UDC 616.517 doi: https://doi.org/10.15407/ubj96.06.047

PLASMA GELSOLIN AND MATRIX METALLOPROTEINASE-3 LEVELS AS DIAGNOSTIC MARKERS FOR PSORIATIC ARTHRITIS

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Received: 18 June 2024; **Revised:** 10 August 2024; **Accepted:** 21 November 2024

Recent studies have revealed a high prevalence of undiagnosed psoriatic arthritis (PsA) in patients with psoriasis. Diagnosis of psoriatic arthritis has proven challenging because the symptoms of the disease are nonspecific, rheumatoid factor is not detectable, and acute phase reactant levels may be normal. Therefore, identifying soluble biomarkers for diagnosing PsA in psoriasis patients may help in early diagnosis and proper management. The aim of the work was to evaluate plasma gelsolin and matrix metalloproteinase-3 (MMP-3) levels as potential markers for PsA. This case-control study included 25 healthy controls and 50 psoriasis patients, who were divided into 25 patients with psoriasis only and 25 patients with psoriatic arthritis. Plasma levels of gelsolin and MMP-3 were measured using ELISA. It was shown that patients with PsA had significantly lower gelsolin and significantly higher MMP-3 plasma levels compared to patients with psoriasis only. For detecting PsA, gelsolin and MMP-3 had sensitivity of 96% and specificity of 92 and 80% for each, respectively. Gelsolin level negatively while MMP-3 level positively correlated with such parameters as disease activity for psoriatic arthritis, composite psoriatic disease activity index, and inflammatory markers including high-sensitivity C-reactive protein and erythrocyte sedimentation rate. It was concluded that plasma gelsolin and MMP-3 levels could serve as potential biomarkers for diagnosing PsA and monitoring the disease progression in PsA patients.

K e y w o r d s: gelsolin, MMP-3, psoriatic arthritis, psoriasis.

Psoriasis is a chronic inflammatory skin disorder, characterized by erythematous plaques and disfiguring scaling. Approximately one-third of psoriasis patients can eventually develop psoriatic arthritis (PsA) [1, 2]. Psoriatic arthritis is defined as a musculoskeletal inflammatory disease associated with cutaneous psoriasis and is usually seronegative for rheumatoid factor. PsA affects women and men almost equally with a peak age at 40 and 50 years [3, 4].

PsA is a diverse aggressive condition that affects multiple organ systems including peripheral and axial joints, skin, entheses, and nails [5, 6]. Progressive joint damage, extensive inflammation, and comorbidities are usually associated with PsA. Moreover, the severity of PsA at the time of presentation is considered a risk factor for mortality [7, 8]. Given the heterogeneity of the disease, PsA diagnosis is challenging, studies have revealed a high prevalence of undiagnosed PsA in patients with psoriasis. This might be due to the fact that detecting inflammatory musculoskeletal disease in psoriasis patients by non-rheumatologists is quite difficult since acute-phase reactants may be normal and the symptoms are nonspecific [9, 10]. Therefore, identifying soluble biomarkers for predicting PsA in psoriasis patients may help in early diagnosis and proper management, which leads to better outcomes [11].

Gelsolin is an actin-depolymerizing protein of the gelsolin superfamily. It is a highly conserved, multifunctional protein, which was first described in the macrophages' cytosol and later in multiple other

cells [12, 13]. Gelsolin is considered an anti-inflammatory modulator and is involved in the process of immune response. It has also been reported to be involved in the cytoskeletal structure remodeling that determines the morphology of cells and chemotaxis [14, 15]. Plasma gelsolin has been identified as a promising biomarker of inflammatory conditions, for predicting disease severity, clinical outcome and treatment response [16]. Reduction of plasma gelsolin levels has been linked with chronic inflammatory disorders, organs failure, sepsis, and cancers [17, 18].

Matrix metalloproteinase-3 (MMP-3) is a key member of the MMPs family, it is an enzyme encoded by the MMP-3 gene on chromosome 11q22.3 in humans [19, 20]. MMP-3 is involved in the degradation of extracellular matrix proteins during tissue remodeling in normal physiological processes, as well as in pathological conditions [21]. MMP-3 is produced by chondrocytes and synovial fibroblasts in joints. It was reported that MMP-3 can actively accelerate joint damage in rheumatoid arthritis [22]. Studies have also revealed the implication of MMP-3 in systemic sclerosis, mixed connective tissue disease and ankylosing spondylitis [23].

Our study sought to evaluate plasma gelsolin and MMP-3 levels as potential biomarkers for PsA, and to assess their correlation with PsA severity.

Materials and Methods

Study design and participants. This is a prospective case-control study that was conducted on three groups: group I: 25 patients with psoriasis and PsA (PsA patients), group II: 25 patients with psoriasis only without PsA (psoriasis patients), and group III: 25 healthy controls. All participants were matched for age and sex. The patients were recruited during the period between July 2022 and June 2023, from Dermatology, Rheumatology, and internal medicine departments, Tanta University Hospital, Egypt. The biochemical assays (which will be discussed later), conducted on blood samples of the studied subjects, were performed in the Clinical Pathology department, Tanta University Hospital, Egypt.

Ethics approval and consent to participate. Our study was approved by the ethics committee of the Faculty of Medicine, Tanta University (approval code: 36264PR679) and it was conducted in full adherence to the Declaration of Helsinki. At the beginning of the study, written informed consents were collected from all subjects involved in the study.

Inclusion criteria. The psoriasis patients were clinically diagnosed by its characteristic lesions and were assessed by a rheumatologist to exclude PsA.

PsA patients had psoriasis, were diagnosed according to classification criteria for psoriatic arthritis (CASPAR) [24], were seronegative for rheumatoid factor (RF) and had active PsA (at least 3 swollen and tender joints).

Exclusion criteria. Patients with any autoimmune disease, cardiovascular disease, malignancy, liver diseases, inflammatory bowel disease, uncontrolled diabetes mellitus, and patients on biological treatment were excluded from the study.

Data collection and clinical assessment. Each participant underwent a full medical history taking and a complete physical examination. Psoriasis area and severity index (PASI) was measured for all patients to evaluate the severity of psoriasis lesions. Disease Activity for Psoriatic Arthritis (DAPSA) [25] and Composite Psoriatic Disease Activity Index (CPDAI) were used to measure the disease activity in PsA patients [26].

Sample collection and biochemical assays. After overnight fasting, 10 ml venous blood samples were obtained under complete aseptic conditions for measuring the following; erythrocyte sedimentation rate (ESR) using the Westergren method, high-sensitivity C-Reactive Protein (hs-CRP) and RF using the nephelometric technique on Konelab 60i Thermo Scientific autoanalyzer (Thermo Scientific -Finland), gelsolin and MMP-3 assay using enzyme-linked immunosorbent assay (ELISA).

Assay of gelsolin and MMP-3 using ELISA. Gelsolin and MMP-3 levels were measured in plasma samples using sandwich-type ELISA, strictly following the manufacturer's instruction of each kit. The ELISA kits utilized in the study were provided by Abcam, Cambridge, UK, for gelsolin assay, and Elabscience Biotechnology Inc., USA, for MMP-3 assay.

Statistical analysis. Data were assessed using IBM SPSS software package version 24.0 (Armonk, NY, USA: IBM Corp). Quantitative data were expressed as mean ± SD. Qualitative data were expressed as frequency and percentage. The Student's *t*-test was utilized for comparing two groups, whereas F-test (analysis of variance) was employed to compare between multiple groups. To compare categorical ones, the chi-squared test was used. The diagnostic value of gelsolin and MMP-3 for predicting PsA was evaluated using receiver operating

characteristics (ROC) curve analysis. The Pearson's correlation test was employed to evaluate the correlation between two quantitative variables that were normally distributed. For all statistical procedures, significance threshold was set if $P \leq 0.05$.

Results

There was no significant statistical difference between the three studied groups regarding age, sex and BMI ($P = 0.778$, 0.850 and 0.513, respectively) (Table 1). Regarding the characteristics of patients, the mean PASI score of PsA and psoriasis pateints was 6.76 ± 3.11 and 5.60 ± 3.18, respectively, and showed no significant difference ($P = 0.198$). There was a statistically significant difference regarding nail involvement ($P = 0.024$), 64% of PsA patients showed nail dystrophy, whereas 32% of psoriasis patients had nail dystrophy. The mean levels of hs-CRP and ESR of PsA patients (4.62 ± 3.33 mg/l, and 30.24 ± 11.63 mm/h, respectively) were signifcantly higher than psoriasis group (2.52 ± 1.63 mg/l and 18.64 ± 4.37 mm/h, respectively). The mean DAPSA and CPDAI scores of PsA patients were 24.16 ± 13.60 and 8.80 ± 4.79, respectively. PsA disease activity was classified by DAPSA and CPDAS scores into low activity (32%), moderate activity (40%) and high activity (28%). According to PsA types, 52% of PsA patients had asymmetrical oligoarthritis, 40% showed polyarthritis and 8% had DIP joint (Table 1).

In regard to the biomarkers in the studied groups, plasma gelsolin levels were significantly decreased in PsA patients (mean: 129.34 ± 20.52 mg/l) compared to psoriasis patients and controls (mean; 173.24 ± 11.71 and 193.36 ± 12.86 mg/l, respectively). Whereas plasma MMP-3 levels were significantly increased in PsA patients (31.38 ± 10.93 pg/ml) in comparison to psoriasis patients and controls (12.36 ± 3.78 and 11.46 ± 3.28 pg/ml, respectively). Both gelsolin and MMP-3 showed a significant difference between PsA and psoriasis groups ($P < 0.001$) (Table 2).

ROC curve analysis was conducted to assess the diagnostic performance of plasma gelsolin and MMP-3 in detecting PsA and in discriminating between PsA and psoriasis. Regarding PsA detection; at a cut-off value ≤163.2 mg/l, gelsolin had

Table 1. Demographic data and patients' characteristics in the studied groups

Parameters	PsA patients	Psoriasis patients	Controls	*P* value
Age, years	47.92 ± 9.77	46.68 ± 10.09	45.80 ± 11.84	0.778
Sex, male/female	14/11 (56/44%)	15/10 (60/40%)	13/12 (52/48%)	0.850
BMI, kg/m^2	26.04 ± 2.54	25.52 ± 2.47	26.32 ± 2.41	0.513
PASI	6.76 ± 3.11	5.60 ± 3.18	–	0.198
Nail involvement	16 (64%)	8 (32%)	–	0.024*
hs-CRP, mg/l	4.62 ± 3.33	2.52 ±1.63	–	<0.001*
ESR, mm/h	30.24 ± 11.63	18.64 ± 4.37	–	<0.001*
Arthritis duration, years	6.92 ± 2.89	–	–	
DAPSA	24.16 ± 13.60	–	–	
CPDAI	8.80 ± 4.79	–	–	
PsA activity:				
Low	8 (32%)	–	–	
Moderate	10 (40%)	–	–	
High	7 (28%)	–	–	
PsA types:				
Asymmetrical oligoarthritis	13 (52%)	–	–	
Polyarthritis	10 (40%)	–	–	
DIP joint	2 (8%)	–	–	

Note. *P* value for comparing between the two studied groups. *Statistically significant at $P \leq 0.05$; $n = 25$, mean ± SD

96.0% sensitivity, 92.0% specificity, 92.3% positive predictive value (PPV), 95.8% negative predictive value (NPV) and area under curve (AUC) of 0.953 ($P < 0.001$). While, MMP-3, at a cut-off value >14.6 pg/ml, had 96.0% sensitivity, 80.0% specificity, 82.8% PPV, 95.2% NPV and AUC of 0.953 ($P < 0.001$). As for their combination, it had 96.0% sensitivity, 88.0% specificity, 88.9% PPV, 95.7% NPV and AUC of 0.968 ($P < 0.001$) (Table 3 and Fig. 1).

Regarding discriminating between PsA and psoriasis; gelsolin, at a cut off value ≤156.8 mg/l, showed 92% sensitivity, 88% specificity, 88.5% PPV, 91.7% NPV and AUC of 0.966 ($P < 0.001$). Moreover, MMP-3, at a cut-off value >14.6 pg/ml, showed 96% sensitivity, 80% specificity, 82.8% PPV, 95.2% NPV and AUC of 0.957 ($P < 0.001$). The integrated use of gelsolin and MMP-3 improved their validity, their combination had 96% sensitivity, 100% specificity, 100% PPV, 96.2% NPV and AUC of 0.998 ($P < 0.001$) (Table 4 and Fig. 2).

Regarding PsA activity, plasma gelsolin and MMP-3 showed significant differences ($P < 0.001$) between the different PsA patients' subgroups. Plasma gelsolin levels fell with increased PsA activity (low: 156.88 ± 4.45 mg/l, moderate: 120.97 ± 7.39 mg/l and high: 109.81 ± 2.65 mg/l) However, plasma MMP-3 levels increased with PsA activity (low: 18.09 ± 4.82 pg/ml, moderate: 33.12 ± 3.50 pg/ml and high: 44.09 ± 1.80 pg/ml) (Table 5).

In PsA patients, plasma gelsolin levels showed a significant negative correlation with the duration of arthritis ($P < 0.001$), PsA activity scores (DAP-

Table 2. Comparison between PsA and psoriasis according to plasma gelsolin and MMP-3

Parameters	PsA patients	Psoriasis patients	Controls	*P* value
Gelsolin, mg/l	129.34 ± 20.52	173.24 ± 11.71	193.36 ± 12.86	<0.001*
MMP-3, pg/ml	31.38 ± 10.93	12.36 ± 3.78	11.46 ± 3.28	<0.001*

Note. *Statistically significant at $P \leq 0.05$; $n = 25$, mean ± SD

Table 3. Diagnostic performance of plasma MMP-3, gelsolin and their combinations for detecting PsA

Parameters	AUC	*P* value	95% C.I	cut-off	Sensitivity	Specificity	PPV	NPV
MMP3, pg/ml	0.957	<0.001*	0.910–1.000	>14.6	96.0	80.0	82.8	95.2
Gelsolin, mg/l	0.953	<0.001*	0.886–1.000	≤163.2	96.0	92.0	92.3	95.8
Combination	0.968	<0.001*	0.927–1.000		96.0	88.0	88.9	95.7

Note. *Statistically significant at $P \leq 0.05$

Table 4. Diagnostic performance of plasma MMP-3, gelsolin and their combinations to discriminate PsA from psoriasis

Parameters	AUC	*P* value	95% C.I	cut-off	Sensitivity	Specificity	PPV	NPV
MMP3, pg/ml	0.957	<0.001*	0.909–1.000	>14.6	96.0	80.0	82.8	95.2
Gelsolin, mg/l	0.966	<0.001*	0.924–1.000	≤156.8	92.0	88.0	88.5	91.7
Combination	0.998	<0.001*	0.993–1.000		96.0	100.0	100.0	96.2

Note. *Statistically significant at $P \leq 0.05$

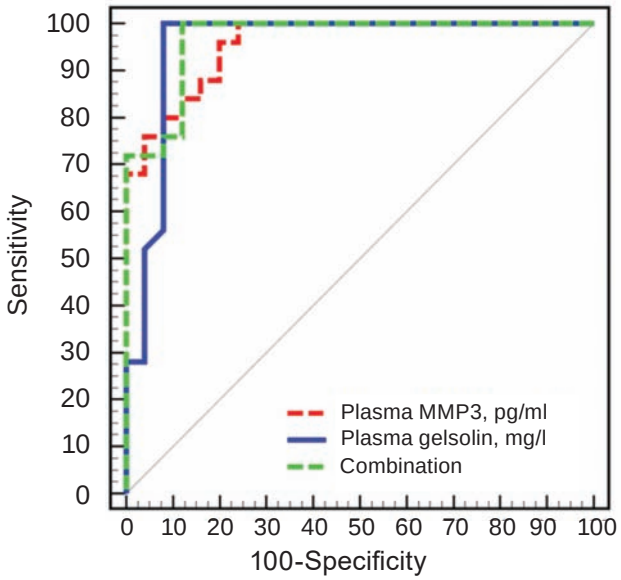

Fig. 1. ROC curve of plasma MMP-3, gelsolin and their combinations for detecting PsA

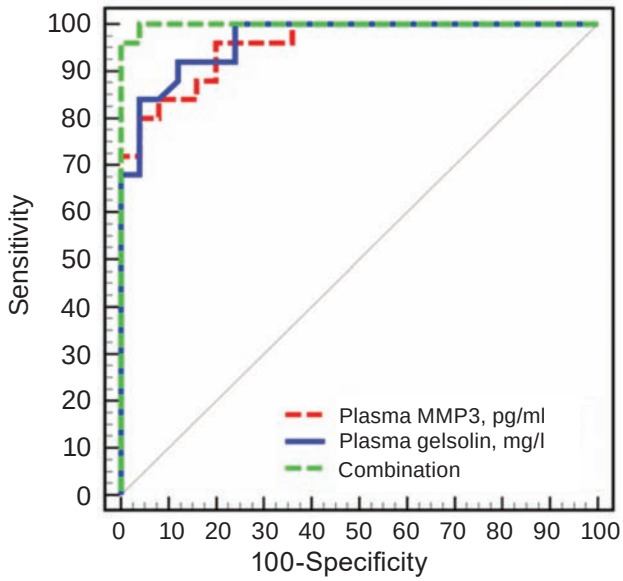

Fig. 2. ROC curve of plasma MMP-3, gelsolin and their combinations to discriminate PsA from psoriasis

Table 5. Relationship of plasma MMP-3 and gelsolin with disease activity in PsA patients group

PsA activity	Low, *n* = 8	Moderate, *n* = 10	High, *n* = 7	*P* value
MMP-3	18.09 ± 4.82	33.12 ± 3.50	44.09 ± 1.80	<0.001*
Gelsolin	156.88 ± 4.45	120.97 ± 7.39	109.81 ± 2.65	<0.001*

Note. *P* value for relation between disease activity with different markers. *Statistically significant at $P \leq 0.05$; mean ± SD

Table 6. Correlation between MMP-3, gelsolin and different parameters in PsA patients group

Parameters	Plasma MMP-3		Plasma gelsolin	
	r	*P* value	*r*	*P* value
BMI	0.147	0.484	-0.238	0.252
Arthritis duration	0.476	0.016*	-0.602	<0.001*
Nail involvement	-0.230	0.268	0.248	0.231
PASI	0.344	0.092	-0.300	0.146
DAPSA	0.918	<0.001*	-0.881	<0.001*
CPDAI	0.850	<0.001*	-0.868	<0.001*
ESR	0.566	0.003*	-0.595	0.002*
hs-CRP	0.827	<0.001*	-0.661	<0.001*
Gelsolin	-0.898	<0.001*		

Note. *r* – Pearson correlation coefficient. *Statistically significant at $P \leq 0.05$

SA, CPDAI) ($P < 0.001$), inflammatory markers (ESR, hs-CRP) ($P = 0.002$ and <0.001) and MMP-3 ($P < 0.001$). Whereas, plasma MMP-3 levels showed a significant positive correlation with arthritis duration ($P = 0.016$), DAPSA, CPDAI ($P < 0.001$), ESR ($P = 0.003$) and hs-CRP ($P < 0.001$) (Table 6).

Discussion

Patients with PsA have a higher inflammatory burden and poorer quality of life in comparison to psoriasis patients without PsA [27]. Soluble biomarkers could be effective tools for screening

patients with psoriasis for underlying PsA in order to start the appropriate treatment and prevent the eventual debilitation of PsA patients [8]. In the present study, we aimed to evaluate plasma gelsolin and MMP-3 as potential biomarkers for PsA, and to explore their correlation with PsA severity.

In the current study, the incidence of nail involvement was significantly elevated in PsA patients than in those with psoriasis alone. This was in agreement with previous studies that hypothesized that nails involvement and joints affection could have a similar mechanism and are closely related. It had been suggested that nail involvement might be a predictor for the development of PsA in psoriasis patients [28, 29].

Our results revealed no significant difference between PsA and psoriasis patients regarding psoriasis severity (PASI). Past studies reported that the extent and severity of skin lesions do not correlate well with the severity of joint disease [30, 31].

In the present study, inflammatory markers hs-CRP and ESR were significantly higher in PsA patients than in psoriasis. Like most inflammatory disorders, acute phase reactants such as CRP and ESR could be increased. However, they are elevated in only about 40% of patients, therefore, normal levels of CRP and ESR should not be used to rule out a diagnosis of PSA [32]. To date, there are no specific laboratory tests for PSA diagnosis [5].

Our study demonstrated that PsA patients had significantly decreased plasma gelsolin levels and significantly elevated plasma MMP-3 levels compared to psoriasis patients and controls.

Plasma gelsolin plays a significant role in inflammation. It can stimulate an anti-inflammatory response by binding to pro-inflammatory mediators, in addition, gelsolin improves the functions of macrophages by activating the nitric oxide synthase [33]. It was reported that when recombinant plasma gelsolin was administered to animal models, it suppressed the inflammatory reaction [34]. A past study hypothesized that the reduction of plasma gelsolin levels in rheumatoid arthritis patients might be explained by allocations of plasma gelsolin in the inflammation sites.Furthermore, it was proposed that gelsolin binding to macromolecules present in the inflamed joints leads to the consumption of plasma gelsolin [35].

In the current study, we confirmed the findings of Esawy et al.[36] who reported diminished plasma gelsolin levels in PsA patients compared to psoriasis patients and controls. Previous studies reported that plasma gelsolin levels were reduced in various disorders such as Alzheimer's disease [37], organ failure, rheumatoid arthritis, systemic lupus erythematosus [38]. So, our findings are in the same line with past studies confirming that plasma gelsolin levels are reduced in chronic inflammatory disorders.

As regards to MMP-3, our results showed significantly increased levels of plasma MMP-3 in PsA patients compared to psoriasis group and controls. This was in accordance with previous studies [39, 40]. MMP-3 is a protease which is involved in cartilage and bone destruction, as well as in remodeling of connective tissue. It breaks down collagen types II, III, IV, IX, X, fibronectin, elastin, proteoglycans and laminin [41]. It was reported that MMP-3 in synovial fluid is a marker of inflammation that correlates with inflammatory cytokines such as interleukins-6 and 17. In addition, increased levels of inflammatory cytokines induce the expression of the metalloproteinases including MMP-3, MMP-2 and MMP-9, which cause destruction in non-collagen matrix components of the joint [42, 43]. Consequently, plasma MMP-3 could serve as a marker of tissue destruction and joint inflammation.

Roc curve was used in the current study to assess the diagnostic performance of plasma gelsolin and MMP-3 for detecting PsA as well as differentiating between PsA and psoriasis. For detecting PsA, gelsolin and MMP-3 had sensitivity of 96% for each and specificity of 92% and 80%, respectively As for differentiating between PsA and psoriasis, gelsolin showed 92% sensitivity and 88% specificity, whereas MMP-3 showed 96.0% sensitivity and 80% specificity. The integration of gelsolin and MMP-3 markedly improved their validity in differentiating PsA from psoriasis, their combination showed 96.0% sensitivity and 100% specificity.

The present study demonstrated a significant association of plasma gelsolin and MMP-3 levels with PsA activity. Plasma gelsolin fell with increased PsA activity, while plasma MMP-3 levels increased with high PsA activity. Indeed, plasma gelsolin showed a significant inverse correlation with DAPSA, CPDAI (PsA activity scores), hs-CRP, ESR (inflammatory markers), and the duration of arthritis. On the other hand, plasma MMP-3 levels showed a significant positive correlation with DAPSA, CPDAI, hs-CRP, ESR and arthritis duration. Regarding psoriasis activity, plasma gelsolin and MMP-3 levels did not correlate with PASI scores

in PsA patients. These findings were in accordance with other studies [36, 39, 40, 44].

The present study also showed a significant inverse correlation between gelsolin and MMP-3. As a whole, our results revealed that low plasma gelsolin and high plasma MMP-3 levels were associated with PsA severity and the intensity inflammation, indicatinghat they could serve as inflammatory markers.

Conclusions. PsA patients had significantly lower plasma gelsolin levels and higher plasma MMP-3 levels compared to psoriasis without PsA patients and controls. Plasma levels of gelsolin and MMP-3 were also significantly associated with PsA severity. Therefore, plasma gelsolin and MMP-3 levels could serve as potential biomarkers for diagnosing of PsA as well as for monitoring the disease activity in PsA patients.

Limitation of the study. The small sample size is considered a limitation in the current study. So, future studies with larger sample sizes are recommended to corroborate the current experimental results.

Conflict of interest. The authors have completed the Unified Conflicts of Interest form at http://ukrbiochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

РІВНІ ПЛАЗМОВОГО ГЕЛСОЛІНУ ТА МАТРИКСНОЇ МЕТАЛОПРОТЕЇНАЗИ-3 ЯК ДІАГНОСТИЧНІ МАРКЕРИ ПСОРІАТИЧНОГО АРТРИТУ

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Дослідження останніх років виявили високу поширеність недіагностованого псоріатичного артриту (ПсА) серед пацієнтів хворих на псоріаз. Діагностувати псоріатичний артрит часто буває непросто, оскільки симптоми захворювання неспецифічні, ревматоїдний фактор не визначається, а рівень гострофазових реактантів може залишатися в нормі. Тому визначення розчинних біомаркерів у пацієнтів із псоріазом сприятиме ранній діагностиці та ефективному лікуванню цього захворювання. Метою роботи було оцінити рівні гелсоліну та матриксної металопротеїнази-3 (ММР-3) у плазмі крові як потенційних біомаркерів ПсА. Це дослідження «випадок-контроль» проводилося із залученням 25 здорових осіб та 50 осіб, хворих на псоріаз, серед яких було 25 пацієнтів із псоріазом та 25 пацієнтів із псоріатичним артритом. Рівні гелсоліну та ММР-3 вимірювали за допомогою ІФА. Показано, що пацієнти з ПсА мали значно нижчий рівень гелсоліну та значно вищий рівень ММР-3 у плазмі крові порівняно з пацієнтами, хворими лише на псоріаз. Під час діагностування ПсА, чутливість гелсоліну та ММП-3 становила 96%, а специфічність – 92 та 80%, відповідно. Рівень гелсоліну негативно, а рівень ММП-3 позитивно корелював із такими параметрами як активність захворювання при псоріатичному артриті, комплексний індекс активності псоріатичного захворювання та маркери запалення, зокрема високочутливий С-реактивний протеїн та швидкість седиментації еритроцитів. Зроблено висновок, що рівні гелсоліну та ММП-3 у плазмі крові можуть бути використані як потенційні маркери для діагностування ПсА та моніторингу прогресування захворювання у пацієнтів із псоріатичним артритом.

Ключові слова: гелсолін, ММП-3, псоріатичний артрит, псоріаз.

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