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ORIGINAL ARTICLE

Examining the functions of the vascular endothelial growth factor/hypoxia-inducible factor signaling pathway in psoriatic arthritis

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ABSTRACT

Objectives: The present study aimed to examine the roles of the vascular endothelial growth factor (VEGF), hypoxia-inducible factor (HIF), and heme oxygenase-1 (HO-1) in psoriatic arthritis (PsA).

Patients and methods: In this cross-sectional study conducted between November 2020 and May 2021, 64 patients (43 female, 21 male; mean age: 43.2±10.4 years; range, 22 to 60 years) with active PsA were included in the patient group, and 64 healthy volunteers (43 females, 21 males; mean age: 42.8±10.5 years; range, 23 to 61 years) were included in the control group. The demographic features of all cases were recorded. The following indices were used to assess the activity of PsA: Bath Ankylosing Spondylitis Disease Activity Index, Disease Activity Score in 28 joints (DAS28), and Visual Analog Scale. Additionally, Disease Activity in Psoriatic Arthritis (DAPSA) and Psoriasis Area and Severity Index (PASI) were used to evaluate the patients. The biochemical parameters of the patients were calculated. The serum levels of VEGF, HIF, and HO-1 were determined using an enzyme-linked immunosorbent assay.

Results: When the molecule levels and clinical features of the groups were evaluated, it was found that the VEGF and HIF-1 levels were higher in the patient group compared to the control group ($p<0.05$). No difference was observed in the comparison of the HO-1 levels of the patient group and the control group ($p<0.05$). A positive correlation was found between VEGF, HIF-1, and HO-1 ($p<0.05$). A positive relationship was found between VEGF and HIF-1 and erythrocyte sedimentation rate, C-reactive protein, DAPSA score, and PASI score ($p<0.05$). It was also determined that there was a positive relationship between the HIF molecule and DAS28 ($p<0.05$).

Conclusion: According to the results obtained in the present study, VEGF and HIF play a role in the etiology of PsA, and the observation of intermolecular correlation suggests that these molecules move together in pathogenesis.

Keywords: Angiogenesis, HIF, hypoxia, psoriatic arthritis, vascular endothelial growth factor.

Psoriatic arthritis (PsA) is a disease that affects the peripheral and axial spine and progresses with dactylitis and enthesitis. Although PsA has traditionally been regarded as a disease of the joints, the term "psoriatic disease" or "psoriatic syndrome" defines this heterogeneity as it shows a wide variation in phenotype.[1] The main pathologic features of the inflamed synovial tissues of patients with PsA are hyperplasia of the joint surface, increased vascularity, and inflammatory cells.[2] PsA has a prevalence of 2 to 3%, and this rate ranges from 7 to 42% in patients with psoriasis.[3,4] The etiology of PsA is not fully known, although genetic, environmental, and cellular factors play a role.[3,5,6]

Angiogenesis is the formation of new blood vessels. It may develop under physiological and certain pathological conditions. Angiogenesis occurs with the control of various growth factors and G proteins.[7] The leading one among these is the vascular endothelial growth factor (VEGF), which is a multifunctional growth factor with effects specific to endothelial cells. It causes endothelial cells to proliferate, migrate, and differentiate. VEGF is required for vasculogenesis and angiogenesis.[8] In cases such as hypoxia and inflammation, VEGF release is stimulated.[9] Angiogenesis response is

disrupted in inflammatory diseases, certain types of cancer, peripheral vascular diseases, and delayed wound healing.[7] VEGF levels were reported to be high in rheumatoid arthritis (RA), PsA, ankylosing spondylitis (AS), and Psoriasis.[10] In previous studies conducted with arthritic mice, anti-VEGF agents were reported to reduce angiogenesis and the severity of the disease.[11] VEGF inhibitors may have a therapeutic effect in inflammatory disorders,[12] and anti-VEGF treatment may also serve as a therapeutic approach for PsA patients who are prone to high levels of VEGF production.[11]

The hypoxia-inducible factor (HIF), which is synthesized under hypoxic conditions, is tasked with signal transduction in response to hypoxia.[13] HIF induction causes the activation of angiogenic factors.[14] Consequently, new blood vessels are formed, and oxygen and nutrient needs are fulfilled. Other than being an important regulator of angiogenesis, HIF is also effective in energy metabolism, erythrocyte formation, and cellular proliferation.[13-15] In addition to hypoxia, certain oncogenic and inflammatory cases activate HIF-1.[16] There are several studies demonstrating that HIF plays a role in psoriasis. The HIF molecule induces psoriasis lesions by inducing VEGF expression.[17] HIF isoforms play a role in the control of inflammatory cells and keratinocyte metabolic remodeling in chronic skin inflammation.[18] HIF and VEGF may therefore be effective in the initiation and progression of PsA.[19]

Heme oxygenase-1 (HO-1) has anti-inflammatory and antioxidant effects and is a potential therapeutic target for autoimmune diseases.[20] HO-1 catabolizes the heme to biliverdin, carbon monoxide, and free iron. Inflammatory abnormalities play a role in various pathological cases, such as angiogenesis and tumor progression, and are regulated by HIF-1.[21,22] Additionally, HO-1 is related to autoimmune inflammatory diseases.[22] While VEGF is induced by HIF-1, which is directly stimulated by hypoxia, it is also induced by HO-1, which is activated by HIF-1, through the ERK/JNK (extracellular signal-regulated kinase/c-Jun N-terminal kinase) pathway.[23] It was shown in previous studies that the inhibition of HO-1 aggravates the symptoms of psoriasis; therefore, HO-1 may also be among the therapeutic targets in PsA.[24] In the literature, no studies were found investigating the roles of these molecules in PsA. The hypothesis of the present study is that VEGF, HIF, and HO-1 levels of PsA patients differ from those of healthy individuals. In the present study, it was aimed to examine the roles of VEGF, HIF, and HO-1 in PsA and their relationship with disease parameters.

PATIENTS AND METHODS

This cross-sectional study was conducted at the Sakarya University Faculty of Medicine Physical Medicine and Rehabilitation clinic between November 2020 and May 2021. Sixty-four PsA patients (43 female, 21 male; mean age: 43.2±10.4 years; range, 22 to 60 years) who applied to the rheumatology outpatient clinic with active disease and fit the CASPAR (Classification Criteria for Psoriatic Arthritis) and a control group of 64 individuals (43 female, 21 male; mean age: 42.8±10.5 years; range, 23 to 61 years) were included in the study. A Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥4 or a Disease Activity Score in 28 joints (DAS28) ≥2.6 was considered an active disease.[25,26] Classification criteria for PsA were first defined by Moll and Wright[27] in 1973. According to these criteria, a patient with rheumatoid factor (RF) negative psoriasis can be classified as PsA if they have inflammatory arthritis and possesses one of the following clinical conditions: *(i)* oligoarthritis (≤4 tender and swollen joints, usually exhibiting asymmetrical involvement), *(ii)* polyarticular arthritis (≥5 affected joints), *(iii)* distal involvement (distal interphalangeal joint involvement), *(iv)* presence of spondylitis, and *(v)* arthritis mutilans.[27]

Examination findings and disease-related indices were evaluated by a rheumatologist. The demographic features of the patients as well as disease-related examination and laboratory parameters were recorded. Additionally, the participants with no known chronic or rheumatologic diseases (the control group) had similar features to the patient group in terms of age and sex.

Pregnant and breastfeeding women, individuals with active infection, individuals who have any rheumatologic diseases other than PsA, individuals who underwent iron treatment,

those who received blood and blood product treatment in the last three months, and those with psychological and chronic neurological diseases or a chronic heart, kidney, or liver disease were not included in the study.

The BASDAI index was used in evaluating the disease activity of PsA patients.[28,29] This index includes six sections in which the duration and severity of fatigue, spinal and peripheral joint pain, sensitivity to pressure by touching, and morning stiffness are investigated. The patients answered each question on a 10-item Visual Analog Scale (VAS), taking into consideration their general condition in the last week. For the score calculation, the average of the sum of the scores of the fifth and sixth questions and the scores of the first four questions was added up and divided by five.[30]

The severity of the disease was determined using the DAS28. DAS28 is a scale in which a total of 28 peripheral joints consisting of bilateral knee, shoulder, elbow, wrist, and knuckle joints are evaluated in terms of sensitivity and swelling. It is calculated by taking into consideration the tender joint count in 28 joints, as well as the swollen joint count, erythrocyte sedimentation rate (ESR), and the VAS score.[31] DAS28 is an important tool in the evaluation of the disease activity of PsA patients[29] and is widely used in studies conducted with PsA patients.[32]

The VAS is a 10-item horizontal scale on which patients score the severity of their pain with "no pain=0" on one end and "very severe pain=10" on the other. The values provided by the patients were used in the calculation of the indices.[33]

The Bath Ankylosing Spondylitis Functional Index (BASFI) was used to determine functional capacity.[34] In this scale, patients are asked to score 10 different activities on a 10-cm VAS taking into consideration their current condition and their condition in the past week. The BASFI score ranges from 0 to 10. Higher scores indicate a worse functional condition.[35]

The Disease Activity in Psoriatic Arthritis (DAPSA) is a scale developed to assess the disease activity of PsA patients[36] and was used to evaluate the patients in this study. Five different parameters are used in the DAPSA: 68 tender joints, 66 swollen joints, patient's global assessment with VAS, patient's pain assessment with VAS, and C-reactive protein (CRP) (mg/dL). The total score is calculated by summing all the scores obtained.

Another scale used in this study was the Psoriasis Area and Severity Index (PASI), one of the most widely used scales for the assessment of psoriasis severity. It rates the symptoms of the disease, such as erythema, desquamation, and induration, according to their anatomical localization. PASI is a reliable and repeatable assessment method in adult psoriasis.[37]

Venous blood samples of 3 mL were taken from the voluntary participants into a tube with no anticoagulants and left at room temperature for 2 h to complete the coagulation process. Afterward, the samples were centrifuged for 15 min at 4°C and 1000 g, and the reserved serum was placed into Eppendorf tubes and stored at –80°C.

Following the completion of all samples, the samples were taken out of the storage and left until they reached room temperature for the enzyme-linked immunosorbent assay. The commercial kits obtained were operated on the VEGF level (Catalog No: E0080 Hu; Bioassay Technology Laboratory (BT Lab), Shanghai, China), HIF-1 level (Catalog No: E0422 Hu; BT Lab, China), and HO-1 level (Catalog No: E0932 Hu; BT Lab, China) serum samples in line with the kit protocols.

Statistical analysis

Statistical analysis was conducted using IBM SPSS version 22.0 (IBM Corp., Armonk, NY, USA). The mean ± standard deviation values of the data were stated. The Shapiro-Wilk test was used to test the normality of variable distribution. Student's t-test was used to compare the mean vbalues of the normally distributed variables, while the Mann-Whitney U test was used for the variables with nonnormal distribution. The Pearson correlation analysis was used for the correlations of the normally distributed variables, whereas the Spearman correlation analysis was used for the variables with nonnormal distribution. The level of statistical significance was accepted as $p<0.05$.

Table 1. Demographic features of the control and patient groups

	Control group			Patient group		
Participants' features	n	%	Mean±SD	n	%	Mean±SD
Age (year)			42.8±10.5			43.2±10.4
Sex						
Female	43			43		
Male	21			21		
Body mass index (kg/m²)			28.0±6.1			25.3±3.6
Number of smokers	18	28.12		17	26.56	

SD: Standard deviation.

RESULTS

The results of the 128 cases in the present study were evaluated. When the groups were compared in terms of demographic features, no statistically significant difference was found ($p<0.05$). The demographic data of the groups are summarized in Table 1.

Tables 3 and 4 show the VEGF, HIF, and HO-1 levels of each group and the correlations between them. According to the findings of the present study, the VEGF concentration in the control group was 419.27±221.12 ng/L, while it was 557.27±399.74 ng/L in the patient group. In the statistical evaluation performed, a statistically significant increase was determined in the serum VEGF levels in the patient group compared to the control group ($p=0.017$).

When VEGF was compared with the other parameters, a positive relationship was determined in HIF levels ($r=0.861$; $p<0.001$), HO-1 concentration ($r=0.616$; $p<0.001$), ESR ($r=0.243$; $p=0.05$), CRP ($r=0.471$; $p=0.004$), DAPSA ($r=0.280$; $p=0.025$), and PASI scores ($r=0.353$; $p=0.004$).

The HIF-1 concentration was 289.40±101.16 ng/L in the control group and 351.84±226.09 ng/L in the PsA group. In the statistical examination performed, a statistically significant increase was determined in serum HIF-1 levels in the patient group compared to the control group ($p=0.046$).

A positive relationship was found between HIF-1 concentration and HO-1 ($r=0.554$; $p<0.001$), VEGF ($r=0.861$; $p<0.001$), ESR ($r=0.363$; $p=0.003$), DAS28 ($r=0.318$; $p=0.010$), CRP ($r=0.560$; $p<0.001$), BASFI ($r=0.310$; $p=0.016$), DAPSA ($r=0.410$; $p=0.001$), and PASI scores ($r=0.467$; $p<0.001$).

Table 2. The disease activities, clinical findings, and laboratory findings of the psoriatic patients

	Evaluation result		
Disease-related parameters	n	%	Mean±SD
Duration of disease (year)			6.5±7.27
ESR (mm/h)			21.3±16.6
CRP (mg/L)			8.3±9.0
Tender joint count			8.2±10.6
Swollen joint count			3.2±3.8
Morning stiffness (min)			36.3±5 8.8
RF negativity	61	95.32	
Anti CCP negativity	62	96.88	
DIF joint involvement	13	20.31	
Asymmetric oligoarticular arthritis	14	21.87	
Symmetrical polyarthritis	21	32.81	
Spondyloarthritis	23	35.93	
Arthritis mutilans	0	0	
Dactylitis	14	21.87	
Enthesitis	30	46.85	
Presence of skin lesion	54	84.37	
Presence of nail findings	27	42.18	
Presence of PsA history in family	13	20.31	
Presence of psoriasis history in family	28	43.75	
DAS28			4.1±1.3
BASDAI			6.1±2.2
VAS			6.1±2.7
PASI score			4.5±4.2
DAPSA score			27.1±16.3

SD: Standard deviation; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; RF: Rheumatoid factor; CCP: Cyclic citrullinated peptide; DIF: Distal interphalangeal; DAS28: Disease Activity Score in 28 joints; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; VAS: Visual Analog Scale; PASI: Psoriasis Area and Severity Index; DAPSA: Disease Activity in Psoriatic Arthritis.

Table 3. VEGF, HIF, and HO-1 levels of the control and patient groups

	Healthy controls	PsA patients	
Serum molecule concentrations	Mean±SD	Mean±SD	*p*
VEGF(ng/L)	419.3±221.1	557.3±399.7	0.017
HIF (ng/L)	289.4±101.2	351.8±226.1	0.046
HO-1 (ng/L)	0.8±0.6	0.7±0.8	0.475

VEGF: Vascular endothelial growth factor; HIF: Hypoxia-inducible factor; HO-1: Heme oxygenase-1; SD: Standard deviation.

Table 4. Serum VEGF, HIF, and HO-1 Levels, and the evaluation of the relationship between the clinical features of the patients and the biomarker levels

Biomarker	HIF	HO-1	DAS28	CRP	ESR	DAPSA Score	PASI score
VEGF							
r	0.861**	0.616**	0.075	0.471*	0.243*	0.280*	0.353
p	<0.001*	<0.001	>0.05	0.004	0.05	0.025	0.004**
HIF							
r	1	0.554**	0.318**	0.560**	0.363*	0.410**	0.467
p		<0.001	0.010	<0.001	0.003	0.001	0.000**
BASFI Score							
r	0.310*	0.085	0.404**	0.254	0.422**	0.176	0.294
p	0.016	>0.05	<0.001	>0.05	<0.001	>0.05	0.023*

VEGF: Vascular endothelial growth factor; HIF: Hypoxia-inducible factor; HO-1: Heme oxygenase-1; DAS28: Disease Activity Score in 28 joints; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; DAPSA: Disease Activity in Psoriatic Arthritis; PASI: Psoriasis Area and Severity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; * Correlation is significant at the 0.05 level (2-tailed); ** Correlation is significant at the 0.01 level (2-tailed).

The HO-1 concentration was 0.76±0.63 ng/L in the control group and 0.67±0.84 ng/L in the patient group. No significant difference was observed in the comparison between the serum HO-1 levels of the patient group and the control group (p=0.475).

A positive correlation was determined between HO-1 concentration and VEGF levels (r=0.616; p<0.001) and HIF-1 concentration (r=0.554; p<0.001). No correlation was found with other parameters (Table 4).

No significant correlation was found in the comparison of biomolecules and the subclassification performed in line with the classification criteria specified by Moll and Wright[27] (p<0.05).

DISCUSSION

Although complex immunological molecular mechanisms and their interaction with genetic and environmental factors are regarded as responsible in the etiology of PsA, the cause is not fully identified. Since PsA does not have a specific biomarker or diagnosis method, the revelation of new molecular mechanisms is of importance for new and stronger therapeutic approaches.

In the present study, the VEGF, HIF, and HO-1 molecule levels in the serums of patients diagnosed with active PsA and healthy individuals were compared for the first time in the literature, and the correlations between these molecule levels and the parameters related to the severity

of the disease were evaluated. As a result of the study, the VEGF and HIF levels in the patient group were determined to be statistically higher compared to the control group; however, this relationship could not be shown in HO-1. A positive relationship was found between all three molecules. Additionally, a positive relationship was found between VEGF, DAPSA score, PASI score, ESR, and CRP levels, as well as between HIF, ESR, CRP levels and DAS28, DAPSA, PASI, and BASFI scores.

VEGF, an important signal protein in angiogenesis and vasculogenesis, causes migration, proliferation, and differentiation in endothelial cells.[38,39] VEGF is involved in the pathogenesis of RA and PsA through its impact on endothelial cell growth and its properties to increase vascular permeability.[12] Ballara et al.[40] examined 134 patients diagnosed with early RA, self-limiting arthritis (viral, reactive, and idiopathic inflammatory arthritis), and PsA and found that serum VEGF levels were significantly high in all patient groups with inflammatory arthritis compared to the control group with no arthritis. In the study conducted by Watanabe et al.,[41] serum VEGF levels were found to be high in PsA patients, and following systemic treatment, it was determined that the serum VEGF levels of the PsA patients approached the serum VEGF levels of the control group. In the study conducted by Sakalyte et al.[42] on early undifferentiated arthritis patients, a positive correlation was found between VEGF and ESR, CRP, and RF, while no significant correlation was found between VEGF and DAS28. In the study conducted by Fink et al.[43] to determine VEGF levels in patients with active and inactive PsA and healthy controls, it was shown that patients with active PsA had significantly higher levels of VEGF compared to patients with inactive PsA and healthy individuals. In a previous study, VEGF serum levels of patients with active PsA were found to be higher compared to PsA patients in remission.[44] In the study conducted by Nofal et al.,[45] it was aimed to evaluate the possible role of VEGF in psoriasis pathogenesis and its importance as an indicator of disease severity and control. According to the results of the study, the mean serum VEGF levels in the patient group were found to be significantly higher compared to the control group. A very significant correlation was found between VEGF and PASI scores. As a result of the study, the proposed role of VEGF in psoriasis pathogenesis was supported, and it was argued that VEGF could be a good indicator of disease severity and control. In the present study, the statistically significant increase in the serum VEGF level of the patient group compared to the control group and the positive correlation between VEGF and CRP, PASI score, and DAPSA score are in line with the studies in the literature.

Hypoxia is one of the most important factors that stimulate angiogenesis.[46,47] HIF is synthesized under hypoxic conditions.[13] Stimulation of HIF causes the activation of angiogenic factors.[15] HIF-1, which serves in response to hypoxia, is effective in the pathogenesis of inflammatory arthritis.[48] Rosenberger et al.[49] conducted a study to demonstrate that major oxygen-dependent HIF isoforms are strongly upregulated in psoriatic skin. According to the findings the study, hypoxia triggered physiological growth in hair follicles and skin glands and caused an increase in HIF and VEGF levels. The results of the study revealed that HIF activation plays an important role in patients with psoriasis. Torales-Cardeña et al.[50] investigated the role of HIF-1α between the cytokines and cells of the immunological system present in psoriasis pathogenesis and stated that psoriasis is a chronic, inflammatory skin disease that progresses with the altered regulation of keratinocyte proliferation, inflammation, and angiogenesis. They also reported that the increase in the transcription factor HIF-1α played a role in the homeostasis of these three biological phenomena. As a result of the study, it was understood that HIF-1α and its regulators could be significant pharmacological targets to address the lack of regulation in the immunological processes within angiogenesis and psoriasis. Angiogenesis plays an important role in the pathogenesis of other inflammatory diseases as well.[51] The location, size, and joint destruction of inflammation in synovium depends on the formation of new blood vessels. In this direction, it was reported that HIF-1 plays a critical role in the regulation of hypoxia-induced angiogenesis.[52] It was reported that HIF levels were upregulated in the lesions of patients with psoriasis.[17] It is thought that insufficient oxygenation triggers the increase in synovial

angiogenesis in RA, which takes place through the expression of hypoxia-inducible molecules, including VEGF.[53] In the study conducted by Zhang et al.[54] on rats, a significant increase was observed in serum VEGF and HIF-1α levels in the comparison between the data of the arthritis model group and the control group. Additionally, a positive correlation was determined between the HIF-1α protein and the arthritis index. In the study conducted by Hu et al.[55] on rats, a collagen-induced arthritis model was applied to the animals and HIF-1 and VEGF levels were examined. In the immunohistochemical examinations, in relation to hypoxia in the synovial membrane and areas of osteonecrosis, a significant increase was observed in the HIF-1 and VEGF levels of the group subjected to the arthritis model compared to the control group. Additionally, a positive correlation was found between HIF-1 and VEGF. In the study conducted by Wahba et al.,[56] it was found that HIF-1α and VEGF levels were higher in patients with RA. In another study, it was reported that HIF and VEGF levels of patients with RA were elevated compared to the control group and that a positive correlation was found between HIF and VEGF.[57] In the present study, the significant increase in the serum HIF-1α level in the patient group compared to the control group and the positive correlation between HIF-1, DAS28, and VEGF are in line with the results of Wahba et al.'s[56] study. The high levels of HIF-1 and VEGF in PsA patients suggest that these molecules cooperate in the etiology of the disease.

Heme oxygenase-1 is an enzyme tasked in the destruction process of the heme molecule.[58] The human body upregulates HO-1 in cases such as ischemia and inflammation to sustain homeostasis.[59,60] HO-1 plays a role in inflammatory diseases.[61,62] In a previous study, it was argued that deterioration in the oxidant-antioxidant system could be effective in psoriasis pathogenesis.[63] In this context, it was found that the HO-1 enzyme possessed antioxidant, anti-inflammatory, and cytoprotective features and caused expression on psoriatic skin.[64]

In the literature, there are no studies showing the relationship between HO-1 and PsA. In this respect, the present study is the first of its kind in the literature. Some studies examined the relationships between HO-1 and inflammatory arthritis. In the study conducted by Kobayashi et al.,[65] with the aim of examining the pathogenetic roles and expression of the anti-inflammatory inducible HO-1 enzyme in RA, HO-1 expression in synovial tissue taken from osteoarthritis (OA) patients and patients with noninflammatory joint diseases was identified with immunoblotting and immunohistochemistry. HO-1 levels were found to be higher in the synovial tissue lesions taken from RA patients compared to the other patient groups, and the data show that HO-1 is expressed in RA synovial tissue and plays a regulatory role in inflammation development. In the study conducted by Yang et al.,[66] it was found that the number of HO-1 cells in the RA synovium was higher compared to that obtained from the OA synovium. In the animal experiment carried out by Takada et al.,[67] it was determined that HO-1 expression could be beneficial in the prevention of OA. In the study conducted by Liu et al.,[68] whether HO-1 could serve as a potential therapeutic approach in rheumatic diseases was investigated, and it was stated that HO-1 exhibits anti-inflammatory effects in certain rheumatic diseases, while HO-1 density and activation could cause unwanted immunosuppression in other cases. In the study conducted by Zwerina et al.[69] investigating the role of HO-1 in osteonecrosis as part of osteoclastogenesis and inflammatory diseases, it was found that HO-1 induction suppressed osteonecrosis in osteoclastogenesis and inflammatory diseases. In the present study, no statistically significant difference was found in the serum HO-1 molecule levels in the patient group compared to the control group. However, a positive correlation was found between the HO-1 molecule and the VEGF and HIF-1 molecules. This suggests that the HO-1 molecule moves together with these molecules, and perhaps a similar conclusion could be reached for this molecule with bigger sample sizes or patients with more severe PsA involvement. The anti-inflammatory properties of HO-1 were observed in psoriasis and there are reports stating that HO-1 expression is protective in psoriatic animal models.[70] In the study conducted by Xu et al.,[20] a positive correlation was found between HO-1 expression and ESR and CRP. According to the results of the study conducted by Zhao et al.,[24] HO-1 activation alleviates inflammation and controls psoriasis by suppressing cell proliferation.

In conclusion, levels of VEGF and HIF molecules, which play a role in angiogenesis, increase in patients with PsA, an inflammatory disease, compared to healthy individuals. Additionally, there was a positive correlation between the two molecules. The reason behind this increase could be that angiogenesis and inflammation occupy an important place together in the pathology of PsA. Although the HO-1 concentration did not vary, the fact that a positive correlation was identified between the HO-1 molecule and VEGF and HIF-1 among the patients and the healthy individuals suggests that this molecule serves as a regulator. Signal pathways between these molecules can be reinforced with experimental studies, and effective therapeutic approaches can be obtained.

Ethics Committee Approval: The study protocol was approved by the Sakarya University Faculty of Medicine Clinical Studies Ethical Committee (date: 20.05.2021, no: E16214662-050.01.04-29845-64). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: All three authors have contributed to the study in conception and design, acquisition of data, analysis and interpretation of data, supervision, and drafting the manuscript.

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