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Original Research

Relationship Between Cd74 Levels, Macrophage Migration Inhibitory Factor Gene Polymorphism, and Clinical Features in Patients with Ankylosing Spondylitis

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ABSTRACT

Objective: Firstly, in this study, we aimed to compare CD74 antigen levels between patients with ankylosing spondylitis (AS) and healthy controls. Secondly, we investigated the distribution of macrophage migration inhibitory factor (MIF) 173 G/C polymorphisms in patients with AS and the control group. Finally, we determined the relationship between CD74 antigen levels and MIF 173 G/C polymorphism.

Methods: We enrolled 82 healthy blood donors and 79 patients with AS. MIF 173 G/C polymorphism and CD74 levels in the patient and control groups were investigated using enzyme-linked immunosorbent assay. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Metrology Index (BASMI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Radiology Index (BASRI), Visual Analogue Scale (VAS), and Ankylosing Spondylitis Quality of Life (AS-QoL) scores were calculated and recorded.

Results: No significant difference was observed between the patient and control groups in terms of age, gender, and body mass index. The median CD74 level in the patient group was 1.17 (0.93-2.1), which was significantly lower than that in the control group [2.16 (1.6-4.41)]. CD74 antigen levels were not correlated with BASDAI, BASMI, BASFI, BASRI, VAS, and AS-QoL scores. The number of patients with the C allele was higher in the patient group than in the control group; however, the difference was not statistically significant ($p>0.05$). Moreover, no correlation was observed between the genotypes and BASDAI, BASMI, BASFI, BASRI, VAS, and AS-QoL scores ($p>0.05$). The comparison of median CD74 levels among individuals in the patient group according to their HLA-B27 status and genotypes did not reveal any statistically significant difference.

Conclusion: As a result, we think that CD 74 antigen levels can be used in the diagnosis of AS. More studies are needed for the role of MIF gene polymorphism in etiology.

Keywords: Ankylosing spondylitis, CD74, MIF gene, polymorphism

INTRODUCTION

Ankylosing spondylitis (AS) is a progressive chronic inflammatory disease characterized by axial skeletal and sacroiliac joint involvement (1). AS is the most prevalent type of spondyloarthropathies (SpA). AS causes enthesitis and peripheral joint involvement and exhibits extra-articular involvement (2). Furthermore, AS onset is generally manifested during late adolescence and early adulthood. One of the most important characteristics of the disease is axial involvement, wherein approximately 90% patients exhibit radiographic sacroiliitis as the disease progresses. Diagnosis can be delayed because it takes years to observe the radiographical signs, although the clinical signs of the disease can be observed earlier (3).

The etiology of AS is not entirely known. However, it is thought to stem from environmental factors linked to genetic factors (4). Among the genetic factors, human leukocyte antigen (HLA-B27) aids in the diagnosis of AS. Further, new biomarkers are needed for the diagnosis, follow-up, and determination of prognosis because some HLA B-27-positive individuals develop AS and healthy individuals can also be HLA-B27-positive (5). From the genetic viewpoint, besides HLA-B27, AS is also associated with

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endoplasmic reticulum aminopeptidase I and tumor necrosis factor alpha (TNF-α) genes (6, 7).

CD74 antigen, a transmembrane glycoprotein, prevents the early binding of proteins to the major histocompatibility complex class II. The CD74 molecule possesses intracellular regulatory functions such as signal transduction, cell migration, and endosomal trafficking (8, 9). It also plays a considerable role in innate and acquired immunities as well as in B-cell proliferation. As a result of antibody binding to the CD74 antigen, proinflammatory cytokines are released (8). Therefore, it is believed that CD74 can be a potential factor in the etiopathogenesis of AS.

Macrophage migration inhibitory factor (MIF) is a multifunctioning mediator protein comprising 115 amino acids with enzyme, hormone, and cytokine properties that can inhibit macrophage migration *in vivo* (10). After extracellular secretion, MIF promotes proinflammatory activity and increases the release of tumor necrosis factor (TNF) by affecting the immune response via autocrine, paracrine, and endocrine routes. Furthermore, MIF acts as a regulator against the immunosuppressive effects of glucocorticoids; therefore, MIF is considered to be a gene possibly associated with autoimmune-inflammatory diseases (11). It has been proven that MIF is capable of reversing the effects of glucocorticoids on inflammation in an antigen-related arthritis model (12). Tetranucleotide (CATT) polymorphisms and 173 G/C polymorphism of the MIF gene are associated with inflammation (13, 14).

CD74 antigen that is located on the cell surface acts as a MIF receptor. CD74 and MIF binding plays an important role in maintaining cell proliferation and viability (15).

In this study, our primary objective was to determine whether CD74 antigen levels measured using enzyme-linked immunosorbent assay (ELISA) could be used as a parameter in the diagnosis, treatment, and follow-up of AS. The secondary objective was to investigate the role of 173 G/C polymorphism of the MIF gene in the development of AS. Furthermore, we aimed to determine the relationship between CD74 antigen levels and MIF gene polymorphisms.

METHODS

We enrolled 82 healthy subjects and 79 patients diagnosed with AS who presented at Gaziantep University Medical Faculty Research Hospital, Physical Medicine, and Rehabilitation Department or Rheumatology outpatient clinic between December 2016 and April 2017. Patients with AS were selected according to the modified New York criteria. Blood donors who did not have any chronic disease or history of inflammatory disease were included in the control group. Patients with inflammatory diseases, other than AS; pregnant or breast-feeding women; and those with a history of malignancy were excluded from the patient group. Consent was obtained from all participating individuals in the study. The study was approved by Gaziantep University Ethics Committee (dated 11.28.2016 and approval number 308) and performed in accordance with the Declaration of Helsinki.

Main Points:

- The CD74 antigen levels of the patients with AS were significantly lower compared to the control group.
- Although the C allele among the MIF 173 G/C polymorphisms was more frequently observed in the patient group, the difference was not statistically significant.
- There was no significant relationship between CD 74 antigen levels and polymorphisms.

Patient data like their age, gender, height, weight, date of onset of complaints associated with the disease, duration of the disease, drug prescriptions, family history, and extra-articular involvement were collected. General physical examinations as well as detailed musculoskeletal examinations were performed by the same physician. In the patient group, the disease activity was evaluated using Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), metrologic evaluation using Bath Ankylosing Spondylitis Metrology Index (BASMI), functional evaluation using Bath Ankylosing Spondylitis Functional Index (BASFI), radiologic changes using Bath Ankylosing Spondylitis Radiology Index (BASRI), night-time and daytime pain statuses using Visual Analogue Scale (VAS), and quality of life using Ankylosing Spondylitis Quality of Life (AS-QoL) scale.

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values were evaluated from patients' blood samples on the same day and recorded.

Genomic DNA was extracted by salting out method from mononuclear cells obtained from peripheral venous blood treated with ethylenediaminetetraacetic acid. Polymerase chain reaction (PCR)-restriction fragment length polymorphism was used to evaluate MIF gene polymorphisms. Moreover, MIF-173C *rs755622 variant was identified using the following primers: 5′-ACTAAGAAAGACCCGAGG-3′ and 5′-TGGAGAAAGGACCAGGAGAC-3′. MIF-173 G/C sequences were amplified to a reaction volume of 25 µL using 100–500 ng DNA, 1.0 mM of each primer, 250 mM of each nucleotide, 1.5 U Taq polymerase, (Fermentas International, Burlington, Ontario, Canada), and 2 mL of 10X PCR buffer. PCR was performed using GeneAmp® PCR System 9700 (Applied Biosystems, Singapore).

A 330-bp fragment was amplified for MIF-173 G/C and then digested with Alu I restriction endonuclease (Invitrogen, Carlsbad, CA, USA) at 37°C overnight. Digestion products were dissolved in 3% agarose gel and viewed under UV light. PCR products of 330 bp have consistent restriction regions that lead to 62- and 268-bp fragments. The GG genotype did not have a second cutting point for Alu I. However, the CC genotype had a second cutting point, which led to three fragments, i.e., 205-, 62-, and 63-bp fragments. The experiment was repeated for 20% samples to prevent sampling or reading errors.

The CD74 concentration was measured using Elabscience ELISA kits. The measurement was performed in accordance with the user manual of the kit. The microplates in the kit were spectrophotometrically read at 450 nm with an EL 312 Microplate ELISA reader. The optical density values were used to create standard curves, and concentration values were obtained in ng/mL.

Statistical Analysis

The normal distribution of numerical variables was assessed using Shapiro-Wilk test when n was <50 and Kolmogorov–Smirnov test when n was >50. Independent samples *t*-test, a parametric test, was used to compare two independent groups when numerical variables had a normal distribution, and Mann–Whitney's U test was used in case of non-normal distribution. Kruskal–Wallis test was used to compare more than two independent groups with non-normal distribution of numerical variables. In nonparametric tests, the differences between the groups were compared using Mann–Whitney's U test and evaluated using Bonferroni correction. Pearson's Chi-squared test was used to compare the differences between categorical variables in 2×2 tables and Fisher–Freeman–Halton exact test in R×C tables. Relationships between numerical variables without normal distribution were evaluated using Spearman's rank correlation coefficient. Statistical analyses were performed using R 3.3.2 v (open source) software, and p values of <0.05 were considered to be significant.

Table 1. Comparison of the demographic characteristics between the patient and control groups

		Group		
		Patient (n=79)	Control (n=82)	p
Gender	Male	64 (81.01)	73 (89.02)	0.154*
	Female	15 (18.99)	9 (10.98)	
Age		36.01±9.14	36.63±10.31	0.687**
BMI		27.95±4.61	26.76±4.09	0.084**

*Chi–squared test. Descriptive statistics are provided in numbers (%). **Independent sample t–test. Descriptive statistics are expressed as mean ± standard deviation. BMI: body mass index

Table 2. Comparison of CD74 antigen levels and polymorphisms between the patient and control groups

		Group		
		Patient (n=79)	Control (n=82)	p
CD74		1.17 (0.93–2.1)	2.16 (1.6–4.41)	<0.001**
Genotype	GG	56 (70.89)	62 (75.61)	0.581*
	GC	20 (25.32)	19 (23.17)	
	CC	3 (3.8)	1 (1.22)	

*Chi–squared test. Descriptive statistics are provided in numbers (%). **Mann–Whitney's U test. Descriptive statistics are expressed as median values (Q1–Q3)

Table 3. Comparison of CD74 antigen levels according to HLA–B27 and polymorphism status in the patient group

		CD 74	
		M(Q1–Q3)	p
HLA–B27	HLA–B27+ (n=49)	1.39 (0.89–2.27)	0.377*
	HLA–B27– (n=30)	1.08 (0.97–1.48)	
Genotype	GG (n=56)	1.17 (0.9–2.06)	0.077**
	GC (n=20)	1.1 (0.93–1.855)	
	CC (n=3)	5.24 (1.77–11.82)	

*Mann–Whitney's U test. Descriptive statistics are expressed as median values (Q1–Q3). **Kruskal–Wallis test. Descriptive statistics are expressed as median values (Q1–Q3)

RESULTS

A total of 79 patients and 82 healthy subjects were enrolled in the study. Age, gender, and body mass index (BMI) distributions were similar in the patient and control groups (p>0.05 for each; Table 1). The mean time until diagnosis was 6.87±5.55 years in the patient group. Among the 79 patients, 29 were on disease-modifying drugs and 50 were receiving anti-TNF therapy.

The median CD74 level in the patient group was 1.17 (0.93-2.1), which was significantly lower than that in the control group, i.e., 2.16 (1.6-4.41; p<0.001). The prevalence of C allele was higher in the patient group (29.12%) than in the control group (24.39%); however, the difference was not statistically significant (p>0.05; Table 2).

CRP levels increased in parallel to CD74 levels in the patient group (p=0.015). The comparison of the CD74 scores with BMI, time until diagnosis, ESR, night-time VAS, daytime VAS, BASDAI, BASMI, BASRI vertebra, BASRI hip, BASRI total, and AS-QoL in the patient group did not reveal any significant linear relationship (p>0.05 for each).

A total of 49 individuals (62%) in the patient group were HLA-B27-positive, whereas 30 (38%) were HLA-B27-negative. The comparison of median CD74 levels in individuals in the patient group according to their HLA-B27 status and genotypes did not show any significant difference (p>0.05 for each; Table 3).

CD74 levels among individuals in the patient group according to the drugs prescribed, presence or absence of arthritis, uveitis, and enthesitis did not reveal any statistically significant difference in terms of median values (p>0.05 for each). No significant relationship was observed between genotypes and clinical parameters of individuals in the patient group (p>0.05 for each).

DISCUSSION

AS is a chronic progressive inflammatory disease that initially manifests with axial skeletal and sacroiliac joint involvement. However, its etiology is not entirely known. Delayed diagnosis is one of the most important concerns of AS. Diagnosis can be delayed for 7-10 years due to the lack of testing to directly establish AS diagnosis. Therefore, new biomarkers are required for the diagnosis, follow-up, and determination of AS prognosis.

Several different factors together with its genetic causes may play a role in the etiology of AS. Some HLA-B27-positive patients develop AS; therefore, HLA-B27 can only partly account for a genetic susceptibility, despite being the most commonly recognized genetic factor for the disease (16).

MIF is a molecule that plays a vital role in the regulation of innate and acquired immunities as well as carcinogenesis and inflammation (17, 18). Suppression of the biological activity of

MIF can considerably limit TNF-α, interferon-γ, and matrix metalloproteinase production in the large intestinal tissues in an experimentally-induced murine colitis model (19). MIF gene and its polymorphisms in inflammatory diseases have been widely examined due to the close relationship between MIF and inflammation and its role as a regulator against glucocorticoids (18).

MIF gene polymorphism is most commonly investigated in rheumatoid arthritis (RA). MIF gene polymorphism resulted in susceptibility to the disease and was correlated with radiological progression in patients with RA (20). Martinez et al. (20) reported that the MIF-173 C allele in the promotor gene was especially associated with susceptibility in patients with early-onset RA. In another study, MIF-173 C allele or MIF CATT alleles were found to correlate with serum MIF levels, and they could be used as prognostic factors (21).

Zheng et al. (22) investigated MIF levels as well as MIF-173 G/C and -794 CATT polymorphisms in 600 healthy subjects and 600 patients with Behcet's disease. They reported that the prevalence of the C allele was higher in the patient group than in the control group. Further, the MIF levels were higher in the patient group than in the control group and the polymorphisms could have an effect on MIF expression.

Przybyłowska et al. (23) investigated MIF gene polymorphism in inflammatory bowel disease (IBD) in their study conducted on 58 patients with ulcerative colitis, 41 patients with Crohn's disease, and 436 healthy subjects. They found that IBD risk was 2.02- and 1.89-folds higher in the presence of the G/C genotype and C allele, respectively. Considering the genotype distribution according to subgroups, they found a relationship between ulcerative colitis and the C allele. However, no significant relationship was observed between Crohn's disease and the polymorphism.

Gürel et al. (24) investigated AS and MIF-173 G/C polymorphism in the Turkish population. They found no relationship between AS and MIF genotype and alleles, and the onset of the disease was earlier in patients with the C allele. They confirmed that the C allele could lead to earlier onset of the disease. According to the present study, there was no significant relationship between genotype and duration of the disease, but patients who had the C allele experienced a longer disease duration than the control group.

CD74 is an important molecule that plays a role in various processes such as cell migration, premature antigen binding, B-cell maturation, and continuity of cell viability, wherein its association with inflammation has not been completely elucidated (25, 26). Antibody binding to CD74 molecules *in vivo* was thought to result in the production of proinflammatory cytokines and activation in the target cells (26).

Baerlecken et al. (8) conducted a study on 216 patients with SpA and 325 control patients and evaluated the presence of antibodies against CD74. The control group comprised 40 patients with psoriatic arthritis, 40 with systemic lupus erythematosus, 40 with HIV, 80 with RA, and 125 blood donors, wherein the anti-CD74 antibody level was 67% in the SpA group and 6% in the control group. They confirmed that antibody positivity could be useful, especially in the early stage of SpA and in HLA-B27-negative patients, for the diagnosis of the disease with high sensitivity and specificity.

Baraliakos et al. (27) conducted a study on 94 patients with axial SpA and 51 non-SpA patients (13 RA, 17 fibromyalgia, 17 degenerative spine disease, 3 psoriatic arthritis without axial involvement, and 1 polymyalgia rheumatica) to investigate the prevalence of IgG antibody against the CLIP region of CD74. They reported that the prevalence of anti-CLIP antibody was 85.1% in patients with axial SpA and 7.8% in the control group. The sensitivity and specificity of anti-CLIP were 85.1% and 92.2%, respectively, in patients with axial SpA. Moreover, anti-CLIP antibody positivity was detected in HLA-B27-negative patients. Baraliakos et al. (27) did not observe a relationship among antibody positivity and radiological progression and disease activity in their studies. Similarly, no relationship was observed among CD74 antigen levels and disease activity, radiological involvement, drug use, and extra-articular involvement according to this study (8).

In a study by Ranganathan et al. (28) evaluating CD74 antigen levels in patients with AS, the CD74 level was significantly lower in patients with AS than in the control group. Results of this study were consistent with the results of the present study. In the mentioned study, the CD74 level was measured from monocytes obtained from peripheral blood using flow cytometry. It was suggested that this method is not suitable for routine use because it is more expensive and requires advanced laboratory conditions.

The present study demonstrated that CD74 levels were significantly higher in the patient group than in the control group. This can be justified by several mechanisms. It is thought that the N-terminal telopeptide part, i.e., the part that activates NF-κB, of the CD74 molecule undergoes several proteolysis processes. The pathway known as regulated intramembrane proteolysis is more active in patients with AS. Another possible mechanism could be the fact that continuous and increased MIF signal production may lead to the cleavage and consumption of CD74 antigen (28).

Another objective of the study was to determine the relationship between CD74 levels and MIF gene polymorphisms due to the close association between the CD74 molecule and MIF. However, a significant difference between polymorphism distributions and CD74 antigen levels could not be established. Moreover, a similar comparison could not be found in the literature.

This study has some limitations. The mean duration of symptoms was high in the patient group, and the study was cross-sectional by nature. The patient group comprised individuals who were taking drugs, and a pre- and post-treatment evaluation was not performed. Another limitation of the study was the relatively low number of patients.

Finally, CD74 antigen levels and MIF gene polymorphisms can be used in the diagnosis, follow-up, and determination of the disease prognosis after conducting further prospective studies with a greater number of patients.

CONCLUSION

Although MIF 173 G/C polymorphism is more frequently encountered in patients with AS, no statistically significant difference was observed. The aforementioned difference can be significant in future studies with larger patient groups and on different patient populations. Different samples are suggested to be studied because the only study that investigated MIF gene polymorphism in patients with AS had been conducted in the Turkish population. As per the results of the present study, CD74 antigen levels can be used in the diagnosis and follow-up of AS, whereby ELISA can be used in the measurement, as a suitable method in daily practice. Further, such studies can prevent possible complications and delays in diagnosis as well as contribute to the development of new treatment options.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gaziantep University (28.11.2016-308).

Informed Consent: Written informed consent was obtained from individuals who participated in this study.

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Conflict of Interest: Authors have no conflicts of interest to declare.

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