Original paper

Chitinase-3-like protein 1 (YKL-40) is a biomarker of severity of joint involvement in psoriatic arthritis

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Abstract

Introduction: Psoriasis is an inflammatory disease of a complex pathogenesis and arthritis is one of its most common complications. The biological role of chitinase-3-like protein 1 remains unknown. It is suggested that this protein takes part in processes such as proliferation, inflammation and tissue remodelling.

Aim: To determine whether YKL-40 can be a useful biomarker in psoriatic arthritis.

Material and methods: The study was performed on 42 patients with psoriatic arthritis: 28 men and 14 women, aged from 24 to 71 years. All patients met the diagnostic criteria (CASPAR) for psoriatic arthritis. The severity of psoriatic arthritis was assessed using 28-joint Disease Activity Score with CRP. The assessment of skin lesions was performed by Psoriasis Area and Severity Index (PASI) and, additionally, the Body Surface Area (BSA) was calculated. Blood samples were taken to measure the serum concentration of YKL-40, as well as C-reactive protein, erythrocyte sedimentation rate, white blood cell count and neutrophil count.

Results: YKL-40 serum levels were significantly higher in patients with psoriatic arthritis, compared to the control group. Moreover, a significant positive correlation between the activity of psoriatic arthritis measured by DAS 28 and serum level of YKL-40 was found. There was a positive correlation between serum YKL-40 and BSA, as well as a distinct trend towards significance between YKL-40 and PASI score.

Conclusions: YKL-40 can be a useful biomarker for both diagnosing and monitoring joint involvement in psoriatic patients.

Key words: chitinase-3-like protein 1, YKL-40, psoriatic arthritis, inflammation.

Introduction

Psoriasis is an inflammatory skin disease that affects up to 2–3% of the worldwide population [1]. Its pathogenesis is complex and involves a wide variety of processes, including epidermal hyperproliferation, activation of immune and inflammatory pathways or dermal angiogenesis. In the light of the current knowledge, psoriasis cannot be considered to be exclusively a skin problem as the disease may contribute to some general disorders: arthritis, cardiovascular diseases or metabolic disturbances [2]. Psoriatic arthritis is one of the most common complications of psoriasis, with a prevalence of up to 40% among psoriatic patients [3]. In a vast majority of cases, the skin symptoms of psoriasis precede the symptoms of arthritis. However, in some patients arthritis may develop simultaneously or even before the skin disease [4]. The diagnosis of psoriatic arthritis is not obvious in many cases, especially that there are no specific laboratory tests confirming the disease. The diagnostic process is usually based on the presence of arthritic symptoms coexisting with psoriatic lesions, the elevation of non-specific inflammatory markers and findings of imaging procedures, which may be negative in the early stages of the disease. Therefore, there is a need to search for new biomarkers that could facilitate the diagnosis of psoriatic arthritis or could be useful in monitoring the disease progress.

Chitinase-3-like protein 1 (YKL-40) is one of the 18 glycosyl hydrolases, a mammalian chitinase family. Its biological role is still not fully understood and remains to be discovered. However, it is suggested that this protein takes part in many important biological processes, such as proliferation, inflammation, angiogenesis and tissue remodelling [5]. YKL-40 is released by human chondro-

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cytes and synovial cells but also by endothelial cells, activated macrophages and neutrophils [5, 6]. It has already been evaluated in some cancers, infections, cardiovascular diseases but also in inflammatory disorders, such as Crohn's disease and rheumatoid arthritis [7–9]. The results of the research conducted so far have encouraged the authors to investigate whether YKL-40 can be a useful biomarker in psoriatic arthritis.

Aim

The aim of this study was to determine whether YKL-40 can be a useful biomarker in psoriatic arthritis.

Material and methods

The study was performed on a group of 42 patients with psoriatic arthritis, including 28 men and 14 women, aged from 24 to 71 years (mean: 45.9 ±13 years). All patients met the diagnostic criteria (CASPAR) for psoriatic arthritis [10]. The disease duration ranged from 0.5 to 60 years (mean: 19 ±15.7 years). Joint symptoms lasted from 0.2 to 35 years (mean: 7.1 ±7 years). Most patients (35 patients, 83.3%) developed arthritis after skin psoriasis had started. The severity of psoriatic arthritis was assessed using the 28-joint Disease Activity Score with CRP (DAS 28-CRP), which varied from 1.58 to 6.21 points (mean: 3.97 ±0.93 points). The patients were divided into 3 groups on the basis of the activity of arthritis according to the ACR (former ARA) criteria [11]. Patients with DAS 28 between 2.6 and 3.2 formed group I (low disease activity), group II consisted of patients with DAS 28 between 3.2 and 5.1, and, finally, patients with DAS 28 over 5.1 were enrolled in group III (high disease activity). The assessment of skin lesions was performed using the Psoriasis Area and Severity Index (PASI) and, additionally, the Body Surface Area (BSA) was calculated. Only one patient did not have any psoriatic skin lesions. Other patients had skin psoriasis of various severity with PASI between 0.5 and 38.4 points (mean: 10.2 ±8.6) and BSA between 0.2% and 88% (mean: 19.6 ±20.7%). A complete description of the examined group is provided in Table 1. All patients had a negative history of any significant comorbidities or systemic treatment which could influence the study results. The control group consisted of 37 healthy, non-psoriatic volunteers with a negative history of joint problems, matched for age and gender.

Blood samples were taken from the patients to measure the serum concentration of YKL-40, as well as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cell count (WBC) and neutrophil count. For the assessment of serum YKL-40, venous blood samples were collected, then serum was separated and kept frozen at the temperature of –70°C until it was analysed. The measurements were performed using enzyme-linked immunosorbent assay (ELISA) by R&D systems, Minneapolis, USA (catalogue number DC3L10), according to the manufacturer's instructions.

The study was conducted in compliance with ethic regulations and follows the principles of the Declaration of Helsinki. The study has been approved by the Bioethics Committee of the Wrocław Medical University (opinion no. 153/2017). The written informed consent was obtained from all participants.

Statistical analysis

The Kolmogorov-Smirnov test was used to check the data distribution. All the quantitative variables were described in the form of medians and ranges. Comparisons between the groups were performed by Mann-Whitney *U* test. Correlations between the variables were calculated using Spearman's rank correlation. *P*-value less than 0.05 was considered to be statistically significant.

Results

YKL-40 serum levels were significantly higher ($p < 0.00001$) in patients with psoriatic arthritis compared to the control group. The mean YKL-40 serum level in the group of patients was 103.31 ±76.1 ng/ml. Among the control subjects, the mean value of this parameter amounted to 25.5 ±18.5 ng/ml. The ROC analysis presented the large area under the curve (AUC) (Figure 1). The optimal cut-off value for serum YKL-40 level was 49.88 with high negative (NPV) and positive predicting values (PPV) of 0.778 and 0.946, respectively.

Table 1. Clinical characteristics of the examined group of patients with psoriatic arthritis ($n = 42$)

Parameter	Mean ± SD	Minimal value	Maximal value
Age [years]	45.9 ±13	24	71
Duration of psoriasis [years]	19 ±15.7	0.5	60
Duration of arthritis [years]	7.1 ±7	0.2	35
PASI score	10.2 ±8.6	0	38.4
BSA %	19.6 ±20.7	0	88
DAS 28 score	3.97 ±0.93	1.58	6.21

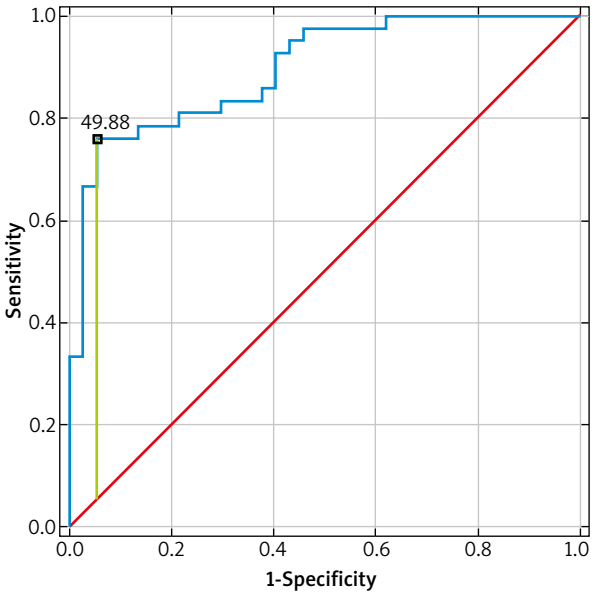

Figure 1. ROC analysis and the area under the curve (AUC) for YKL-40 serum level in patients with psoriatic arthritis

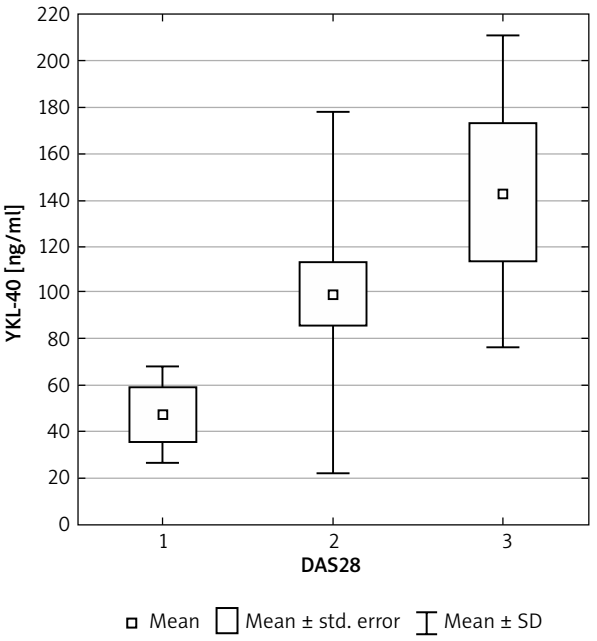

Figure 2. The serum YKL-40 concentration in the groups of patients with various activity of psoriatic arthritis according to DAS 28

Moreover, the achieved data were analysed against the severity of the disease. A significant positive relationship (p = 0.037) was found between the activity of psoriatic arthritis measured by DAS 28 and the serum level of YKL-40. The serum YKL-40 concentration in the groups of patients with various activity of arthritis according to DAS 28 is illustrated in Figure 2. Two patients with remission of arthritis according to ACR criteria (DAS 28 equal or lower than 2.6) were excluded from that analysis [11]. The detailed clinical data are shown in Table 2. The severity of psoriasis skin symptoms also had an impact on the YKL-40 serum level. There was a positive correlation between serum YKL-40 and BSA (p = 0.029) and a distinct trend towards significance between YKL-40 and PASI score (p = 0.071). No significant correlations were found between serum YKL-40 levels and other clinical or laboratory parameters, such as age, gender, CRP, ESR, WBC or neutrophil count. CRP mean value in psoriatic arthritis patients was 13.56 ±14 mg/ml and was elevated in 22 (52.3%) patients. The WBC amounted to a mean of 7.68 ±2.5 × 10^3/ml and was slightly above the normal ranges for only 4 (9.5%) patients. All the laboratory results in the group of patients with psoriatic arthritis are shown in Table 3.

Table 2. Serum YKL-40 concentrations according to the activity of psoriatic arthritis (ng/ml)

Group	DAS 28	Mean ± SD	Minimal value	Maximal value
I (n = 3)	> 2.6 and ≤ 3.2	47.23 ±20.8	23.21	60.4
II (n = 32)	> 3.2 and ≤ 5.1	99.68 ±78.1	16.63	301.71
III (n = 5)	> 5.1	143.15 ±66.9	66.92	209.91

Table 3. Laboratory findings in patients with psoriatic arthritis (n = 42)

Parameter	Mean ± SD	Minimal value	Maximal value
YKL-40 [ng/ml]	83.66 ±200.14	15.07	1570
CRP [mg/ml]	13.6 ±14	0.75	52.4
ESD	21.6 ±11.5	7	47
WBC [× 10^3/ml]	7.68 ±2.5	4.11	15
Neutrophil count [× 10^3/ml]	4.73 ±2.3	1.48	11.51

Discussion

YKL-40 has been studied in joint pathologies for at least 15 years, since it was established that it is secreted by chondrocytes and synovial cells. Is it well documented that a serum concentration of this protein is significantly elevated in patients with rheumatoid arthritis [9, 12, 13]. Moreover, this parameter correlates with a number of swollen joints and with radiological scores. Thus, it is generally considered to be a biomarker of joint inflammation as well as the activity and progression of rheumatoid arthritis, even in early stages. Some reports concerning the role of YKL-40 in osteoarthritis have also been published recently [14–16]. As with rheumatoid arthritis, the serum levels of YKL-40 were elevated and there was a positive correlation between YKL-40 serum and synovial concentration and symptomatic severity of the disease or ultrasonographic findings [14, 16]. Furthermore, it has been clearly proven that YKL-40 is produced by cartilage in pathologic joints and is a cartilage-derived factor involved in pathogenesis of cartilage destruction in inflammatory joint diseases [15, 17]. Additionally, it has been shown that YKL-40 is a useful biomarker of joint involvement in other systemic inflammatory disorders, such as inflammatory bowel disease [18].

There have been limited studies on serum YKL-40 concentration in psoriatic arthritis. In one report, serum levels of this protein were measured in 48 patients with cutaneous psoriasis and 42 patients with psoriatic arthritis [19]. In psoriatic patients, the examined parameter was elevated in 17% of subjects, whereas in patients with psoriatic arthritis, the increase of serum YKL-40 was observed in 43% of subjects. Moreover, the mean serum YKL-40 level was significantly higher in psoriatic patients with arthritis than in patients without joint involvement. The concentration of YKL-40 was re-measured in arthritic patients after 48 weeks of therapy with adalimumab. In the group of patients who responded to treatment, a significant decrease in the studied parameter was observed. The authors concluded that YKL-40 can be a useful marker for monitoring the response to therapy in patients with psoriatic arthritis. However, that study did not evaluate the relationship between serum YKL-40 levels and the severity of arthritis symptoms. Another study evaluated serum levels of YKL-40 in 48 psoriatic patients, including 26 patients with joint involvement [20]. The authors performed the clinical assessment of the patients with additional tests: Composite Psoriatic Disease Activity Index, total joint score and high-resolution power Doppler ultrasound. Serum YKL-40 levels were significantly higher in patients with psoriasis without arthritis than in control subjects but significantly lower compared to patients with psoriatic arthritis. Serum concentration of the examined protein correlated positively with all clinical parameters of the disease, showing that YKL-40 reflects the activity of arthritis. It can also be concluded that YKL-40 serum concentration in psoriatic patients is influenced by both arthritic and cutaneous component of the disease, as the protein is released not only by chondrocytes and synovial cells but also by neutrophils, macrophages or endothelial cells. The increased serum levels of YKL-40 in patients with psoriatic arthritis were also observed in one more study, however, the main purpose of that report was to evaluate the role of YKL-40 as a marker of joint involvement in inflammatory bowel disease. Thus, its authors did not focus on the clinical aspects of the psoriatic subjects [18].

Conclusions

The results of this study extend the knowledge on the role of YKL-40 in psoriatic arthritis. The authors confirmed a significant increase in serum levels of YKL-40 in patients with psoriatic arthritis. The mean value of the parameter measured in that group was about four times higher than in the control subjects. Having established the cut off value based on the ROC curve, it was determined that YKL-40 serum level was elevated in 31 subjects with psoriatic arthritis, which constitutes 73.8% of the examined patients. Furthermore, the results have shown the correlation between serum YKL-40 and DAS 28. To the best of the authors' knowledge, such a relationship has been demonstrated for the first time, which may be additional evidence supporting the hypothesis that the serum concentration of YKL-40 reflects the activity of psoriatic arthritis. To conclude, the authors postulate that YKL-40 can be a good biomarker for both diagnosing and monitoring joint involvement in psoriatic patients.

Conflict of interest

The authors declare no conflict of interest.

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