ORIGINAL ARTICLE

Serum YKL-40 in psoriasis with and without arthritis; correlation with disease activity and high-resolution power Doppler ultrasonographic joint findings

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Abstract

Background YKL-40 may be involved in angiogenesis in psoriasis and psoriatic arthritis (PsA). High-resolution power Doppler ultrasound (PDUS) can detect angiogenesis of synovium in PsA.

Aim To assess serum YKL-40 in psoriasis patients with or without PsA, and to correlate its levels with disease activity and high-resolution PDUS findings.

Methods In this case–control study, 48 patients with psoriasis (26 of them also had PsA) and 30 controls were assessed by high-resolution PDUS, and assayed for serum levels of YKL-40 by ELISA. Patients were clinically assessed using Composite Psoriatic Disease Activity Index (CPDAI). Total joint score (TJS) was used to assess joint involvement in PsA.

Results A statistically significant elevation was found in YKL-40 levels in psoriatics with or without PsA compared with controls ($P < 0.001$), as well as in PsA (group II) compared to patients without arthritis (group I) ($P = 0.002$). CPDAI, synovial thickness score and colour Doppler ultrasound (CDUS) score were highly significantly higher in group II vs. group I ($P < 0.001$). In all patients, CPDAI, synovial thickness and CDUS score were positively correlated to each other, and each of them was positively correlated to serum YKL-40 levels ($P < 0.05$). In either group I or II, serum YKL-40 levels correlated positively with CPDAI ($P < 0.05$). In group II, TJS, synovial thickness and CDUS score were positively correlated to each other ($P < 0.05$).

Conclusions Serum YKL-40 can be used as a new biological marker for angiogenesis and disease activity in psoriasis with or without PsA. High-resolution PDUS is a non-invasive tool for the evaluation of angiogenesis in PsA patients as well as for the detection of early synovial changes in psoriasis patients without arthritis.

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Conflicts of interest

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Introduction

Psoriasis is a complex immune-mediated chronic skin disease affecting approximately 2% of the worldwide population.[1] It is characterized by excessive growth of the epidermal keratinocytes, inflammatory cell accumulation and excessive dermal angiogenesis.[2] Currently, psoriasis is considered an inflammatory autoimmune disease dominated by interleukin (IL)-17-producing CD4+ Th cells (Th17).[3] Infiltrating mast cells and neutrophils are further cellular sources of IL-17 in psoriasis.[4] Moreover, Th17 cells interact with other immune cells and can attract neutrophils to the site of inflammation.[3] On the other hand, proangiogenic environment is induced by helper T cells and regulatory T cells.[5] Psoriatic keratinocytes produce several angiogenic cytokines as well. Additionally, infiltrating neutrophils can be a source of vascular endothelial growth factor (VEGF), which induces neutrophil chemotaxis in an autocrine amplification

manner.[6] Formation of new blood vessels starts with early psoriatic changes and disappears with disease clearance.[2]

Psoriasis is associated with an inflammatory arthritis; psoriatic arthritis (PsA) in up to 40% of cases. A number of common pathogenic features link the skin and the joint inflammatory processes. One of them is angiogenesis, which appears to be a fundamental inflammatory response in the pathogenesis of psoriasis and PsA.[7] The mechanisms responsible for angiogenesis are complex and involve secretion of several angiogenic mediators, such as VEGF.[8]

YKL-40, chitinase 3-like protein 1 (CHI3L1) or cartilage glycoprotein-39 (gp-39) is a member of 18 glycosyl hydrolases (mammalian chitinase) family. YKL-40 is one of the major secreted proteins from human articular chondrocytes, synovial cells, endothelial cells and macrophages, and expressed by mature neutrophils.[9] The exact biological functions of YKL-40 are not well known. However, it is suggested that it participates in many physiological and pathological processes such as proliferation, angiogenesis, mitogenesis and remodelling.[10] It is expressed and secreted by cancer cells of different origins along with a variety of non-malignant cells including inflammatory and structural cells. Thus, it is implicated in cancers, cardiovascular diseases, infections and other disorders.[11] It was also reported that serum levels of YKL-40 were increased in a variety of inflammatory conditions, such as rheumatoid arthritis and Crohn's disease.[12] In addition, YKL-40 was found to play a role in the up-regulation of VEGF expression and enhanced angiogenesis. Thus, both YKL-40 and VEGF may synergistically promote endothelial cell angiogenesis.[13]

The angiogenesis seen in psoriatic skin shares morphological features similar to abnormal vessels found within the synovium during inflammatory arthritis. In addition, the vascularity of the synovium demonstrated on high-resolution power Doppler ultrasound (PDUS) correlates well with histological findings of new vessel formation.[14]

High-resolution PDUS is sensitive in diagnosing synovitis in cases of established arthritis. It is a recently developed technique, and it can detect increased soft tissue vascularity.[15] Thus, it can quantitatively assess the morphologic (synovial thickness) and functional (blood flow) changes of joints during inflammatory arthritis.[16] Therefore, we aimed to assess serum YKL-40; as a possible angiogenesis marker in psoriasis, in patients with and without PsA, and to correlate its level with the clinical disease activity, as well as high-resolution PDUS findings.

Subjects and methods

In this case–control study, 48 patients with psoriasis, 26 of whom also had PsA, were selected from those presenting to the Dermatology, Phototherapy and Physical Medicine, Rheumatology and Rehabilitation Outpatient Clinics of Ain Shams University Hospitals. The control group consisted of 30 healthy, age- and gender-matched non-psoriatic volunteers with no history of joint problem, and no family history of psoriasis. Both patients and controls had no history of cancer, cardiovascular diseases, diabetes, infections or other chronic inflammatory diseases, likely to influence YKL-40 levels. The study protocol was in accordance with Helsinki declaration of human rights, and was approved by the local Ethical Committee.

After signing the informed consent form, patients were subjected to the following:

1 Full history taking and thorough physical examination including detailed skin, nail, hair, mucous membranes and joint examination. The diagnosis of psoriasis was made clinically based on the characteristic lesions.
2 Psoriatic arthritis patients fulfilled the diagnostic criteria defined by the classification of psoriatic arthritis (CASPAR) study.[17]
3 The severity of joint involvement was assessed by the peripheral joint score, with one point for each involved joint (range 0–70). Joint involvement was defined as synovial swelling and/or joint deformity not solely attributed to osteoarthritis.[18]
4 Assessment of disease activity was done by using the Composite Psoriatic Disease Activity Index (CPDAI). Disease involvement was assessed in up to five domains: peripheral joints, skin, enthesitis, dactylitis and spinal manifestations. Domains are scored from 0 to 3 (from uninvolved to severe). Peripheral joint score depends on number of joints involved and the presence or absence of impaired function. Skin disease score depends on Psoriasis Area and Severity Index (PASI) and Dermatology Quality of Life Index. Enthesitis is scored according to the number of involved sites and presence or absence of impaired function. Dactylitis is scored according to the number of involved fingers and the presence or absence of impaired function. Spinal manifestations are scored according to Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the presence or absence of impaired function. Individual domain scores were summed to give an overall composite score (range 0–15).[19]
5 Radiological examination: Plain x-rays of the hands, feet and affected joints were obtained for PsA patients. High-resolution PDUS was done for all patients and controls using a gray-scale US mode (GSUS) (7–18 MHz), Philips HD 11, USA. The assessed joints included bilateral knees, wrists and first, second and third metacarpo-phalengeal and distal inter-phalangeal joints (16 joints). Synovial thickness by GSUS was graded on a semi-quantitative scale from 0 to 3 (grade 0 = absence, grade 1 = mild, a small hypoechoic/anechoic line beneath the joint capsule, grade 2 = moderate, the joint capsule is elevated parallel to the joint area and grade 3 = severe synovitis, a strong distension of the joint capsule).[20] The semi-quantitative findings of colour Doppler US (CDUS) activity for synovitis were

scored as follows: grade 0 = no intra-articular colour signal, grade 1 = up to 3 colour signals or 2 single and 1 confluent signal in the intra-articular area, grade 2 = up to 50% of the intra-articular area filled with colour signals, and grade 3 = more than 50% of the intra-articular area filled with colour signals.[21,22] The sum of the synovial thickness and CDUS signal scores that obtained from each joint were used. Thus, the sum of synovial thickness by GSUS, and CDUS signal scores ranged from 0 to 48 for each score.

6 The assessment of serum YKL-40 level: Two ml of venous blood were collected from patients and controls for quantitative assessment of serum YKL-40 level. Serum was separated and kept at -70 until analysed. The serum level of YKL-40 or human Chitinase 3-like 1 (CHI3L1) was determined using Human Chitinase 3-like 1 Immunoassay; Quantikine ELISA (Enzyme-linked immuno sorbent assay) by R&D systems, USA (catalogue number: DC3L10; Minneapolis, MN, USA). This assay employs the quantitative sandwich enzyme immunoassay technique. A monoclonal antibody specific for CHI3L1 has been pre-coated onto a micro plate. Standards and samples are pipetted into the wells and any CHI3L1 present is bound by the immobilized antibody. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for CHI3L1 is added to the wells. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution is added to the wells and colour develops in proportion to the amount of CHI3L1 bound in the initial step. The colour development is stopped and the intensity of the colour is measured.

Statistical methods

Analysis of data was done by IBM computer using Statistical Program for Social Science version 15 (SPSS Inc., Chicago, IL, USA). The Kolmogrov–Smirnov test was used to test for normality of the data distribution. Quantitative variables were described in the form of medians and ranges, while qualitative variables were described as numbers and percents. Comparisons between groups with regard to categorical parameters were done using Chi-squared test (Fisher's exact test was used for comparing parameters with small sample size; <5). Comparisons between groups with regard to numerical non-parametric data were done using Mann–Whitney test. Spearman's correlation was used to measure the correlation between the quantitative variables. Multiple regression analysis was performed to detect the factors that influence YKL-40 levels. *P*-value less than 0.05 was considered the cut-off value for significance.

Results

This study included 48 patients with psoriasis (28 males and 20 females with age range of 17–55 years), and 30 subjects as controls (20 males and 10 females with age range of 20–55 years). Patients and controls were age and gender matched ($Z = -0.37$ and $P = 0.711$; $X^2 = 0.542$, $P = 0.462$). Patients were divided into 22 with no signs of arthritis [(group I), 16 males and 6 females], and 26 with PsA [(group II), 12 males and 14 females]. Total joint score (TJS) ranged from 1 to 9 in group II with a median of 3.

Group II patients (PsA) were significantly older than group I patients (median of 45 vs. 31 years with $Z = -2.864$ and $P = 0.004$). Group II patients (PsA) had longer disease duration than group I patients, but with no statistically significant difference (range of 1.5–30 years with median of 10 years vs. range of 2–12 years with median of 5 years; $Z = -1.830$ and $P = 0.067$). CPDAI was highly significantly higher in group II vs. group I (median of 4 in group II and 2 in group I; $Z = -6.263$, $P < 0.001$). However, there was no significant difference between psoriasis patients with and without arthritis as regards PASI ($P = 0.679$) (Table 1).

Nail involvement was detected in 4 patients of group I (18.2%) and 6 patients of group II (23.1%), with no statistically significant difference ($P = 0.735$), and with no statistically significant difference in distribution among females vs. male patients ($P = 1$), using Fisher's exact test.

Severity of synovitis, as assessed using high-resolution PDUS, revealed that the range of synovial thickness score in group II (PsA patients) was 10–34 with a median of 18, while the range in

Table 1 Comparison between group I (without PsA) and group II (with PsA) as regards the study parameters

Parameter	Group I ($n = 22$)		Group II ($n = 26$)		*Z*	*P*
	Range	Median	Range	Median		
Age (years)	17–55	31	34–55	45	−2.864	0.004*
Disease duration (years)	2–12	5	1.5–30	10	−1.830	0.067
Psoriasis Area Severity Index	3.6–27.3	11.9	2–30	10	−0.414	0.679
Composite Psoriasis Disease Activity Index	1–7	2	3–8	4	−3.517	<0.001†
Synovial thickness score	0–8	0	10–34	18	−6.085	<0.001†
Colour Doppler US score	0	0	8–30	14	−6.231	<0.001†

*Significant difference.
†Highly significant difference.

group I (without PsA) was 0–8 with a median of 0, with highly significant difference ($Z = -6.085$, $P < 0.001$). CDUS score ranged from 8 to 30 with a median of 14 in group II, while it was zero in group I, with highly significant difference ($Z = -6.231$, $P < 0.001$) (Table 1). Figure 1 shows metacarpo-phalangeal synovitis in PsA patient by both GSUS and CDUS.

Serum YKL-40 levels ranged from 400 to 4000 pg/mL in group I and from 900 to 4000 pg/mL in group II, while compared with a range of 30–220 pg/mL in the control group. A statistically significant elevation was found in YKL-40 levels in group I and group II compared with controls ($P < 0.001$), as well as in group II compared to group I ($P = 0.002$) (Table 2).

Comparing patients with or without synovial thickness, those with synovial thickness had significantly longer disease duration, higher CPDAI, increased TJS, higher CDUS score and elevated serum YKL-40 (Table 3).

In all patients, CPDAI, synovial thickness, and CDUS score were positively correlated to each other, and each of them was positively correlated to serum YKL-40 levels (Table 4). In either group I or II, serum YKL-40 levels correlated positively with CPDAI ($r = 0.487$, $P = 0.022$ in group I and $r = 0.695$, $P < 0.001$ in group II). In PsA patients (group II), TJS, synovial thickness and CDUS score were positively correlated to each other (Table 5). Multiple regression analysis including the factors that could significantly influence YKL-40 levels revealed that PASI score and CPDAI were the most important factors ($P < 0.001$), whether in all patients or in the group of PsA. In addition, TJS was an important factor in the group of PsA ($P = 0.006$).

Discussion

Psoriatic arthritis accounts for approximately 15% of patients attending to Rheumatology clinics therefore it represents the second most common diagnostic category after rheumatoid arthritis.[7] We found PsA patients to be older and had longer disease duration than psoriatics without arthritis. This finding is consistent with the pattern of disease onset, with the majority of patients (84%) experiencing skin symptoms prior to the onset of joint symptoms. Simultaneous onset of arthritic and psoriatic symptoms occurred in only 13% of patients. Only 3% of patients had joint involvement preceding skin involvement.[23] This was also in agreement with Kane *et al.*[24]who reported that the mean age at onset of arthritis was 40.4 years, while the mean age of psoriasis onset was 29.8 years.

We noticed more frequent nail involvement in our PsA patients (23.1%) than in those without arthropathy (18.2%), as PsA is associated with higher rates of nail disease than psoriasis alone.[25] Brazzelli *et al.*[26] reported nail involvement in 10–56% of psoriatic patients and in 85.7% of patients with PsA. Other studies found that the prevalence of nail involvement among patients with PsA is high as 70%.[27,28] It is worth mentioning that our patients with psoriatic nails but lacking arthropathy did not fulfil CASPAR criteria to diagnose PsA,[17] as they did not have any signs or symptoms of inflammatory articular disease in joint (s) or spine, or entheseal inflammation. Thus, psoriatic minimal nail involvement cannot be considered the only sign to diagnose initial PsA.

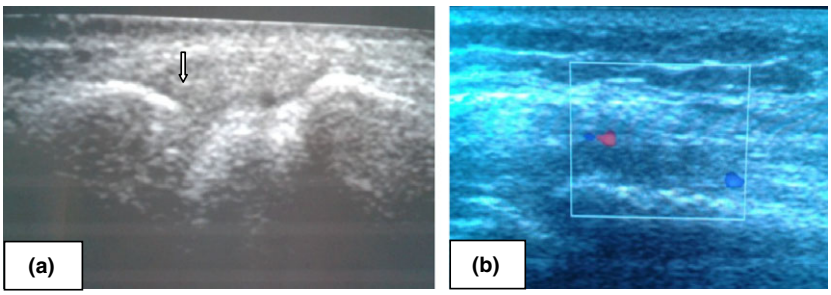

Figure 1 Metacarpo-phalangeal synovitis in PsA patient. (a) Grade 2 synovial thickening by gray-scale US mode (GSUS) (parallel to the joint capsule; arrow). (b) Grade 2 colour Doppler Ultrasound (CDUS) scale.

Table 2 Comparison between patients' subgroups and between each of them and controls regarding serum YKL-40 levels (pg/mL)

YKL-40 (pg/mL)	Group I ($n = 22$)		Group II ($n = 26$)		*Z*	*P*
	Range	Median	Range	Median		
Patients' subgroups	400–4000	900	900–4000	2000	−3.048	0.002*
Controls (n = 30)	30–220	100	30–220	100		
Z	−6.139		−6.421			
P	<0.001†		<0.001†			

*Significant difference.
†Highly significant difference.

Table 3 Comparison between patients with synovial thickness and those without regarding the study parameters

Parameter	Group with synovial thickness (n = 30) (Median)	Group without synovial thickness (n = 18) (Median)	*Z*	*P*
Disease duration (years)	12	5	−2.654	0.008*
Psoriasis Area Severity Index	11.9	10.8	−0.341	0.733
Composite Psoriasis Disease Activity Index	4	2	−3.189	0.001†
Total joint score	3	0	−5.274	<0.001†
Colour Doppler US score	13	0	−5.247	<0.001†
YKL-40 (pg/mL)	2000	900	−2.793	0.005*

*Significant difference.
†Highly significant difference.

Table 4 Results of correlation test between the study' parameters in all patients

Parameters	YKL-40 *r*, *P*-value	Colour Doppler Ultrasound score *r*, *P*-value	Synovial thickness score *r*, *P*-value
Composite Psoriasis Disease Activity Index	0.848, <0.001†	0.482, <0.001†	0.510, <0.001†
Synovial thickness	0.358, 0.007*	0.966, <0.001†	
Colour Doppler Ultrasound score	0.371, 0.009*		

*Significant difference.
†Highly significant difference.

Table 5 Results of correlation test between the study' parameters in group II patients (with arthritis)

Parameters	Colour Doppler Ultrasound score *r*, *P*-value	Synovial thickness *r*, *P*-value
Composite Psoriasis Disease Activity Index	0.065, 0.752	0.164, 0.424
Total joint score	0.668, <0.001*	0.798, <0.001*
Synovial thickness	0.938, <0.001*	

*Highly significant difference.

Our results showed that TJS was less than that reported by McHugh *et al.*[18] probably due to longer disease duration in their study group. Composite Psoriasis Disease Activity Index (CPDAI) was higher in PsA than in psoriasis only patients. This may be due to that four domains of the five main domains of this score are present in PsA rather than in psoriasis without arthritis; namely peripheral joints arthritis, enthesitis, dactylitis and spinal manifestations.

With regard to the radiological scores, patients with synovial thickness had significantly longer disease duration, higher CPDAI, more TJS and higher PDUS score than those without thickened synovium. In accordance, other studies showed that PDUS affords visualization of small vessel flow, showing soft tissue inflammation and reflecting disease activity in peripheral arthritis.[15,29] However, others found that the clinical disease activity of joints in rheumatoid arthritis patients did not show significant correlations with PDUS-detected synovitis.[30]

We reported four psoriasis patients without PsA (18.1%), with thickened synovium by high-resolution PDUS. This is in agreement with De Simone *et al.*[31], who found that US detected synovitis and/or tenosynovitis in at least one finger and/or toe in patients with psoriasis and peripheral joint pain without the diagnosis of PsA. US was also proven to be valuable in detecting synovial abnormalities in the fingers and toes of patients with suspected PsA.[32] These findings confirm previous reports of the ability of US to depict reliably the early changes and soft tissue abnormalities of inflammatory arthritis.[15,33] Therefore, dermatologists, who usually manage psoriatic patients before the onset of the joint disease, are advised consider US to obtain an accurate assessment of suspicious findings, especially in presence of early changes.

Angiogenesis appears to be an early and fundamental process for the evolution of the inflammatory response in synovial joints affected by arthritis, including PsA.[34] PDUS in our psoriasis patients without PsA showed no vascular spots in intra-articular and/or peri-tendinous spaces. On the other hand, Terslev and coworkers found vascular spots in 11% of wrist and finger joints in 28 healthy subjects and concluded that PDUS positivity per se should not be considered as a sign of inflammation,[35] as it is also seen in some normal joints, especially when using highly sensitive devices.[31] However, in our PsA patients, TJS, synovial thickness score and CDUS score were positively correlated to each other, denoting more or less accurate results.

Our results quantify arthro-synovial changes as well as grades of synovial vascularity. Similarly, Hau *et al.*[36] studied

rheumatoid arthritis patients and used a similar scoring system. Clinical diagnosis of enthesitis; one of the components of our CPDAI score, revealed that 15 patients from all patients (psoriasis and PsA) had grade 1 enthesitis. All these patients had tendoachilis enthesitis which was diagnosed clinically only without US.

We found that serum YKL-40 was higher in patients than controls and in PsA than in psoriasis patients. Jensen, *et al.*[37] reported that 43% PsA patients had elevated plasma YKL-40 levels compared with 17% of psoriatics without arthritis. Moreover, Bernardi *et al.*[38] found that YKL-40 concentrations were significantly higher in PsA than in inflammatory bowel disease (IBD) patients. In addition, YKL 40 values in IBD patients with arthritis were significantly higher than in IBD patients without arthritis that may suggest that YKL-40 may be a marker of articular damage in patients with IBD.

Serum YKL-40 levels correlated positively with CPDAI, synovial thickness and CDUS scores in all our psoriasis patients; with or without arthritis. Imai *et al.* revealed that serum levels of YKL-40 might be a useful biomarker for psoriasis vulgaris and pustular psoriasis,[39] and it can reflect the severity of skin lesions as well as arthritis in PsA patients.[12] We revealed that PASI score and CPDAI were the most important factors influencing YKL-40 levels, in all patients as well as in the group of PsA. In addition, TJS was an important factor in PsA patients. To the best of our knowledge, very few data exist on such correlations, for further larger studies.

The present study was not exempted from some limitations. The first limitation is the subjective nature of the synovial and CDUS scoring systems. Secondly, CDUS signals allow only rough estimation of the synovial blood flow. Thus, further longitudinal studies with a greater number of PsA patients, will possibly reveal the connection between systemic angiogenic activity and local intra-articular inflammatory vascular alterations, including angiogenesis.

In conclusion, serum YKL-40 can be used as a new biological marker for angiogenesis and disease activity in psoriasis with or without PsA. Serum YKL-40 levels correlated well with high-resolution PDUS findings. High-resolution PDUS is a non-invasive easily used and reproducible tool for the evaluation of angiogenesis in PsA patients as well as for the detection of early synovial changes in psoriasis patients without arthritis.

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