



## Serum Level of ADAMTS4 and ADAMTS8 in Patients with Psoriatic Arthritis

Irmak İçen Taşkın<sup>1</sup> , Sevgi İrtegin Kandemir<sup>2</sup> , Kemal Nas<sup>3</sup> , Abdullah Zübeyir Dağlı<sup>4</sup>

### ABSTRACT

**Objective:** Psoriatic arthritis (PsA) is a chronic inflammatory disease associated with psoriasis. A disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) is a large family of proteoglycanase enzymes that show proteolytic activity. The expression levels of ADAMTS proteases in osteoarthritis and rheumatoid arthritis are upregulated. However, their expression levels in PsA patients have not been examined yet. The aim of this study was to determine the serum levels of ADAMTS4 and ADAMTS8 in PsA patients.

**Materials and Methods:** This was a case-control study and enrolled 40 PsA patients and 40 individuals as controls. Serum levels of ADAMTS4 and ADAMTS8 were examined by the enzyme-linked immunosorbent assay (ELISA). The relationship between ADAMTS8 levels and demographic and clinical features of PsA patients were analyzed.

**Results:** The results of this study showed that the ADAMTS8 level was significantly elevated in the serum of PsA patients (160.9±49.79 pg/mL) compared to the control groups (<15.6 pg/mL). An association ( $r=0.32$ ,  $p<0.05$ ) was detected between age and serum level of ADAMTS8. However, the level of the ADAMTS4 in many subjects was under the detectable range.

**Conclusion:** Our results conclude that a relationship exists between ADAMTS8 and PsA, but further investigations are required to establish the function of ADAMTS8 proteases in PsA.

**Keywords:** Psoriatic arthritis, ADAMTS4, ADAMTS8, biomarkers

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<sup>1</sup>Department of Molecular Biology and Genetic, İnönü University Faculty of Science and Art, Malatya, Turkey

<sup>2</sup>Department of Medical Biology, Dicle University Faculty of Medicine, Diyarbakır, Turkey

<sup>3</sup>Division of Rheumatology and Immunology, Department of Physical Medicine and Rehabilitation, Sakarya University Faculty of Medicine, Sakarya, Turkey

<sup>4</sup>Department of Physical Medicine and Rehabilitation, Bitlis State Hospital, Bitlis, Turkey

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**Correspondence**  
Sevgi İrtegin Kandemir,  
Dicle University Faculty of  
Medicine, Department of  
Medical Biology,  
Diyarbakır, Turkey  
Phone: +90 412 248 85 61  
e-mail:  
irteginsevgi@hotmail.com

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### INTRODUCTION

Psoriasis is one of the inflammatory skin disorders that affects about 2%–3% of the people (1). Its complex pathogenesis includes a number of processes such as immune and inflammatory pathway activation, epidermal hyperproliferation, and dermal angiogenesis. The disease is not exclusively considered as a skin problem. This is because psoriasis can result in broad diseases including metabolic disturbances and psoriatic arthritis (PsA), which is known as a common complication relevant to cardiovascular diseases and depression (2–4). Up to 30% of patients with psoriasis develop PsA (5). Psoriasis skin symptoms precede joint pains associated with arthritis in most of the cases. Joint inflammation may develop either simultaneously or prior to the skin lesions (6).

The identification of PsA is generally done depending on the arthritic indications that coexist with psoriatic plaques, as specific laboratory tests are not available (7). The diagnosis is also done based on the elevation of the nonspecific inflammatory markers as well as the imaging procedure findings that may be negative during the disease's early developmental stages. For these reasons, the investigation of new biomarkers that can be used in the diagnosis of PsA or monitor the progress of the disease is necessary.

A disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) is a member of proteoglycanase enzymes that exhibit proteolytic activity against hyaluronate proteoglycans like versican, aggrecan, and brevican (8, 9). The degradation of hyaluronate proteoglycans by the ADAMTS is substantial in atherosclerosis and inflammation (9–11) that are shown in PsA patients. The proteases are the causative agents of articular cartilage loss through extracellular matrix (ECM) degradation, and ADAMTS proteases play an essential role in arthritic diseases like rheumatoid arthritis (RA) and osteoarthritis (OA) (11–13). ADAMTS4 and ADAMTS8 are the main members of the ADAMTS family that exhibit aggrecanase activity; however, their roles in PsA patients have not been examined yet. We evaluated the serum level of ADAMTS4 and ADAMTS8 in PsA patients in our study and determined whether ADAMTS4 and ADAMTS8 can be useful biomarkers in PsA.

### MATERIALS and METHODS

#### Study Population

This case-control study was conducted on 40 individuals with PsA aged from 19 to 70 years and 40 healthy

**Table 1.** Overall characteristics of patients with psoriatic arthritis and control group

Variables	Patients (n=40) (mean±SD)	Healthy control (n=40) (mean±SD)
Age (years)	44.85±11.39	43.6±14.67
Height (cm)	166.53±9.06	–
Weight (kg)	77.6±15.12	–
BMI	28.01±5.15	–
Sex (Male/ Female)	17/23	18/22
ESR (mg/l)	21.13±20.36	–
CRP	13.53±32.54	–
WBC count	9.55±8.93	–
ADAMTS8 (pg/mL)	160.9±49.79	≤15.6 pg/ml
ADAMTS4 (pg/mL)	n (34) <625	n (35) <625
	n (6)=32123.60±29046.29	n (5)=10127.684±7607.74
Duration of PsA complaints (years)	11.62±9.14	–
Duration of PsA onset (years)	8.43±9.06	–
Duration of morning stiffness (min/day)	38.19±39.25	–
Visual Analogue Scale (VAS) (0–10)	4±2.76	–
Physician global assessment (0–10)	4±2.09	–
Patient global assessment (0–10)	4.2±2.42	–
Tender/painful joint count	3.68±4.66	–
Swollen joint count	7.15±8.28	–
DAS28-CRP	3.12±1.29	–
BASDAI (0-10)	4.1±2.64	–
BASMI	0.77±1.44	–
BASFI (0-10)	2.97±2.27	–
HAM-D	5.83±3.85	–
HAM-A	6±4.19	–
HAQ (0-3)	0.42±0.55	–
HAQ-SpA (0-3)	0.47±0.54	–
Fatigue Severity Scale	3.37±1.45	–
SF36 PCS	40.55±13.98	–

BMI: Body mass index; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; WBC: White blood cell; PsA: Psoriatic arthritis; SD: Standard deviation; HAM-D: Hamilton Depression Rating Scale; HAM: Hamilton Anxiety Rating Scale; HAQ: Health Assessment Questionnaire; SF-36 PCS: Short form 36 physical component score

control matched for gender and aged from 18 to 68 years. This study was affirmed by the Clinical Trials Ethics Committee of Dicle University (approval date is 05.08.2014 and approval number is 291). A two-sample t-test power analysis was applied to the data from previous research to calculate the required sample size. Results proposed 40 individuals for each group. This research was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients and healthy controls before enrollment. All PsA patients met the classification criteria for the diagnosis of PsA (CASPAR) (14). The illness term extended from 0.5 to 40 years. The harshness of PsA was evaluated by the 28-joint Disease Activity Score with C-reactive protein (CRP) (DAS 28-CRP), which varied from 1.48 to 10 points. PsA patients were subdivided into three groups based on the activity of arthritis according to the American College of

Rheumatology criteria (15). Patients with DAS 28 between 2.6 and 3.2 formed group I (low disease activity), group II consisted of patients with DAS 28 between 3.2 and 5.1 (medium disease activity), and patients with DAS 28 more than 5.1 were included in group III (high disease activity). Patients with other rheumatic diseases, cardiovascular diseases, diabetes, or metabolic syndrome, and individuals under 18 years and pregnant women were excluded from this study.

#### Laboratory Assessment

The whole blood collected for enzyme-linked immunosorbent assay (ELISA) analysis, and allowed to clot at 20°C–25°C for 15–30 minutes. The clot was skimmed by centrifuging at 1,000–2,000 x g for 10 minutes at +4°C. Separated serums were collected at –80°C until the hour of the investigation for the quantification of

**Table 2.** Association of serum level of the ADAMTS8 (pg/mL) with the disease activity, peripheral arthritis, gender, and morning stiffness of PsA patients

Variables	DAS 28 Group	n	Mean	SD	p
ADAMTS8 <sup>++</sup>	I (>2.6 and ≤3.2)	23	157.31	56.72	0.482
	II (>3.2 and ≤5.1)	13	169.98	39.01	
	III (>5.1)	4	152.02	44.56	
Variables	Peripheral arthritis	n	Mean	SD	p
ADAMTS8 <sup>+</sup>	Avaliable	30	154.02	46.95	0.129
	Not avaliable	10	181.54	54.85	
Variables	Sex	n	Mean	SD	p
ADAMTS8 <sup>+</sup>	Male	17	174.31	52.39	0.153
	Famale	23	150.99	46.44	
Variables	Morning stiffness	n	Mean	SD	p
ADAMTS8 <sup>+</sup>	Avaliable	20	158.47	36.23	0.756
	Not avaliable	20	163.33	61.35	

SD: Standard deviation; +: Mann–Whitney U test was used; ++: Kruskal–Wallis test was used

ADAMTS4 and ADAMTS8 levels. Serum levels of ADAMTS4 and ADAMTS8 were evaluated by a human ELISA following the manufacturer's instructions (ADAMTS8; Fine Test, Hubei, China, ADAMTS4; Boster, CA USA) in both controls and PsA patients. The tests were performed on an ELISA reader system (Multiscan Go, Thermo Scientific, USA). Serum levels of ADAMTS4 and ADAMTS8 were estimated from a standard curve expressed as pg/mL. Assay ranges are 625 pg/mL–40,000 pg/mL and 15.6 pg/mL–1,000 pg/mL for ADAMTS4 and ADAMTS8, respectively.

### Statistical Analysis

The statistical analysis was conducted with the SPSS statistical programming (version 22.0; SPSS, Chicago, IL, USA). Data were presented as mean±standard deviation (SD). Mann–Whitney U test and Kruskal–Wallis analysis were used to examine ADAMTS8 level with DAS 28 groups, gender, presence of peripheral arthritis, and joint stiffness. Pearson's correlation coefficient analysis was applied to explore the correlation. P-value of less than 0.05 was considered to be statistically significant.

## RESULTS

Demographic, clinical properties, and serum levels of ADAMTS4 and ADAMTS8 of PsA patients and healthy control were summarized in Table 1. Our result showed that ADAMTS8 serum level was notably elevated in patients with PsA (160.9±49.79 pg/mL) than in controls (≤15.6 pg/mL). However, the serum level of ADAMTS4 in many subjects in both PsA patients and control group was under the detectable range. It was under 625 pg/mL in 34 PsA patients and in 35 healthy controls. ADAMTS4 level was 32123.60±29046.29 pg/mL in six PsA patients and 10127.684±7607.74 pg/mL in five healthy controls (Table 1).

Moreover, the achieved data through evaluating ADAMTS8 serum

level were analyzed against the severity of the disease measured by DAS 28. There was not a significant connection between the activity of the PsA and the serum level of ADAMTS8 concentration (p=0.482) (Table 2). There was no association between peripheral arthritis (p=0.129), gender (p=0.153), morning stiffness (p=0.756), and ADAMTS8 serum level in PsA patients (Table 2).

The correlation between ADAMTS8 and remained clinical and demographic characteristics of patients were evaluated. There were no significant associations between ADAMTS8 level and height, weight, BMI, duration of PsA complaints, duration of PsA onset, duration of morning stiffness, VAS, patient global assessment of PsA, physician global assessment of PsA, fatigue severity scale, tender/painful joint count, swollen joint count, DAS28, BASDAI, BASMI, BASFI, HAM-D score, HAM-A, SF36 physical component scores (SF36 PCS), ESR, CRP, WBC, health assessment questionnaire-SpA (HAQ-S), or HAQ score (Table 3). However, a small but remarkable positive correlation was found between the ages of PsA patients and ADAMTS8 serum level (r=0.32, p=0.044) (Table 3).

## DISCUSSION

The pathogenesis of PsA is not completely comprehended because of the complex interaction of genetic, environmental, and immunological factors. Currently, there is no specific treatment of PsA, and no definitive biomarkers are available to estimate disease progression and therapeutic response (7). Thus, it is very important to discover PsA-specific biomarkers for the diagnosis, prognosis, and development of new therapeutics. Serum expression level of ADAMTS4 and ADAMTS8 in PsA patients and their relationship with disease activity to identify new prognostic and diagnostic biomarkers have been evaluated in our study.

ADAMTS is an extracellular protease family. In the human proteome, 19 ADAMTS proteins have been identified having sim-

**Table 3.** Correlations of clinical and laboratory parameters with serum levels of ADAMTS8 in PsA patients

Variables	Age	Height	Weight	BMI	
ADAMTS8					
r	0.32*	0.16	0.15	0.04	
p	0.044*	0.309	0.354	0.808	
Variables	Duration of PsA complaints (years)	Duration of PsA onset (years)	Duration of morning stiffness (min.)	VAS	Patient global assessment
ADAMTS8					
r	-0.11	-0.01	-0.05	0.06	-0.07
p	0.534	0.949	0.833	0.714	0.685
Variables	Physician global assessment	Fatigue Severity Scale	Tender/painful joint count	Swollen joint count	DAS 28
ADAMTS8					
r	0.01	0.18	-0.01	-0.09	0.19
p	0.999	0.272	0.933	0.568	0.228
Variables	BASDAI	BASMI	BASFI	HAM-D score	HAM-A score
ADAMTS8					
r	0.02	0.05	-0.03	-0.02	0.07
p	0.878	0.762	0.840	0.900	0.672
Variables	SF36 PCS	ESR	CRP mg/l	WBC	HAQ-s
ADAMTS8					
r	0.12	0.24	0.1	0.03	0.19
p	0.456	0.137	0.531	0.892	0.229
Variables	HAQ				
ADAMTS8					
r	0.14				
p	0.382				

\*: p<0.05; BMI: Body mass index; HAQ: Health Assessment Questionnaire; HAQ-S: Health Assessment Questionnaire-SpA; SF-36 PCS: Short form 36 physical component score

ilar domain structure and substrate diversity (16). ADAMTS are nonmembrane-bound enzymes and act with ECM elements such as procollagen, hyaluronan, and cartilage oligomeric matrix protein, and they lead to the degradation of these proteins (8). These proteases are involved in ECM remodeling, adhesion ligands, growth factors and receptors, and release of various cytokines by degrading specific matrix components (16). ADAMTS proteases contribute to many different physiological processes such as developmental regulation, inflammation, cell adhesion, cell signaling, and angiogenesis. The biological significance of these proteases is because of their important function in the pathophysiology of many common illnesses like arthritis (8, 12, 17), cancer (18), and atherosclerosis (9, 10). Articular cartilage loss as a result of ECM fragmentation in arthritis is a distinctive feature in the pathogenesis of the disease. Changes in the degradation of ECM by proteases are related to many pathological inflammatory conditions such as

RA, OA, and atherosclerosis (10). Even though it is well documented that ADAMTS proteases are involved in ECM remodeling, their role in PsA that shows articular cartilage loss in its pathophysiology has not been investigated yet.

ADAMTS4 and ADAMTS8 from the ADAMTS family are included in the group of proteoglycanases because they enzymatically break down the aggrecans, versican, and brevican proteoglycans that results in impairment of ECM (9). The aggrecan is available in the articular cartilage where it has a significant role to resist deterioration during joint movement and to protect collagen from degradation. Aggrecan loss from ECM is the first step in cartilage destruction (19). ADAMTS4 is one of the best characterized aggrecanases with one of the highest aggrecanase activity, and it has a functional role in cartilage degradation in OA (12, 13) and RA (19). In a study that used small interference RNA (siRNA) targeted ADAMTS4 has

been shown that ADAMTS4 is necessary for human cartilage aggrecan degradation, and it contributes to the structural detriment that defines human OA (20). ADAMTS4 mRNA level was found to be lower in the group with the hip degenerative arthritis compared to the healthy individuals, while no important variation was found in protein levels (21). However, in our research, serum level of ADAMTS4 in majority of the both PsA patients and control group were under the detectable range. ADAMTS8 also shows aggrecanase features and is expressed in human articular cartilage (22). It was also an increment in expression of the ADAMTS8 reported in human OA synovium (23). Another study reported that ADAMTS8 mRNA level elevated 3.5-fold in hip degenerative arthritis group, however, there were no differences in protein level between control and patient groups (21). ADAMTS8 protein level was found to be higher in PsA patients (160.9±49.79 pg/mL) compared to the healthy groups (≤15.6 pg/mL) in our study. Such contradicted results maybe because of the selected population for each study. Patients with PsA exhibit symptoms of subclinical atherosclerosis and have a high cardiovascular risk (24, 25). The degradation of versican by ADAMTS proteases is important in coronary artery disease and inflammation. ADAMTS4's ability to cleave versican is particularly significant for atherosclerosis, as versican aggregation is seen in blood vessels sensitive to coronary artery disease (10). ADAMTS8 is identified to be expressed in human atherosclerotic plaques (10). In our study, ADAMTS8 overexpressed in serum of the PsA patients when compared to the control group, suggesting that an elevation in ADAMTS8 serum level may help to monitor the risk of atherosclerosis in PsA patients. Nonetheless, a further study is required to assess the association between ADAMTS8 and atherosclerosis in PsA patients.

There are some limitations to our study. The sensitivity of the commercially available ADAMTS4 ELISA kit is relatively low with the 625 pg/mL lowest detection limit. Our study is a single-centered research. However, enrolled cases represent the majority of patients with different clinical features.

### Conclusion

This study was the first one to evaluate ADAMTS4 and ADAMTS8 expression levels in PsA patients. Even though it was suggested that ADAMTS8 may be a potential target for PsA, additional examinations are necessary to comprehend the physiological and pathological functions of ADAMTS8 in PsA patients.

**Ethics Committee Approval:** This study was approved by the Clinical Trials Ethics Committee of Dicle University (date: 05.08.2014, number: 291).

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

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – SİK, İİT; Design – SİK, İİT; Supervision – SİK; Resource – SİK; Materials – KN, AZD; Data Collection and/or Processing – AZD, KN; Analysis and/or Interpretation – İİT; Literature Search – İİT; Writing – İİT, SİK; Critical Reviews – SİK, İİT, KN, AZD.

**Conflict of Interest:** The authors have no conflict of interest to declare.

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