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Serum calprotectin as an inflammatory marker in psoriatic arthritis patients: Relation to disease activity and musculoskeletal ultrasound findings

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Abstract

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis associated with psoriasis. The use of inflammatory markers can be disappointing in PsA since they are elevated in only about half of the patients. This study aimed to measure serum calprotectin level in PsA patients and to assess its association with disease activity in PsA (DAPSA) and musculoskeletal ultrasound findings. The study included 50 PsA patients and 30 controls. All subjects underwent medical history, musculoskeletal examination, hand and wrist joints ultrasound, and laboratory assessment. The mean age of patients was 41.04±11.8 years with female: male ratio of 3:2, and the median duration of arthritis 2 years (1-4 years) and DAPSA 25 years (3-84 years). The most common finding in patients by ultrasound was synovial hypertrophy in wrist joint (32%) followed by hand joints (28%). Patients' serum calprotectin level was significantly higher (174.2 ng/ml; ranged 127.5-282.6 ng/ml) than controls 41.4 ng/ml; ranged 19.9-59.8 ng/ml) (p<0.001). Serum calprotectin predicted the occurrence of PsA at cutoff >106.4 ng/ml (with sensitivity 98%, and specificity 86.6%; p=0.001) and predicted synovial hypertrophy in hand joints at cutoff >258.9 ng/ml (with sensitivity 71%, and specificity 83%). There was a significant relation between serum calprotectin with synovial hypertrophy (p=0.004), osteophytes (p<0.0001), nail affection (p=0.03) and erosions (p=0.01). Serum calprotectin is a more potential predictor for PsA (p<0.0001) compared to erythrocyte sedimentation rate (p=0.005) and C-reactive protein (p=0.001). In conclusion, serum calprotectin level is significantly high in PsA patients. It is associated with small hand joints synovitis and nail changes. This makes it a promising biomarker for defining patients with suspected PsA who do not meet specific disease criteria.

Keywords: Psoriatic arthritis; serum calprotectin; synovial hypertrophy.

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Introduction

Psoriatic arthritis (PsA) is a seronegative spondyloarthropathy marked by skin disease, enthesitis, dactylitis and joint disability. It affects about 20-30% of patients with psoriasis worldwide and 30% of patients in Egypt,[1] where many show moderate-to-severe disease.[2]

Most cases of PsA debut about a decade after the onset of psoriasis but in 10-20% arthritis develops before their skin disease causing a diagnostic dilemma.[3] The pathogenesis of psoriasis can be explained by dysregulation of immunological cell function as well as keratinocyte proliferation/differentiation. T-helper cells (Th)1 overactivation is thought to induce occurrence of psoriasis and Th17 cells play a key role as they produce various inflammatory cytokines.[4]

PsA induces proinflammatory cytokines which activate circulating neutrophils that are recruited to inflammatory sites following inflammatory signals, where they generate and release large amounts of reactive oxygen in a phenomenon known as respiratory burst which causes tissue destruction in joints.[5]

Laboratory findings in PsA are usually uncertain and are not accurately related to the disease activity.[6] The determination of erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) is frequently inconclusive in PsA, since they are elevated in only half of the patients. Increased ESR was observed in 28% of PsA patients but was related to disease activity, joint damage and PASI (psoriasis area severity index) while increased CRP was observed in 54 % of PsA patients.[7]

Grayscale ultrasound provides a visual representation of joint structures, enabling the differentiation of synovial hypertrophy and various causes of observable joint swelling, such as tenosynovitis or subcutaneous edema. Power Doppler ultrasound (PDUS) is effective in highlighting heightened vascularity in soft tissues, offering superior sensitivity to distinguish between inflamed and non-inflamed synovial swelling.[8]

Calprotectin, a zinc-binding protein present throughout the human body, including the cytoplasm of neutrophils and macrophages, is released during neutrophil activation. It is notably abundant in diverse bodily fluids like plasma, serum, spinal fluid, synovial fluid, urine, saliva, and stool. Elevated calprotectin levels are associated with inflammatory processes, making it a valuable and sensitive marker for local inflammation.[9]

Large amounts of evidence have proven that calprotectin expression is related to the process of development and progression of various immune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and psoriasis.[10]

Serum calprotectin may be used as an inflammatory marker in rheumatological diseases such as RA and axial spondylarthritis (axSpA) and was found to be associated with the presence and severity of the disease.[11] PDUS serves as a valuable instrument for evaluating musculoskeletal and cutaneous engagement, and it also functions as an effective tool for tracking the progress of therapeutic interventions. Therefore, the aim of this work was to assess serum calprotectin level as a promising biomarker in PsA patients and to study its association with disease activity and radiological findings using musculoskeletal ultrasound.

Subjects and Methods

This study included 50 PsA patients enrolled from the outpatient clinic and the inpatient department of the Internal Medicine Rheumatology division at Ain Shams University Hospital (Cairo, Egypt) all fulfilling the Classification criteria for Psoriatic Arthritis (CASPAR) clinical classification criteria.[12] Patients with other autoimmune diseases such as seronegative spondyloarthropathies, inflammatory bowel diseases, malignancies or amyloidosis were excluded. In addition, 30 normal age and sex matched individuals served as a control group.

A full history was taken, and thorough clinical examination was performed with special emphasis on the musculoskeletal system. Blood samples were collected, permitted to coagulate for 10-20 minutes at room temperature, followed by centrifugation at 2000 to 3000 xg for 20 minutes. Serum samples were separated and then stored in a refrigerator for future utilization.[13] All subjects underwent laboratory investigations, including complete blood count (CBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) which were assessed according to standered methods of the

University Hospital. Serum calprotectin was assessed using Human Calprotectin enzyme-linked immunosorbent assay (ELISA) kits; (Cat. No. E4010Hu, Bioassay Technology Laboratory, China), according to the manufacturer's instructions.

Briefly, the ELISA plate wells were pre-coated with anti-human calprotectin antibodies. Calprotectin present in the added serum samples binds to the antibodies coated on the wells and then biotinylated human calprotectin antibody was added, binds to calprotectin and to the added streptavidin-horseradish peroxidase (HRP). After incubation, unbound Streptavidin-HRP was washed away. A substrate solution was introduced, resulting in color development correlating with the quantity of human calprotectin. The reaction was concluded with the addition of an acidic stop solution, and the absorbance was measured at 450 nm, using a microplate photometer (Multiskan™ FC 357, Richmond Scientific Ltd. UK).

Musculoskeletal ultrasound (MSUS) was done for the hands and wrists using semi-quantitative Gray Scale (GS) and Power Doppler (PD) scoring using an ultrasound machine (Esaote, MyLab™Six US machine), equipped with a 6-18 MHz linear probe. GS synovial and PD signal scores and any other findings were also recorded.[8]

The Disease Activity Index for Psoriatic Arthritis (DAPSA) was assessed and categorized as follows: 0-4 remission, 5-14 low disease activity, 15-28 moderate disease activity and >28 high disease activity.[14]

Statistical Analysis

The statistical package for social science (SPSS) version 23 was used for data analysis. Data were presented as number (%), mean ± standered deviation (SD) or median (range) and analyzed using the following tests: Chi-square, independent t, Mann-Whitney, Kruskal-Wallis, Spearman correlation coefficient, logistic regression and receiver operating characteristic curve (ROC). A *p*-value ≤ 0.05 was deemed significant.

Results

The mean age of the 50 patients was 41.04±11.8 years and the female: male ratio was 3:2. The mean age (36.9±9.7 years) and gender (F:M ratio 7:8) of the 30 control was not different than the patient's group (*p*=0.11 and *p*=0.25, respectively). Of the patient's group, 12% were smokers, 20% diabetic and 16% hypertensive. Patients had a significantly lower hemoglobin level, higher ESR, CRP and serum calprotectin compared to the control group (Table 1). Clinical manifestations, used medications, disease activity and MSUS findings are presented in (Table 2).

Table 1. Comparison of demographic data, comorbidities and laboratory parameters between psoriatic patients and control groups.

Studied variables	Patients (n=50)	Controls (n=30)	*p* value
Age (years) mean± SD	41.04±11.8	36.9±9.7	NS
Sex: Female: Male	30:20 (3:2)	14:16 (7:8)	NS
Smoking n (%)	6 (12)	4 (13.3)	NS
Diabetes n (%)	10 (20)	0 (0)	-
Hypertension n (%)	8 (16)	0 (0)	-
TLC (x10^3/mm^3) mean ± SD	7±2.21	6.9 ±1.3	NS
Hemoglobin (g/dl) mean ± SD	13±1.4	14.3±0.93	<0.0001
Platelets (x10^3/mm^3) mean ± SD	231.3±72.1	245.6±68.2	NS
ESR (mm/1^{st} hr) median (IQR)	20 (15-28)	15 (13-20)	0.001
CRP (mg/dl) median (IQR)	10 (5-12)	6 (4-8)	0.005
Serum calprotectin (ng/ml) median (IQR)	174.2 (127.5-282.6)	41.4 (19.9-59.8)	0.001

TLC: total leucocytic count, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein. $p > 0.05$ is not significant (NS).

Table 2. Characteristics of psoriatic arthritis patients.

Studied variables		PsA patients (n=50)
Psoriasis duration (years) [median (IQR)]		10 (7-17)
Arthritis duration (years) [median (IQR)]		2 (1-4)
Arthralgia/Arthritis n (%)		38 (76)
Nail affection n (%)		30 (60)
Enthesitis n (%)		20 (40)
Axial affection n (%)		14 (28)
Dactylitis n (%)		2 (4)
DAPSA [median (IQR)]:		25 (3-84)
Remission (0-4) n (%)		4 (8)
Low (5-14) n (%)		6 (12)
Moderate (15-28) n (%)		16 (32)
High (>28) n (%)		24 (48)
Methotrexate n (%)		10 (20)
Leflunomide n (%)		4 (8)
Sulphasalazine n (%)		4 (8)
Cyclosporin n (%)		6 (12)
Biologics;		
Adalimumab n (%)		2 (4)
Golimumab n (%)		2 (4)
Secukinumab n (%)		4 (8)
Musculoskeletal ultrasound (MSUS) findings:		
Gray Scale (GS) synovial hypertrophy (wrist joint) n (%)	positive	16 (32)
	Grade 1	6 (12)
	Grade 2	10 (20)
Gray Scale (GS) synovial hypertrophy (small joints of hand) n (%)	positive	14 (28)
	Grade 1	10 (20)
	Grade 2	4 (8)
Dactylitis n (%)	positive	2 (4)
Osteophyte n (%)	positive	6 (12)
Nail affection/enthesitis n (%)	positive	8 (16)
Erosion (hand joints/wrist) n (%)	positive	4 (8)

DMARDs: disease-modifying anti-rheumatic drugs, DAPSA: Disease activity index for psoriatic arthritis, MSUS: musculoskeletal ultrasound

There was a significant correlation between the level of serum calprotectin and MSUS findings including synovial hypertrophy, osteophytes, nail bed affection and erosions (Table 3).

Figure 1 illustrates a MSUS image showing grade 1 synovial hypertrophy of the metacarpophalangeal joint.

Table 3. Correlation of serum calprotectin with disease parameters in psoriatic arthritis patients.

Parameters()	Serum calprotectin in PsA patients (n=50)	
	r	*p* value
Age (years)	0.09	NS
Psoriasis duration (years)	0.23	NS
Arthritis duration (years)	0.04	NS
Hemoglobin (g/dl)	-0.05	NS
TLC (x10³/mm³)	0.08	NS
Platelets (x10³/mm³)	-0.11	NS
ESR (mm/1st hr)	-0.08	NS
CRP (mg/dl)	0.26	NS
DAPSA	-0.001	NS
MSUS findings:	Median (IQR)	*p* value
Synovial hypertrophy CMC joint (Wrist joint)	215.6 (122.7 – 331.55)	NS
Synovial hypertrophy small joints of hand	282.6 (174 – 377.2)	0.004
Osteophytes	377.2 (311.1 – 486)	<0.0001
Nail affection	134.65 (116.9 – 172.25)	0.03
Erosions	114.5 (111 – 118)	0.01

PsA: psoriatic arthritis, TLC: total leucocytic count, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein. DAPSA: disease activity in PsA. MSUS: musculoskeletal ultrasound, CMC: carpometacarpal. $p > 0.05$ is not significant (NS).

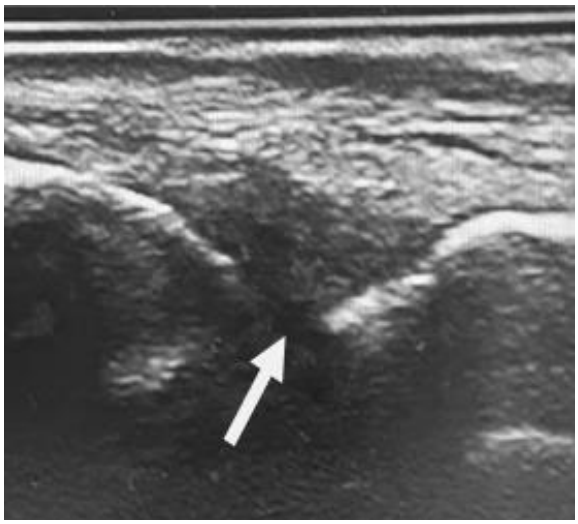

Figure 1. Musculoskeletal ultrasound showing grade 1 synovial hypertrophy in a metacarpophalangeal joint (arrow) in a patient with psoriatic arthritis.

Serum calprotectin predicted the occurrence of PsA in patients with psoriasis at a cutoff point of >106.4 ng/ml (sensitivity 98% and specificity 86.7%) (p=0.001) and predicted synovial hypertrophy at cutoff point of >258.9 ng/ml (sensitivity 71.4% and specificity 83.3%) (p=0.004) (Table 4). Finally, serum calprotectin was the most predictive independent factor for the presence of PsA compared to ESR and CRP in univariate analysis (Table 5).

Table 4. Cut off values of serum calprotectin to discriminate psoriatic arthritis patients from control and those with and without synovial hypertrophy.

Serum calprotectin (ng/ml) predictor of	AUC	Cut off	Sensitivity	Specificity	*p* value
PsA	0.96	>106.4	98	86.7	0.001
Synovial hypertrophy	0.76	>258.9	71.4	83.3	0.004

PsA: psoriatic arthritis, AUC: area under the curve. Significant at $p<0.05$.

Table 5. Regression analysis comparing serum calprotectin to erythrocyte sedimentation rate and C-reactive protein as predictors for psoriatic arthritis patients.

Variable	PsA patients (n=50)		
	P value	OR	95%CI
ESR (>20 mm/hr)	0.005	9.3	(2-43.6)
CRP (>9 mg/l)	0.001	7.04	(2.1-23.1)
Serum calprotectin (>106.4 ng/ml)	<0.0001	318.5	(33.8-2998.7)

ESR: erythrocyte sedimentation rate, CRP: C-reactive protein. Significant at $p<0.05$.

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Discussion

Psoriatic arthritis (PsA) is a chronic, progressive musculoskeletal disease where valid and reliable biomarkers for diagnosis and monitoring are lacking. PsA impacting approximately 0.1-1% of the overall population and occurring in 20-30% of individuals diagnosed with psoriasis worldwide.[2] Diagnosis mainly depends on clinical data. Delayed diagnosis is challenging as 10-20% of patients develop arthritis before onset of their skin disease.[15]

In the present study, the male-to-female ratio was 2:3 which is similar to that presented by a study of Inciarte-Mundo et al., 2016, (9:16),[16] while another study reported no sex differences in psoriasis.[17]

In this work, ESR and CRP were significantly increased in the patients compared to controls and in correlation to the DAPSA score and its different activity levels among psoriatic patients ($p<0.01$). In line with our findings, the study by Yurdakul et al., 2014,[18] found that ESR was elevated in 40% of PsA patients. However, it is noteworthy that ESR is not always elevated in PsA patients. In the study by ElSherbiny et al., 2021,[19] ESR was normal in 50% of PsA patients despite clinically active disease. In harmony with our findings, the study by Ogdie et al., 2020,[20] reported that CRP serves as a crucial non-specific indicator for both acute and chronic inflammation, displaying elevated levels in individuals with PsA disease. However, the study by Sokolova et al., 2020,[21] reported that CRP was normal despite systemic inflammation being detectable in the majority of patients with psoriatic disease. The conflicting data suggests that ESR and CRP do not play a prominent role in decision making for PsA disease.

In the current study, hemoglobin levels were significantly lower in PsA patients compared to controls. Similarly, the study by Yin et al., 2016,[22] reported that PsA is a chronic disease, and patients had a higher frequency of peripheral blood erythropenia or hypochromasia than controls.

The most common medications used in the current study for treatment of PsA patients were methotrexate (MTX, 20%), biologics (16%), and cyclosporine (12%). MTX remains the most common first-line disease-modifying antirheumatic drug (DMARD).[23]

In PsA patients, musculoskeletal involvement is the most debilitating. In this work, the most frequent manifestations were arthralgia/arthritis followed by nail affection, enthesitis and axial symptoms. Peripheral joint affection was similar to the frequency reported by the study of López et al., 2021,[24] and is the most common persistent symptom. In the current study, axial symptoms in the form of inflammatory back pain were found in 28% of patients. This is consistent with that reported by

a study of Gottlieb and Merola, 2021,[25] where axial involvement occurred in 25% of axial PsA disease. However, the study by Poddubnyy et al., 2021,[26] found that axial involvement was observed in 70% of PsA patients. This reflects the lack of agreed-upon classification or diagnostic criteria for axial involvement in PsA, which depends on the definition used.[25] Enthesitis was found in 40% of PsA patients. In accordance with our findings, the study by Polachek et al., 2017,[27] found enthesitis in 35% of PsA patients. However, a lower frequency (19.5%) was reported in a study on PsA patients in the United States reflecting that treatment availability affects remission rate.[28] The frequency of nail involvement in the current work was 60%. Similarly, the study by Mease et al., 2021,[28] found that up to 70–80% of patients with psoriasis have nail problems and the study by Raposo and Torres 2015,[29] found that 80% of PsA patients had nail affection. This is probably attributed to the intimate connection between the nail and the enthesis of the distal extensor tendon.

In the current study, the DAPSA score was used because it has higher face validity.[30] In the current study, 48% of the PsA patients had high disease activity, 32% moderate, 12% low and 8% were in remission. In a study by Queiro et al., 2023,[31] 20.8% of PsA patients had moderate activity. The median DAPSA score was 25, which is similar to that reported (24.4) by the study by Becciolini et al., 2023,[32] and by Romdloni et al., 2020, (21.6).[33]

Ultrasound (US) is a valuable tool in the assessment of PsA disease. The study by Kaeley et al., 2021,[34] and by Naranje et al., 2015,[8] have recognized the efficiency of US in detecting inflammation in the joints of PsA patients, both sub-clinically and actively, in addition to the degree of structural damage. Synovial hypertrophy is characterized by abnormal hypoechoic intra-articular tissue. This tissue is non-displaceable, poorly compressible, and may display Doppler signal.[34] In the current work, 32% of patients had synovial hypertrophy in the wrist joint and 28% in the small joints of hands. This comes in agreement with the study by Naranje et al., 2015,[8] who found that 39% of PsA patients had wrist affection in the form of synovial hypertrophy.

The present study revealed that serum calprotectin levels were significantly higher in patients with PsA than in controls and could significantly discriminate both at a cutoff value of >106.4 ng/ml. This comes in agreement with findings of the study by Elwan et al., 2021,[35] who determined an optimum cutoff value of 111.1±15 ng/ml for serum calprotectin in PsA patients. Furthermore, the study by Li et al., 2023,[30] found that serum calprotectin levels were significantly higher in PsA and psoriasis patients and similarly the study by Jarlborg et al., 2020,[11] found high levels in patients with RA, axial spondylarthritis (axSpA) and PsA disease.

In the current study, serum calprotectin was not related to the age, sex or disease duration. Similarly, the study by Zaki et al., 2019,[36] found no significant relation of serum calprotectin levels with the age, sex or disease duration in patients with psoriasis.

In the present study, serum calprotectin was significantly correlated with MSUS changes especially synovial hypertrophy in the small hand joints. This comes in accordance with findings of a study by Sakellariou et al., 2018,[38] who found that serum calprotectin was correlated with ultrasound measures of disease activity in early PsA disease. In polyarticular PsA, a significant correlation between calprotectin with GS and PD scores was also confirmed. This comes in line with findings of a study by Elwan et al., 2021,[36] who studied serum calprotectin as a potential biomarker for subclinical enthesitis in psoriatic patients and found that serum calprotectin was significantly higher in patients with synovial inflammation, both clinical and subclinical compared to those without synovial involvement and to the control group.

In the current study, DAPSA score was not correlated with serum calprotectin level. This comes in agreement with findings of a study by Sakellariou et al., 2018,[37] who found that calprotectin S100A8/A9 plasma levels were not related with PsA disease activity. And the study by Madland et al., 2007,[38] reported that serum calprotectin did not perform better than traditional biomarkers of disease activity in assessing PsA activity. The study by Jarlborg et

al., 2020,[11] also found that there was no correlation between serum calprotectin and PsA activity, but there was a correlation in case of RA, where higher calprotectin serum levels were associated with more severe forms of the disease. This was explained by the low number of swollen joint count in PsA and the different distribution of calprotectin expression in the synovial tissue of patients with PsA compared to other inflammatory arthritis. In contrast, the study by Li et al., 2023, [30] found that serum calprotectin level was associated with disease activity in PsA and the study by Cheng et al., 2022,[39] considered serum calprotectin as a useful biomarker associated with a high inflammatory burden.

In the present study, the efficacy of serum calprotectin as a diagnostic biomarker was confirmed. It was found that serum calprotectin was the most predictive biomarker for the detection of PsA compared to ESR and CRP. In concordance with our observation, the study by Jarlborg et al., 2020,[11] found that serum calprotectin as a biomarker outperformed ESR and CRP in axSpA.

The present study has several limitations. These include that serum calprotectin was measured at a single time point during the clinical course of each patient. It is better to be measured at multiple time points in the same patient for accurate monitoring of changes in its level during disease activity.

In conclusion, serum calprotectin was significantly higher in patients with PsA and found to be a sensitive and specific marker. It is associated with synovial inflammation in the small joints of hands and nail changes, as assessed by MSUS. This makes it a promising biomarker for defining patients with suspected PsA who do not meet specific disease criteria.

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Author Contributions

The conceptualization and editing of manuscript were done by FMB, engaged in the writing of the manuscript as well as the study by editing and reviewing the work. The data was gathered with help from DAE who significantly aided in the creation and modification of the manuscript. MAMT performed musculoskeletal ultrasound work for patients as well as methodology and data curation. The submitted manuscript was reviewed and approved by all authors.

Declaration of Conflicting Interests

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Ethical approval

The study protocol was reviewed and approved by the Research Ethics Committee, Faculty of Medicine, Ain Shams University (approval # FMASU MD 54/2021).

Informed consent

Before being enrolled in the study, participants submitted their written informed consent.

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