (CRP) seviyeleri ölçüldü ve nötrofil/lenfosit oranı (NLO) hesaplandı. Hasta ve sağlıklı kontrol gruplarında serum eta düzeyi ölçüldü. Hastalık aktivitesini değerlendirmek için

Received: 24.02.2023
Accepted: 26.05.2023
Publication date: 01.06.2023

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Bath Ankilozan Spondilit Hastalığı Aktivite İndeksi (BASDAI) ve Ankilozan Spondilit Hastalığı Aktivite Skoru (ASDAS) kullanıldı. Hastaların sakroiliak eklem grafileri değerlendirildi ve sakroiliit derecelendirildi.
Bulgular: Sakroiliit derecesi, hastalık aktivite indeksleri ve eta seviyeleri arasında istatistiksel anlamlı ilişki bulunmadı. Eta düzeyleri ile hematolojik parametreler arasında CRP dışında istatistiksel olarak anlamlı bir ilişki bulunmadı. Hastaların eta düzeyleri ile CRP arasında negatif, zayıf ve istatistiksel olarak anlamlı ilişki vardı (r=-0,277; p=0,049). AS hastalarında sakroiliit derecesi, hastalık aktivite indeksleri ve serum eta düzeyleri arasında ilişki bulamadık.
Sonuç: Serum eta seviyeleri, ankilozan spondilitli hastalarda hastalık aktivitesini saptamak için güvenilir bir biyobelirteç değildir. 14-3-3η proteini, periferik eklem tutulumunun ön planda olduğu romatizmal hastalıklarda daha aktif rol oynayabilir.

Anahtar kelimeler: 14-3-3 proteinler, ankilozan spondilit, inflamasyon mediatörleri, biyobelirteçler

INTRODUCTION

Ankylosing spondylitis (AS), the classic form of axial spondyloarthritis, is a chronic, systemic inflammatory, and progressive disease that primarily affects the spine and sacroiliac joints (1). Its prevalence ranges from 9-30 per 10,000 (2). It is usually seen in young adults. It may be accompanied by peripheral joint involvement and extra-articular clinical findings (3,4). Although its etiopathogenesis is not clear, cytokines like tumor necrosis factor (TNF) may play a role (5). Inflammation and progressive degeneration seen in the natural course of the disease reduce the functional capacity of the patients and negatively affect their daily lives and psychological conditions.

It is important to evaluate patients in terms of disease activity in their follow-up. In patients with AS, disease activity is evaluated with scoring systems that evaluate many clinical and radiological parameters. "The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Disease Activity Score (ASDAS)" are the main scales used to evaluate AS patients (6). Automatic calculators are generally used for the calculation of BASDAI and ASDAS.

Eukaryotic cells in our body contain intracellular chaperones. One of them is 14-3-3, and it has seven isoforms: β, γ, ε, ζ, η, σ, and τ (beta, gamma, epsilon, zeta, eta, sigma, and tau) (6,7). These proteins are involved in the regulation of intracellular activities by binding to various intracellular proteins (8). The 14-3-3η protein is involved in a variety of biological processes, including cell proliferation, differentiation, and apoptosis, which are involved in inflammation (9,10). The 14-3-3η protein is encoded by genes located on chromosomes, and more than 200 proteins are known to interact with eta proteins (11).

It is known that proinflammatory cytokines like interleukin-1(IL-1), interleukin-6 (IL-6), and tumor necrosis factor (TNF)-α are stimulated by eta. In addition, it has been shown that matrix metalloproteinase MMP1, MMP9, receptor activator nuclear factor-kB ligand (RANKL) proteins, which are known to play a role in joint damage, are stimulated by 14-3-3η (7,12,13).

The relationship between rheumatic diseases and eta protein was first demonstrated in 2007 by Kilani et al (7). In their study, Kilani et al. showed that eta levels were increased in the serum and joint fluid of rheumatoid arthritis (RA) patients compared to healthy controls, and there was a positive correlation between eta and MMP (7). MMPs are associated with structural damage in RA and are potential markers of progressive joint damage and disease activity (14). Subsequent studies have investigated the relationship between various rheumatic diseases and serum eta levels (10,12,15).

Although acute phase responses are used in the diagnosis and follow-up of many inflammatory rheumatic diseases, only 50-70% of AS patients with active disease have elevated ESR and CRP. Therefore, their efficacy in demonstrating disease activity is not sufficient (16,17). Spoorenberg et al.[16] reported that there was no significant relationship between CRP and ESR and disease activity in AS patients. The relationship between disease activity and acute phase reactants in AS

patients with pure axial involvement is much weaker than in AS patients with peripheral joint involvement (17,18). Considering this difference, we aimed to investigate a new biochemical parameter that can guide the determination of disease activity in AS patients with pure axial involvement.

MATERIALS and METHODS

The study protocol was approved by the Ethics Committee of our institution (Number: E1-21-1594). The individuals participating in the study were informed about the study and their written informed consent was obtained. The study was conducted in accordance with the ethical principles described by the Declaration of Helsinki.

The study included 51 AS patients, aged 20-65 years, diagnosed according to the Modified New York Criteria, who had a sacroiliac radiograph in the last 6 months, and 49 healthy controls (19).

Sacroiliac joint radiographs of the patients were evaluated by an experienced rheumatologist. In this evaluation, sclerosis, erosion, ankylosis, and expansion/contraction in the joint space were taken into account in both joints and scoring was done. For patients with bilateral sacroiliitis, the higher grade was considered the grade of sacroiliitis.

In the patient and control groups, those with uncontrolled diabetes, hypertension, severe cardiovascular disease, acute or chronic infection, liver, or kidney failure (creatinine clearance <60 mL/min), malignancy, smokers, severe obesity [body mass index (BMI) >35 kg/m^2], pregnant women were not included in the study.

Those with peripheral joint involvement and those with rheumatic diseases other than AS were not included in the study group.

In the control group, those who has any rheumatic or chronic disease were not included.

In addition to routine hemogram, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels, biochemical tests, and eta levels were measured in the patients.

The neutrophil/lymphocyte ratio (NLR) was calculated as the ratio of the absolute neutrophil count and absolute lymphocyte count. The serum eta level was also measured in the healthy control group.

Ankylosing spondylitis activity was evaluated with BASDAI, ASDAS-CRP, and ASDAS-ESR indexes.

BASDAI consists of 6 questions related to the 5 major symptoms of AS: level of fatigue/weakness, spinal pain, peripheral joint pain/swelling, local tenderness, and morning stiffness. Patients are asked to rate the severity of their symptoms in the past week. The BASDAI score is calculated by adding the average of the scores from the fifth and sixth questions and the sum of the scores from the first four questions. The BASDAI score is obtained by dividing the total score obtained by 5. The BASDAI >4 indicates active disease (6). In 2009, the ASAS group developed the Ankylosing Spondylitis Disease Activity Score (ASDAS) to assess disease activity. In this scoring system, sedimentation rate and CRP are also used in addition to clinical findings. The ASDAS less than 1.3 indicates inactive disease, while a value greater than 3.5 indicates very high disease activity (20).

Venous blood samples were taken from the individuals included in the study in serum tubes with gel and plasma tubes with EDTA. After the serum samples were taken, they were centrifuged at 1300xg for 10 minutes after waiting for 20 minutes to complete the coagulation. Samples were divided into Eppendorf tubes were kept at -80 °C until analysis. Calculation of eta levels was performed with an ELISA kit (Fine Test, Wuhan, China; catalog no: EH2534; lot no: H2534G109 E) using a quantitative sandwich enzyme immunoassay technique. The detection

range in the analysis of samples for the Human 14-3-3 Eta protein ELISA kit (LOT:H2534G109 E) has been reported as 0.625-40 ng/mL and the sensitivity as 0.375 ng/mL. The intra and inter-assay precision were <8% and <10%, respectively.

The hemogram was studied on the ADVIA 2120 hematology analyzer (Siemens Healthineers, Germany). Sedimentation rates were studied on the Vision C (Shenzhen Yhlo Biotech, Shenzhen, China) automated analyzer. CRP levels were measured by the immunoturbidimetric method in the Atellica Solutions (Siemens Healthineers, Germany) autoanalyzer.

Statistical analysis

SPSS (IBM SPSS Statistics 24) package program was used for statistical analysis. Frequency tables and descriptive statistics were used to evaluate the findings. Parametric methods were used to evaluate normally distributed data. In accordance with parametric methods, the independent sample t-test (t-table value) method was used to compare the measurements of two independent groups. Non-parametric methods were used to evaluate non-normally distributed data. The Mann-Whitney U test (Z-table value) was used to compare the measurements of two independent groups in accordance with non-parametric methods. The Kruskal-Wallis H test (χ^2-table value) method was used to compare three or more independent groups. Pearson-χ^2 crosstabs were used to examine the relationships between two qualitative variables. Spearman's correlation coefficient was used to examine the relationships between two quantitative variables that are not normally distributed.

RESULTS

There was no statistically significant difference between the groups in terms of BMI (kg/m^2), age, and eta level (p>0.05) (Table 1).

There was no statistically significant difference between the groups in terms of gender (p>0.05).

No statistically significant relationship was found between the drugs used by the patients for treatment and their eta levels.

No statistically significant correlation was found between the degree of sacroiliitis and eta levels (Table 2).

Table 1. Comparison of age, BMI and eta levels by groups.

Variable	Patient group (n=51)		Control group (n=49)		Statistical analysis* Probability
	$\bar{X}$±SD	Median [Min-Max]	$\bar{X}$±SD	Median [Min-Max]	
Age (year)	41,35±10,84	40,0 [21,0-65,0]	40,79±13,35	38,0 [20,0-65,0]	Z=-0,369 p=0,712
BMI (kg/m^2)	25,76±3,48	25,0 [19,3-33,0]	25,98±3,57	25,3 [19,3-33,0]	t=-0,324 p=0,747
ETA levels	2,63±1,83	2,3 [0,8-10,6]	2,66±1,81	2,2 [0,9-9,6]	Z=-0,141 p=0,888

** Independent Sample t-test (t-table value) statistics were used to compare two normally distributed independent groups. The "Mann-Whitney U" test (Z-table value) statistic was used to compare the measurement values of two independent groups that did not show normal distribution. BMI: Body Mass Index*
SD: Standard deviation

Table 2. Comparison of ETA levels with the degree of sacroiliitis.

Variable	Patients (n=51)			Statistical analysis * Probability
	N	$\bar{X}$±SD	Median [Min-Max]	
Sacroiliitis				
Grade 2	22	2,44±1,16	2,3 [1,1-5,5]	χ^2=1,157
Grade 3	23	3,00±2,41	2,2 [0,8-10,6]	p=0,561
Grade 4	6	1,94±0,98	1,9 [0,8-3,1]	

** Kruskal-Wallis H test statistics (χ^2-table value) were used to compare three or more independent groups that did not have a normal distribution.*

Table 3. Comparison of patients' eta levels with haematological parameters and disease activity indexes.

Correlation* (n=51)	ETA level	
	R	P
ESR	-0,095	0,507
CRP	-0,277	0,049
WBC	-0,046	0,755
Neutrophil	-0,176	0,217
Lymphocyte	0,184	0,196
Neutrophil/lymphocyte ratio	-0,222	0,118
Platelet	-0,198	0,163
BASDAI	0,192	0,176
ASDAS-CRP	-0,112	0,435
ASDAS-ESR	0,122	0,395

** Spearman's correlation coefficient was used to examine the relationships of two quantitative variables that do not have a normal distribution.*
CRP: C-Reactive Protein, WBC: white blood count,
BASDAI: Ankylosing Spondylitis Disease Activity Index,
ASDAS: Ankylosing Spondylitis Disease Activity Score,
ESR: Erythrocyte Sedimentation Rate

No statistically significant correlation was found between eta levels and ESR, WBC, neutrophil, lymphocyte, NLR, PLT levels in patients. There was a negative, weak, and statistically significant relationship between the patients' ETA levels and CRP values (r=-0.277; p=0.049) (Table III). No statistically significant relationship was found between disease activity indices and eta levels (Table 3).

DISCUSSION

In this case-control study, serum eta levels were evaluated in AS patients with pure axial involvement and healthy controls. According to our research, this is the first study in the literature published in English to investigate the relationship between serum eta protein and AS activity. In our study, we could not detect a relationship between AS activity scores and eta levels. In the literature, a relationship has been shown between disease activity and disease progression and the levels of eta in patients with RA (13,21). 14-3-3η has been detected in the serum and more specifically in the synovial fluid of patients with RA, and it is a valuable marker for the diagnosis of patients and also indicates the severity of the disease and joint destruction (13,22-24).

It is a well-known fact that the eta protein contributes to the inflammation seen in RA (25). However, no correlation has been shown between serum eta levels and disease activity in juvenile inflammatory arthritis (JIA) and systemic lupus erythematosus, which are among other rheumatic diseases (10,15).

Spondyloarthropathies define a heterogeneous group of autoinflammatory diseases. They are divided into 2 groups: peripheral and axial spondyloarthropathies. Axial spondyloarthropathies are divided into non-radiographic axial spondyloarthritis (nr-axSpA) and AS (26). AS is a disease characterized by sacroiliac joint and spinal damage that can lead to joint fusion (27). In this disease, there is spinal inflammation in which the sacroiliac joints are primarily affected. With the progression of the disease, the fusion that starts in the sacroiliac joint progresses to the spine (28). There are data suggesting that increased serum eta levels in RA patients may also be associated with peripheral arthralgia and joint damage (22). In a study conducted in rheumatoid factor (RF) and/or anti-citrullinated protein antibodies (ACPA) positive patients with arthralgia, the incidence of arthritis was found to be higher in patients with high 14-3-3η eta protein levels (12). Hammam et al.[15] found that there was no significant relationship between eta level and disease activity (DAS-28) and acute phase responses in their study of RA patients. However, they showed that there is a relationship between radiological damage and eta level (15). With the limited data we have, it is difficult to explain the mechanism of foreground joint damage in RA patients with high eta levels. Maksymowych et al.[29] reported that autoantibodies developed against serum eta protein were at higher levels in AS patients compared to the healthy control group, and these autoantibodies were related to sacroiliac joint inflammation detected on magnetic resonance imaging (MRI) (29). However, we could not find a relationship between the degree of sacroiliac joint damage and serum eta levels in our patient group.

A non-strong relationship between acute phase reactants and AS activity is known (16,17). Although we could not find a relationship between serum eta levels and disease activity, a weak inverse relationship was found between serum eta levels and CRP. In our study, we also could not detect a relationship between eta levels and inflammatory parameters such as WBC and NLR. This may be explained by the small number of our patients and the weak effectiveness of inflammatory parameters in demonstrating disease activity in AS patients.

Hirata et al.[30] reported no difference between eta levels of RA patients before and after adalimumab, tofacitinib, or methotrexate treatment. However, in the present study, all of the AS patients were receiving treatment, which is one of the shortcomings of our study. Another limitation of our study is the small number of patients, the lack of a prospective study, and the exclusion of peripheral AS patients from the study.

In conclusion, we could not find a correlation between the degree of sacroiliitis, disease activity indexes, and serum eta levels in AS patients. However, this result does not change the fact that eta has a role in inflammation. Considering both our study and the data in the literature, we can conclude that eta may play a more active role in inflammatory diseases in which peripheral joint damage is at the forefront. To confirm this hypothesis, prospective controlled studies examining eta levels in serum and joint fluids are needed.

Ethics Committee Approval: The study protocol was approved by the Ankara City Hospital Clinical Research Ethics Committee (17.03.2021 / E1-21-1594).

Conflict of Interest: The authors have declared that they have no conflict of interest.

Funding: This study is funded by Yıldırım Beyazıt University Scientific Research Projects Coordination Unit.

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