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Galectin-1 in Psoriatic arthritis, Psoriasis, Rheumatoid arthritis and its relation with disease activity and skin lesion

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Abstract

Immune mediated inflammatory diseases (IMIDs) are a diverse range of diseases that affect joints with early overlapping symptoms. Rheumatoid arthritis (RA) and psoriatic arthritis (PsA) are the most common disorders sharing immune-pathogenic mechanisms that cause peripheral arthritis. Psoriasis (Ps) is a chronic inflammatory autoimmune skin disease characterized by epidermal hyperplasia with significant invasion by inflammatory cells. New biomarkers are required to enable an early diagnosis and differentiation between different types of IMIDs. In autoimmune disorders, galectin 1 (Gal-1) is a recognized as negative immune system regulator. This study aimed to determine the possibility of using gal–1 as a diagnostic marker to differentiate between RA and PsA with polyarthritis pattern, and between PsA and Ps, and to assess its relationship with disease activity and with skin lesion. In this case-control study included 40 PsA patients with polyarthritis pattern, 40 psoriatic patients, 40 RA patients and 20 normal controls. Gal-1 levels were measured in serum and skin biopsy and disease Activity Score (DAS-ESR) was assessed. Serum gal-1 level was significantly higher in RA group in comparison to PsA, psoriatic and control. In addition, compared to the normal group, psoriatic skin lesions from PsA and Ps patients had lower levels of gal-1. Serum gal-1 levels in the RA group did not correlate with other factors such as age, disease duration, deformity, extra-articular symptoms, or DAS-ESR. Furthermore, there was no correlation between the skin's level of gal-1 and psoriatic area and severity index (PASI) score, body surface area (BSA). In conclusion, serum Gal-1 concentration may serve as a diagnostic biomarker to distinguish between RA and PsA. However, it cannot assess activity or severity of RA, and cannot differentiate psoriatic lesion either from only Ps or PsA.

Keywords: Gal-1, IMIDs, PsA, Ps, RA.

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Introduction

Immune mediated inflammatory diseases (IMIDs) are a diverse range of disorders which include rheumatoid arthritis (RA), psoriatic arthritis (PsA) and psoriasis, ankylosing arthritis and connective tissue diseases. IMIDs share pathogenic mechanisms in innate and adaptive immunity that cause peripheral arthritis.[1] RA is the most prevalent chronic autoimmune disease that primary affects small joints of hand leading to bone, cartilage, and articular deformities.[2] Many cytokines and effector cells infiltrate the synovial membrane leading to synovitis which is the hallmark of RA.[3]. PsA is the second most common autoimmune disease. It is a seronegative chronic heterogenous disease which is recognized as one of the spondyloarthritis family known for its diversity in presentation, expression, and clinical course with wide diverse articular and dermatological features.[4] It is characterized by abundant overexpression of pro-inflammatory cytokines.[5] Psoriasis (Ps) is a chronic inflammatory autoimmune skin disease characterized by epidermal hyperplasia with intense invasion by inflammatory cells.[6] Hyperactive keratinocytes and inflammatory cells, secrete several cytokines that plays role in pathogenesis.[7] Although these diseases have common early manifestations with superficial similarity, but they have significant differences at many levels, leading to different outcomes and different responses to therapies due to their different pathogenesis.[1]

Galectins are a family of lectins that play a main role in regulation of immune system through various effects in both physiological and pathological processes.[8] They have become one of the leading immune system homeostasis controllers, amplifying or suppressing inflammatory processes, respectively.[9,10] They are soluble lectins defined by their affinity toward galactose-β1-4-*N*-acetylglucosamine (*N*-acetyl-lactosamine, LacNAc)-enriched glycoconjugates found on the cell surface or extracellular matrix. Currently, 15 galectins have been identified in vertebrates. Even though some galectins (such as Gal-1 and Gal-3) show wide tissue localization, other galectins display a more confined pattern of distribution.[10] Many members of the galectin family exhibit pro-inflammatory activity, promoting innate and adaptive immunity, though other galectins induce anti-inflammatory responses and behave as pro-resolving mediators.[11] They can act both in physiological and pathological conditions, they play important role in a variety of pathologic disorders, as inflammation, autoimmune diseases, and tumor cell metastasis.[12-16] Any altered pattern of expression will be associated with inflammation and progression of diseases. Many diseases are associated with decreased gal-1[17-21] and increased gal-3 expression.[12-16, 22-26] Moreover, the functional consequence of galectin signaling may vary significantly, depending on the specific type of galectin involved, the quantity and branching of particular glycans functioning as possible ligand and the molecular nature of these multivalent interactions.[8] In this regard, inflammation evokes changes in the glycosylation signature of both immune and inflamed tissue, leading to either masking or unmasking of galectin-specific glycoepitopes.[8,12] Hence, a proper understanding of the exaggerated immune response seen in many diseases is based mainly on up-regulated pro-inflammatory molecules and its effects on many cells. In physiological conditions, gal-1 adversely restrict the immune response in a variety of ways as, supporting apoptosis of Th-1 cells, inducing IL-10, or down-regulation of pro-inflammatory cytokines. However, the main driving force that shapes the net result is, the bi-directional effect and unidirectional effect of gal-1 on different cytokines and different cells.[12] Gal-1 can down regulates the level of IL-17 and IL-23 leading to increase the profile of RA, however, in PsA there is exacerbation of Th1/Th17 effector cells, and up regulation of IL-17 and IL-23 leading to direct depression of gal-1.[1] The aim of our study was to determine the possibility of using gal-1 as a diagnostic marker to discriminate between RA and PsA with polyarthritis pattern, and between PsA and Ps, and to assess its relationship with disease activity and with skin lesion.

Subjects and Methods

Study subjects and Design

In this case-control study, a total of 120 patients and 20 normal controls were recruited. The patient group included 40 RA patients fulfilling the 2010 American College of Rheumatology and European League Against Rheumatism (ACR/EULAR) classification criteria for RA,[27] 40 PsA patients diagnosed according to CASPAR (Classification criteria for Psoriatic Arthritis) criteria (28) and presented with polyarticular pattern of peripheral arthritis, and 40 patients with Ps. Psoriatic plaques are erythematous, scaly, well-demarcated plaques, covered by silvery white scaling in the most commonly affected areas as the extensor surfaces of elbows and knees, the sacral region, and the scalp.[29, 30] Study subjects were recruited from outpatients' clinics of Ain Shams University Hospitals. The study was carried out at the Ain Shams University Hospitals' Physical Medicine, Rheumatology and Rehabilitation, and Dermatological Outpatient Clinics. Patients with other rheumatologic diseases, history of malignancy, active infections, uncontrolled medical illness, and adults less than 18 years old were excluded.

Study methods

All patients were subjected to: 1-Careful history taking, general, musculoskeletal and dermatological examination, 2-Assessment of RA disease activity by using the modified disease activity score (DAS-28) which include the following parameters: number of tender joints, number of swollen joints, erythrocyte sedimentation rate (ESR) 1st hour and patient global assessment on visual analogue scale (VAS), 3-Assessment of body surface area (BSA) of the psoriatic skin lesion in PsA and Ps groups, 4-Psoriasis area and severity index (PASI) score in PsA and Ps groups which is an index used to determine the severity of psoriasis. It combines the severity (erythema, induration, and desquamation) and the percentage of affected areas. 5-A blood sample (5 ml) was collected from each study participant to estimate a-complete blood picture using an automated blood cell counter (Beckman Coulter Diagnostics, 900 Seventh Street, Washington, U.S.), b- screening tests for diagnosis and activity of RA disease which included; ESR levels using the Westergren methods and C-reactive protein (CRP) titer using latex agglutination methods (Sigma-Aldrich, Merck Darmstadt, Germany), c-rheumatoid factor (RF) using latex agglutination methods (Sigma-Aldrich, Merck Darmstadt, Germany), d-fasting blood sugar and 2-hours post prandial blood sugar, serum uric acid, liver and kidney function tests using an automated blood chemistry analyzer (Beckman Synchron CX5 Clinical Analyzer, 900 Seventh Street, Washington, U.S.). 6- A 5 mm punch biopsy was taken under local anesthesia from the normal control subjects and from the most recent non-exposed lesions of psoriatic skin in patients with Ps and PsA. Topical treatment of the psoriasis was stopped for at least one week before the biopsy was taken while systemic treatment was stopped for two weeks. Skin homogenization was done by pulverization and grinding method to all skin frozen samples. We used a tissue pulverizer followed by mortar and pestle to crush the frozen tissues into a powder-like form. Extensive washing after each sample to prevent carryover and cross-contamination. Powdered skin tissue was resuspended in solution and finally samples were centrifuged, and the supernatant collected. The supernatant was used for gal-1 analysis by commercially available ELISA kit. 7- Gal-1 levels in the serum and supernatant samples were determined through a commercially available ELISA kit (Bioassay Technology Laboratory, BT LAB-419 Shanghai, Korain, Biotech Co., Ltd, China), according to the manufacturer's instructions.

Statistical analysis

The 28th version of IBM Corp.'s SPSS program, published in 2021, was used to examine the data that had been gathered. Quantitative parametric variables were defined using standard deviations and means, whilst categorical variables were represented using absolute frequencies and compared using the chi-square test. Numbers and percentages were used to represent the qualitative characteristics. The Chi-square test was utilized to compare groups using qualitative data. Quantitative data

from two groups were compared using the Student T test. Although the Mann-Whitney test was used to compare two groups with quantitative data and a non-parametric distribution, the Kruskall-Wallis test was used to compare more than two groups with quantitative data and a non-parametric distribution. The correlation between two numerical parameters within the same group was evaluated using Spearman correlation coefficients. Gal-1's sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were assessed using the receiver operating characteristic (ROC) curve. It was deemed significant if p 0.05.

Results

This research involved 40 RA patients, 40 PsA patients presented with polyarticular pattern of peripheral arthritis, 40 patients with Ps and 20 healthy controls. Demographic, clinical and laboratory characteristics of patients and control group are described in Table 1.

Table 1. Demographic, clinical and laboratory characteristics of RA, PsA, Ps patients and the control group.

		RA group (n=40)		PsA group (n=40)		Ps group (n=40)		Control group (n=20)	
Age (years)		42.65±12.90		44.85±12.98		41.53±14.38		43.05±12.61	
Disease Duration (years)		7.9±3.1		7.8±2.88		5.8±2.68		-	
		No.	%	No.	%	No.	%	No.	%
Deformity		6	15	8	20	-	-	-	-
Extra-articular manifestations		28	70	24	60	-	-	-	-
Swollen joints		20	50	24	60	-	-	-	-
Tender joints		24	60	20	50	-	-	-	-
BSA of Psoriatic skin lesion	<3%	-	-	23	57.5	8	20	-	-
	3-10%			16	40	29	72.5		
	>10%			1	2.5	3	7.5		
PASI of Psoriatic skin lesion	<5%	-	-	26	65	12	30	-	-
	5-10%			13	32.5	25	62.5		
	>10%			1	2.5	3	7.5		
ESR (mm/h)		51.9±21.6		55.6±23.66		31.5±15.4		9.5±1.15	
DAS-ESR		5.09±1.54		2.74±0.91		-		-	

RA: Rheumatoid arthritis, PsA: Psoriatic arthritis, BSA: Body surface area, PASI: Psoriasis area and severity index, ESR: Erythrocyte sedimentation rate, DAS: Disease Activity score, SD: Standard Deviation, No: number, %: percentage.

Our data showed that serum level of gal-1 in RA patients ranged from 20 to 56 ng/ml. In the PsA group it ranged from 5 to 14 ng/ml, in the Ps group from 5.5 to 12 ng/ml, while within the control group it ranged from 3 to 11 ng/ml. In comparison to the PsA, Ps, and control groups, the RA cases group's serum gal-1 level showed a statistically significantly increase (Figure 1 and Table 2).

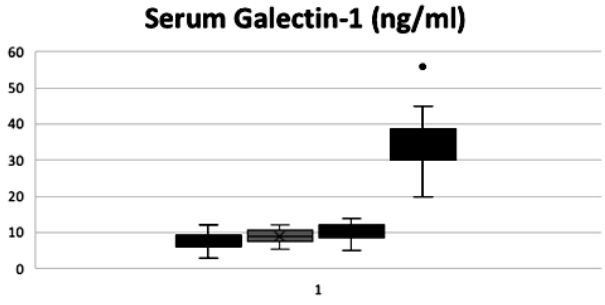

Figure 1. Comparison between control group, Ps group, PsA group and RA group regarding serum gal-1 level (ng/ml).

Table 2. Comparison between serum gal-1 levels in RA, PsA, Ps and control groups.

Serum Galectin-1 (ng/ml)	RA Group No.= 40	PsA Group No.= 40	Ps Group No.= 40	Control Group No. = 20	*p* value
Range	20-56	5-14	5 to 12	3-11	<0.0001
Mean ±- SD	34.8 ±- 3.2	10.5 ±-2.9	8.45±2.62	9.1 ±- 1.89	

p-value < 0.05: Significant.

As demonstrated in Table 3 and Figure 2, the Receiver operating characteristic curve (ROC) curve indicated that the optimal cut off point between the control group and the RA group for serum gal-1 level was > 15 ng/ml with 100% sensitivity, 95% specificity, and 99.9% area under the curve (AUC).

Table 3. The area under the ROC curve (AUC) for serum galectin-1 level in RA Cases.

Cut off point	AUC	Sensitivity	Specificity	PPV	NPV
>15ng/mL	0.999	100.00	95.00	95.2	100

AUC=area under curve, PPV=positive predictive value, NPV=negative predictive values.

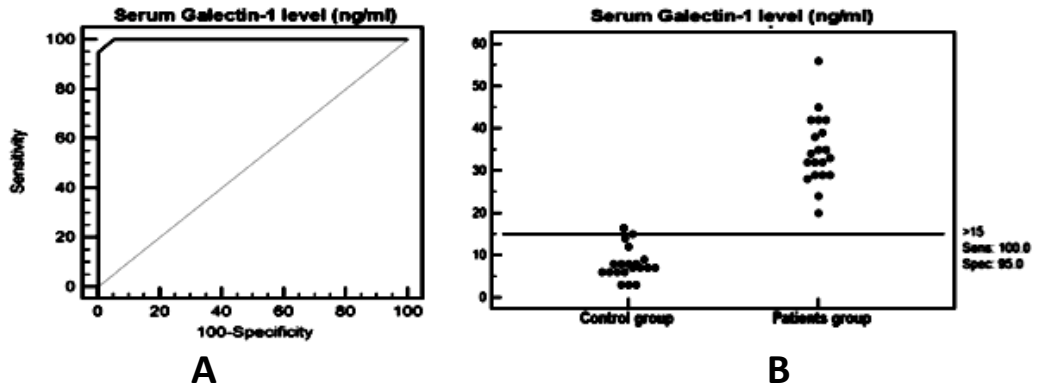

Figure 2. (A) ROC curve for serum gal-1 levels; (B) comparison between serum gal-1 levels in patients and control groups.

To determine whether gal-1 serum levels could be used as a biomarker of severity in RA, we studied their correlation with disease duration, deformity, extra-articular manifestations, and activity assessed by DAS-ESR. We found that there was no significant correlation between serum gal-1 level and studied disease parameters (Table 4).

Table 4. Correlation between serum ga-1 level and each of age, disease duration, deformity, extra-articular manifestations and DASESR in RA group.

	r	*p* value
Age (years)	-0.064	NS
Disease Duration (years)	-0.139	NS
Deformity	-1.119	NS•
Extra- articular manifestations	-0.043	NS•
DAS-ESR	1.262	NS≠

ESR: Erythrocyte sedimentation rate, DAS: Disease Activity score, *P* > 0.05 is not significant (NS);
•: Mann-Whitney test, ≠: Kruskal-Wallis test.

We measured the level of gal-1 in skin biopsy from psoriatic skin sample in patients with Ps and PsA as well as from normal control persons. Our results found that the level of gal-1 in the skin biopsies from psoriatic skin (either from PsA or Ps patients) is lower than that in the

normal controls but this difference did not reach statistical significance (Table 5 and Figure 3). In addition, we found that there was no correlation between the level of gal-1 in skin and BSA or PASI index (Table 6).

Table 5. Comparison between Ps, PsA and control groups as regards skin level of gal-1.

Skin level of Gal-1 (ng/ml)	Ps Group	PsA Group	Control Group	*p*- value
	No.= 40	No.= 40	No. = 20	
Range	2 - 5	2 - 4	5 - 9	NS
Mean ± SD	3.1±0.2	3.5±0.3	7.4±1.2	

P > 0.05 is not significant (NS).

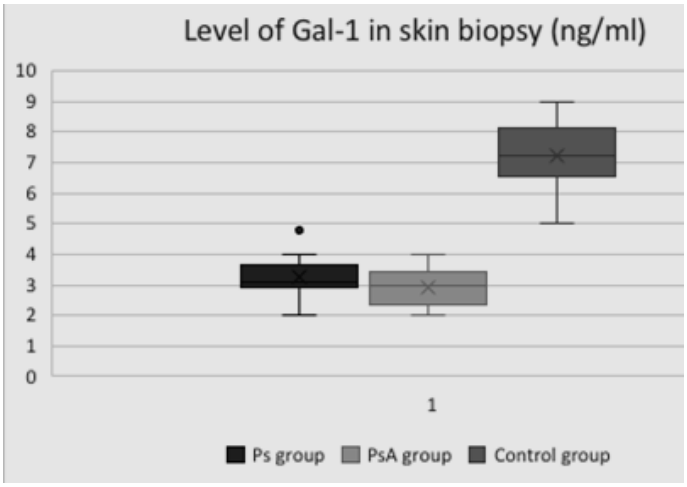

Figure 3. Comparison between control group, Ps group and PsA group regarding level of skin gal-1 (ng/ml).

Table 6. Correlation between each of BSA and PASI and skin level of ga-1 in Ps and PsA group.

Skin level of gal-1 (ng/dl) in	Ps group		PsA group	
	r	*p* value	r	*p* value
BSA (%)	-0.688	NS	-0.656	NS
PASI index	-0.192	NS	-0.243	NS

P > 0.05 is not significant (NS).

Discussion

Inflammatory immune reaction is found in RA and PsA diseases but more evident in RA than PsA. However, the systemic immune response is less marked in PsA which is not associated with elevation of inflammatory markers along with the absence of any specific autoantibodies which means that although PsA has autoinflammatory nature it is still lacking any evidence of autoimmune reactivity. Using new laboratory markers as gal-1, if proved useful, can be used in distinguishing between these two diseases aiming to decide the correct therapy for each of them[1, 31,32] Therefore, this study aimed to determine the possibility of using gal-1 as a diagnostic marker to discriminate between RA and PsA with polyarthritis pattern, and between PsA and Ps, and to assess its relationship with disease activity and with skin lesion.

The relation between age and sex in RA and gal-1 had been studied by many authors, as Triguero-Martínez, et al., 2022[1] who could not find a difference between patients and control group which agreed with our study finding. In contrast to Xibille-Friedmann et al., 2021[22] results which showed statistical difference between cases and control groups as regards age and sex. Triguero-Martínez et al., 2022 reported that increasing level of gal-1 with age was one of its limitations as a diagnostic

biomarker. However, many authors as Martínez et al., 2020 reported that gal-1 can prevent age-dependent autoimmunity indicating its important role in mediating tolerance.[1,33] In our study, we found a significant difference as regards serum gal- 1 levels in RA group in comparison to PsA group and the control group. This agreed with Triguero-Martínez et al., 2022,[1] Mendez-Huergo et al., 2019[9] and Vilar et al., 2019,[34] as they reported that gal-1 level in RA patients was significantly increase compared to controls and PsA. All previous studies recorded that increased gal-1 level is an indication of its important role in RA pathogenesis. But this finding was contradicted with findings of a study by Xibille–Friedmann et al., 2012[22] who measured serum gal-1 level in RA cases and compared it with controls and did not find any difference in serum gal-1 level between RA cases and controls. Also, we did not find any statistical correlation as regards serum gal-1 level in RA group and each of disease duration, presence of deformities and extra-articular manifestations, this agreed with findings of Mendez-Huergo et al., 2019[9] and Triguero-Martínez et al., 2022.[1]

There was no statistical correlation as regards serum gal-1 and ESR level which was not in agreement with Mendez-Huergo et al., 2019[9] who found a strong positive correlation between gal-1 serum levels and ESR. Concerning serum gal-1 level and DAS, there was no correlation between them which agreed with Mendez-Huergo et al., 2019[9] and Triguero-Martinez et al., 2022,[1] they could not find any association between gal-1 serum levels and activity in RA cases. While Salamanna et al., 2019[35] reported a positive correlation between DAS and gal-1 levels. However, gal-1 was still elevated without any significant fluctuations throughout the follow-up and not affected by treatment. There is great controversy regarding fluctuation of its level with activity and treatment, as Vilar et al., 2019[34] stated that high levels of gal-1 are associated with moderate and high disease activity and low levels were seen in remission or low activity.

We found that gal-1 concentration above 15ng/ml was the best cut off to discriminate between RA and other groups with 100% sensitivity and 95% specificity, as the control and PsA groups had nearly the same results. Other two different cut off levels were set-up by Triguero-Martínez et al., 2022[1] and Mendez-Huergo et al., 2019[9] (above 19.12 ng/ml with 71% sensitivity and 79% specificity and above 17.95 ng/ml with 72% sensitivity and 72.73% specificity, respectively). Different ELISA kits is the cause of difference between the cut-off points between our study and others.

Although both RA and PsA are inflammatory autoimmune diseases, gal-1 level decreased in PsA in contrast to RA. Many authors such as Ilarregui et al., 2009, Cedeno-Laurent et al., 2010, Kuo et al., 2011, Camby et al., 2006 and Santucci et al., 2000, could explain this difference according to the nature of each disease and type of cytokines secreted in them. PsA was known as a sero-negative autoinflammatory disease. Few markers may be positive in 5% of PsA patients only and other markers are negative, this was noted regarding gal-1 in our study which was very low even reached the same level as the control group. Also, discrepancy between RA and PsA according to the type of cytokines released in both diseases which affect many cells and pathways. It has been reported that TH17 cytokines (IL-17, IL-23 and interferon-γ) are elevated in PsA. While TH1 cytokines (IL-1, IL-6, IL-22, IL-33, TNF-α) are elevated in RA.[36-40]

Finally, we studied the level of gal-1 in psoriatic skin either from Ps or PsA patients compared to normal controls. There was a decrease in the level of gal-1 in psoriatic skin compared to normal control although it did not reach statistical significance. The same was found by many authors as de la Fuente et al., 2012, Chen et al., 2012, Pasmatzi et al., 2019 and Corrêa et al., 2022.[42-45] They found a decrease of gal-1 level in both lesioned and non-lesioned skin samples from psoriatic patients. Contrary to normal epidermis, the psoriatic epithelium expressed no gal-1 and no glycoligands for gal-1. A study by Corrêa et al., 2022 suggested that gal-1 downregulation is the leading cause of exacerbation of the inflammatory responses in psoriatic skin.[45] As any decrease in gal-1 level can lead to increase in the level of INF-γ and decrease of IL-10. The

inflammatory changes started with activation of antigen-presenting Langerhans cells leading to T-cell stimulation and finally cytokines release. Pro-inflammatory cytokines will lead to hyperproliferation of keratinocytes and dermal vascular expansion which is the major histopathological changes of psoriatic lesions. Also, Pasmatzi et al., 2019 reported that gal-1 has an important role in the pathogenesis of the disease as they reported that the addition of exogenous gal-1 can attenuates Th-1 response, which lead to increase secretion of IL-10 from dendritic cells which can be used in treatment of the disease.[44]

Even in RA, gal-1 has many limitations, concerning its low level in synovial fluids compared to serum, also has never been present at sites of invasion, its level not affected by activity or even therapy reflecting its role in pathogenesis but not in activity as gal-3. As we analyzed three separate PsA subpopulations, sample size and demographic heterogeneity were taken into consideration. However, level of gal-1 was similar in them. Also increasing level of gal-1 with age highlight the importance of setting different cut-offs depending on each age group. In addition, gal-1 level must be studied in other connective tissue disease as Sjögren syndrome, systemic sclerosis, and systemic lupus erythematosus. Also, we need to study correlation between gal-1 and other diagnostic markers used in diagnosis of IMIDs, and the value to combine different panel of galectins as gal-1 and gal-3 in the diagnosis and follow up.

In conclusion, our data indicated that serum levels of gal-1 could be used as diagnostic biomarker to differentiate between RA and PsA. However, it cannot assess activity or severity of RA. Also, it cannot differentiate psoriatic lesion either from Ps or PsA.

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Author Contributions

MM; designed the protocol, coordinated with the Ethical committee to get Ethical approval. DM, MA SA, and AS; performed the laboratory investigation, prepared the skin biopsy, underwent the quantitative assessment of serum Galactin-1 levels, as well as data entry, and data analysis. DM and SA; were the primary authors for this article. MM and NN; was contributor in patients' recruitment and clinical examination and assessment, collected and analyzed data, and underwent data tabulation and statistical analysis, and interpreted the patient's data. AS; performed skin biopsy, shared in editing and revision. The final manuscript was read and approved by all writers.

Declaration of Conflicting Interests

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Ethical approval

The Research Ethics Committee, Faculty of Medicine, Ain Shams University reviewed and approved the study protocol (FMASU R 106/2022).

Informed consent

Each subject who participated in the study provided written, informed consent.

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