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The Role of Chitinase-3-Like Protein 1(YKL-40) as A Biomarker of Psoriatic Arthritis

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ABSTRACT

Background: Psoriatic arthritis (PsA) is a chronic multifaceted seronegative arthritis of inflammatory origin. Plasma YKL-40 is an inflammatory biomarker.

Objective: To evaluate the role of Chitinase-3-like protein 1 (YKL-40) as a diagnostic biomarker in psoriatic arthritis (PsA) patients and determine its value in assessment of psoriatic arthritis activity and severity.

Patients and Methods: Our study included 25 adult patients with evidence of PsA and twenty-five healthy matching controls. All underwent history, laboratory investigation, clinical examination, assessment of activity and severity according to different scores.

Results: We observed the presence of a high statistically significant difference between the patients and controls in terms of the blood levels of YKL-40 with a high sensitivity and specificity for diagnosing PsA. Both the PASI score and the DAPSA score had statistically significant positive associations with the YKL- 40 levels serum levels.

Conclusion: YKL-40 measurement may act as a biomarker for diagnosis of PsA, as it has the potential to contribute to the fundamental processes underlying the pathogenesis of PsA. So, we concluded that the addition of YKL-40 as a serological marker has a valuable role in diagnosis and severity assessment of PsA.

Keywords: Psoriatic arthritis, YKL-40, disease activity.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic, autoimmune, inflammatory disease that is manifested by arthropathy of peripheral joints with axial skeleton and also entheseal affection. It is also strongly linked to a significant rate of mortality caused by cardiac related diseases [1].

The definite diagnosis of psoriatic arthritis may not always be evident due to the lacking of particular laboratory tests that can confirm the condition. The existence of arthritic symptoms, which may coexist with psoriatic skin lesions, as well as the increase of non-specific markers of inflammation, and the results of imaging studies, which may not be conclusive in the beginning of the disease development, are all the main factors used to confirm the diagnosis. This might cause a delay in the diagnosis of the disease causing more affection of the joints and unfavorable treatment outcome. This makes it necessary to look for novel biological biomarkers that might help to diagnose psoriatic arthritis early or could be beneficial for following up the condition and detecting responds to different treatment regimen the patients receive [2].

One of the 18 glycosyl hydrolase proteins is the YKL-40, one of the mammalian Chitinase family. Several crucial biological processes, including tissue remodeling, angiogenesis, proliferation, and inflammation are shown to depend on this protein [3]. Chondrocytes, synovial cells, as well as endothelial cells, active macrophages, and neutrophils, all are known to be a source of YKL-40 protein [4].

Our research aimed to evaluate the role of YKL-40 as a diagnostic biomarker in PsA patients and determine its value in assessment of psoriatic arthritis activity and severity.

PATIENTS AND METHODS

Our study included twenty-five psoriatic arthritis patients and twenty-five healthy controls from Ain Shams University Hospitals Outpatient Clinics.

Inclusion Criteria: every patient with psoriatic arthritis who met the CASPAR diagnostic criteria for the condition [5].

Exclusion criteria: Patients with other rheumatological diseases, liver diseases, previous history of malignant disease, diabetes mellitus, severe uncontrolled medical illness, chronic obstructive pulmonary disease and pregnancy.

The following were done to the patients:

1. **Full medical history taking:** including history of joint pain and swelling, disease duration, age at onset, treatments received, family history of psoriatic arthritis or other rheumatological disorders.

2. **Thorough clinical examination:** general and local examinations with special concern about skin, nail, hair, enthesitis, dactylitis, mucous membranes, peripheral and axial joint examination.
   - Skin examination to assess the extent and severity of psoriatic skin lesions using Psoriasis Activity and Severity Index (PASI) [6].
   - Nail examination to assess the disease severity using Nail Psoriasis Severity Index (NAPSI) [7].

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- Axial assessment: using Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [8].
- Enthesis examination using Leeds Enthesitis Index (LEI) [8].
- Examination of dactylitis that may be acute or chronic [9].

3. Assessment of disease activity using Disease Activity in Psoriatic Arthritis (DAPSA) Score:

DAPSA Score: As remission: ≤ 4, 4 < low activity ≤ 14, 14 < moderate activity (MDA) ≤ 28, and high activity > 28 [10].

4. Laboratory investigations:

All patients were subjected to: Complete blood count (CBC), Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP), Fasting blood sugar (FBS), Rheumatoid factor (RF), Liver function tests (SGPT, Albumin, Bilirubin).

5. Chest X-ray.

6. Specific tests: Quantitative measurement of serum YKL-40 level:

Venous blood samples were taken from the antecubital vein for the assessment of serum YKL-40, and the sera were separated and stored at -70°C until analysis. Enzyme-linked immunosorbent assay (ELISA) was used for the measurements.

Ethical approval:

This experiment was ethically approved by the Ain Shams University's. After being fully informed, all participants provided written consent. The study was conducted out in line with the Helsinki Declaration.

Statistical analyses

Using the SPSS, application on a personal computer, all data were gathered, tabulated, and statistically evaluated as follows: Quantitative variables were described using the terms mean, standard deviation (SD), range, median, and interquartile range (IQR). Qualitative variables were described as a number (no.) and a percentage (%). The discovery of correlation between two quantitative variables in one group was done using the linear correlation coefficient (r). P value less than 0.05 was regarded as significant.

RESULTS

Demographic data

Table 1 shows the demographic data of both the studied groups. For age, sex, and BMI, there was a statistically insignificant difference between the two groups (Table 1).

Table (1): Age, sex and BMI of patients and control

		Control group	Patients	T-value	P-value	Sig.
		No. = 25	No. = 25			
Age	Mean ± SD	42.88 ± 12.11	39.72 ± 11.94	0.929•	0.357	NS
	Range	18 – 68	16 – 71			
Sex	Female	18 (72.0%)	18 (72.0%)	0.000*	1.000	NS
	Male	7 (28.0%)	7 (28.0%)			
BMI	Mean ± SD	27.47 ± 5.30	29.71 ± 5.52	-1.463•	0.150	NS
	Range	19.15 – 43	20.5 – 44.9			

*: Chi-square test; •: Independent t-test

Clinical data:

The median (IQR) of PSAI score to assess the severity of skin affection was 7.2 (3.4 – 12.6), of NAPSI score to assess the extent of nail affection was 14 (7 – 19), of LEI score to assess enthesitis was 2 (0 – 4), of BASDAI score to assess the severity of axial joints was 4.2 (3.9 – 5.6), and of DAPSA score to assess the disease activity of PsA was 65.1 (35 – 81.6) (Table 2).

Table (2): Clinical indices among cases

	Cases	
	Median (IQR)	Range
PASI score	7.2 (3.4 – 12.6)	1.2 – 26.7
NAPSI score	14 (7 – 19)	0 - 32
LEI score	2 (0 – 4)	0 – 6
BASDAI score	4.2 (3.9 – 5.6)	3.2 – 6.8
DAPSA score	65.1 (35 – 81.6)	19.8 - 158

Comparison studies:

There was high statistically significant difference between the patient and control groups' blood levels of YKL-40 (Table 3).

Table (3): Comparison between the patients and control groups regarding YKL 40 marker

YKL- 40	Control group	Patients group	Test value‡	P-value	Sig.
	No. = 25	No. = 25			
Median (IQR)	20 (15 – 30)	100 (85 – 135)	-5.949	<0.001	HS
Range	10 – 50	35 – 375			

Median, (IQR): non parametric test

‡: Mann Whitney test, HS: Highly significant

ROC curve of YKL-40 as a predictor between patients and control:

The ROC curve showed that the sensitivity and the specificity of YKL- 40 in diagnosis of PsA were 96% and 92% respectively (Table 4 and Figure 1).

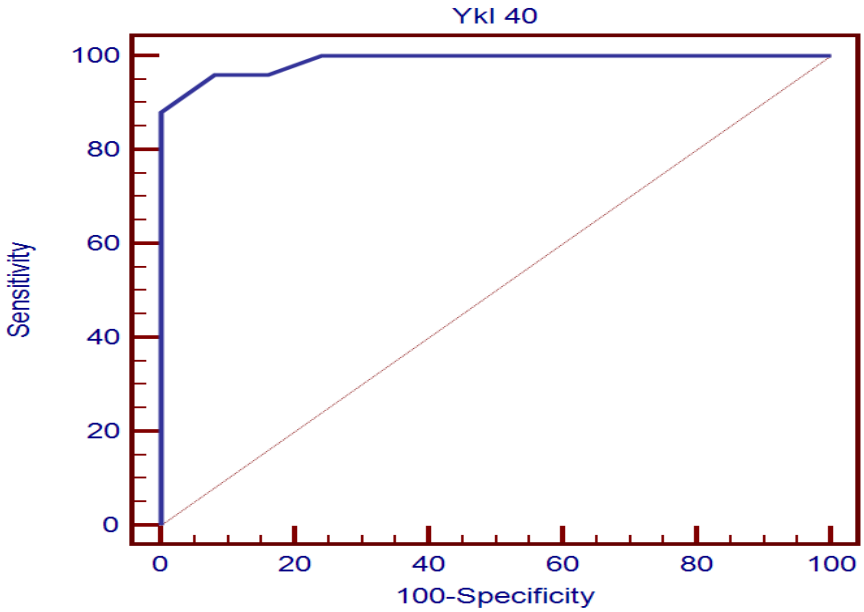

Figure (1): Receiver operating characteristic curve (ROC) for YKL-40 marker as a diagnostic marker for PsA

Table (4): ROC curve of YKL-40 marker as a predictor for patients with PsA

	AUC	Cut off Point	Sensitivity	Specificity	PPV	NPV
YKL- 40	**0.989**	**>40**	**96.0**	**92.0**	**92.3**	**95.8**

Correlation studies:

There were statistically significant positive correlations between YKL-40 (µl/mL) and each of tender joint's count and swollen joint count. Also, there were statistically significant positive correlations between YKL-40 levels (µl/mL) and each of PASI score and DAPSA score (Table 5).

Table (5): Correlations between YKL-40 marker (µl/mL) and each of BMI, psoriasis, PsA duration, tender joints count, swollen joints count and severity scales among the patients.

	YKL- 40	
	r	P-value
BMI	0.095	0.651
Duration of psoriasis	-0.040	0.848
Duration of psoriatic arthritis	-0.051	0.807
Tender joints	**0.459**	**0.021**
Swollen joints	**0.523**	**0.015**
PASI score	**0.539**	**0.005**
DAPSA	**0.526**	**0.007**
NAPSI	0.153	0.466
LEI	-0.024	0.910
BASDAI score	0.065	0.756

Metacarpophalangeal (MCP) and distal interphalangeal (DIP) joint discomfort were statistically significantly positively correlated with YKL- 40 levels (µl /mL). YKL- 40 levels (µl /mL) and the frequency of temporomandibular, sternoclavicular, acromioclavicular, glenohumeral, elbow, wrist, proximal interphalangeal (PIP), hip, knee, and ankle joint affection were not statistically significantly correlated (Table 6).

Table (6): Correlations between YKL- 40 levels (µl/mL) and frequencies of joints affection among the patients

Frequency of joints affection	YKL 40	
	r	P-value
Temporomandibular	0.227	0.275
Sternoclavicular	-0.128	0.543
Acromioclavicular	0.286	0.166
Glenohumeral	0.200	0.338
Elbow	-0.327	0.110
Wrist	-0.237	0.253
MCP	**0.405**	**0.045**
PIP	0.390	0.054
DIP	**0.468**	**0.018**
Hip	-0.340	0.096
Knee	-0.017	0.936
Ankle	-0.112	0.594

DISCUSSION

The immune-mediated inflammatory disease, psoriatic arthritis (PsA), is characterized by causing axial and peripheral arthritis, enthesitis, dactylitis, skin psoriasis and nail involvement, as well as a number of

extra-articular manifestations, including anterior uveitis and inflammatory bowel disease [11]. Owing to the variety of clinical characteristics, evaluating PsA patients may be difficult [12]. The absence of well validated serum autoantibodies or other PsA-specific biomarkers has made screening and early diagnosis challenging, if not impossible, unlike many other rheumatological conditions, such as rheumatoid arthritis (RA). The absence of a biomarker has been identified as an unmet need in psoriatic disease therapy**.** Many research trails are being done trying to establish novel biomarkers that will help to make a definitive diagnosis [13].

Many cells, including macrophages, neutrophils, synoviocytes, chondrocytes, fibroblast-like cells and tumour cells, produce and secrete YKL-40 protein (also known as Chitinase-3-like protein 1). It plays a significant part in the inflammatory, tissue healing, and remodeling reactions after tissue damage [14]. In our study, the role of serum YKL-40 protein in PsA as a diagnostic and severity marker in connection to clinical findings is being investigated.

The nail involvement was found in 84% of PsA patients in our study. It is proven that psoriatic arthritis and nail psoriasis are significantly correlated and nearly eighty percent of psoriatic patients with arthritis have nail involvement. There is solid evidence that nail psoriasis predicts joint affection and could potentially manifest years before symptoms of arthritis [15]. It has been hypothesized that nail dystrophy's pathogenesis is more closely related to joint symptoms than skin symptoms. There are some suggested causes for this association that includes (a) the synovial membrane and nail apparatus share an unidentified autoantigen, (b) nail structures and DIP joints are anatomically connected, or (c) trauma (the Koebner phenomenon) plays a similar role in both psoriatic arthropathy and nail affection [16]**.** Also, our study revealed that 9 (36%) of the PsA patients had dactylitis, which is one of the hallmark features of the psoriatic arthritis.

In this study, 52% of the PsA patients had enthesitis involvement. The pathophysiology of PsA is thought to be heavily influenced by enthesitis [17]. The idea that PsA-related inflammation starts in enthesis, which experience repetitive micro trauma in addition to metabolic stress, is supported by evidence. Micro trauma to enthesis in genetically susceptible people may cause inflammation, which subsequently spreads to other tissues, including the nail matrix and synovium[18].

As regards the serum levels of YKL-40, showing a higher range in patients' serum level in comparison to controls' serum level was confirmed by the highly statistically significant difference regarding its serum levels between patients and control groups, it was elevated in all the PsA patients (100%) denoting that YKL-40 may be over produced or expressed in PsA and involved in its pathogenesis. These findings were in accordance with those of **Waszczykowski *et al.* [19],** who discovered that the studied patients' blood concentrations of YKL-40 were statistically significantly higher than those of the control group. Due to the possibility that YKL-40 might be a sensitive marker in the diagnosis of osteoarthritis, this significance was shown in both OA and PsA patients.

Moreover, YKL-40 concentrations were observed to be considerably greater in PsA compared to inflammatory bowel disease (IBD) patients and controls by **Bernardi *et al.* [20]**. Also, YKL- 40 levels were considerably greater in IBD patients with arthritis than in IBD patients without arthritis, which may indicate that YKL- 40 is a measure of joint injury in IBD patients. Moreover, **Jensen *et al.* [21]** observed that compared to 17% of psoriasis patients without arthritis, 43% of PsA patients exhibited higher plasma YKL 40 levels.

YKL-40 was identified to increase VEGF expression and improved angiogenesis. As a result, YKL- 40 and VEGF may work together to induce endothelial cell angiogenesis [22]. Angiogenesis, mitogenesis, and remodeling are few examples of the physiological and pathological processes that it may contribute to disease pathogenesis [23].

ROC curve analysis of serum YKL-40 comparing PSA patients with controls regarding cut off value > 40 µl/ml showed sensitivity (96.0%) and specificity (92.0%) with an AUC = 0.989 and high negative (NPV) and positive predicting values (PPV) of 95.8% and 92.3%, correspondingly implicating strong ability of serum YKL- 40 to differentiate between cases and controls, showing its potential value as a diagnostic biomarker for psoriatic arthritis. This was in line with **Salomon *et al.* [2]** observation that the serum YKL-40 ROC curve had a significant area under the curve (AUC). They observed that the ideal cut off value for serum YKL-40 was 49.88, which had a high positive predictive value (PPV) of 94.6% and a high negative predictive value (NPV) of 77.8%. These values were more or less in line with the findings of our investigation.

In our investigation, there was a statistically significant positive association (r = 0.526) between the levels of YKL-40 (ng/mL) and the activity of PsA as determined by the DAPSA. Blood level of YKL-40 and PsA activity were also shown to be significantly positively correlated (p = 0.037), according to **Salomon *et al.* [24].** Despite the fact that their study differed from ours in terms of study design and analytical approach and that their study used the Disease Activity Score 28 to quantify PsA activity (DAS 28). These findings could provide more proof for the theory put out by **Salomon *et al.* [2]** that the serum concentration of YKL-40 is a good indicator of PsA activity.

Moreover, **Boyd *et al.* [25]** revealed that YKL-40 had the highest correlation to the disease activity

composite indices of PsA and disease domains, which is consistent with the results of the current investigation.

YKL- 40 levels (µl /mL) and PASI score had a statistically significant positive connection (r = 0.539) between them. These results were in line with research by **Ahmed *et al.*** [26] who found that the PASI score had a significant impact on the levels of the YKL- 40 in all psoriatic patients.

According to **Volck *et al.*** [27], neutrophil granulocytes and macrophages have a similar ancestor, and neutrophil precursors start producing YKL-40 during the stage of myelocyte metamyelocyte. YKL-40 is kept in the specialized granules of neutrophils and released following complete activation of the neutrophil.

By activation of the NF-B signaling pathway, it has been suggested that YKL-40 might stimulate the production of pro-inflammatory cytokines such interleukin-6 (IL-6), IL-12, and tumour necrosis factor- (TNF-), which could assist the development of psoriasis [28].

According to **Salomon *et al.*** [24], the studied protein's blood concentration had a favorable correlation with the clinical indicators of the disease, demonstrating that YKL-40 is a good indicator of arthritis activity. Additionally, given that the protein is released by cells other than chondrocytes and synovial cells, such as neutrophils, macrophages, and endothelial cells, it can be inferred that the arthritic and cutaneous components of psoriatic disease have an effect on the serum concentration of YKL-40 in psoriatic patients.

In our investigation, there were statistically significant positive correlation between YKL- 40 levels (µl /mL) and the prevalence of MCP and DIP joint affection. The DIP joints of the hands and feet, the major joints in the lower extremities, the axial spine, and the sacroiliac joints are frequently affected in PsA patients, also the wrist, metatarsophalangeal joints, and MCP can also be affected.

YKL- 40 levels (µl /mL) and the number of tender joints (p = 0.021; r = 0.459) and swollen joints (p = 0.015; r = 0.523) both showed statistically significant positive correlation. **Salomon *et al.*** [2] noted that this measure corresponds with a number of swollen joints and with radiological ratings. Additionally, it has been obviously established that YKL-40, a cartilage-derived factor implicated in the pathophysiology of cartilaginous loss in inflammatory joint disorders, is generated by cartilage in pathologic joints.

CONCLUSION

Serum YKL-40 levels were elevated in PsA cases compared to controls. Also, a strong correlation between serum YKL- 40 concentrations and the disease activity and severity of psoriatic lesions in PsA patients was discovered. The outcomes of this work indicated that the inclusion of YKL-40 as a serological marker plays a significant role in the diagnosis of PsA and reflects the extent of activity and severity of psoriatic arthritis.

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