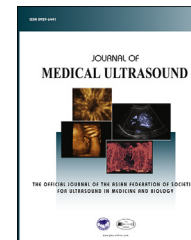


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ORIGINAL ARTICLE

Serum Calprotectin in Rheumatoid Arthritis: A Promising Diagnostic Marker, How Far Is It Related to Activity and Sonographic Findings?

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Abstract *Background:* In the past 2 decades, there has been increasing interest in calprotectin. It is released and detected in serum and body fluids as a potentially useful clinical inflammatory marker. The protein has been described in synovial tissue in rheumatoid arthritis (RA) patients, specifically in the lining layer adjacent to the cartilage–pannus junction, which is the primary site of cartilage destruction and bone erosion. Assessment of inflammatory activity in RA is of pivotal importance for the optimal treatment. Our aim in this study is to measure the serum calprotectin levels in RA patients and to assess its association—if there is any—with disease activity score and radiological findings using the musculoskeletal ultrasound.

Patients and methods: In our case control study, we included 44 RA patients (Group I) and 20 age- and sex-matched healthy volunteers who served as the control group (Group II). Both groups were subjected to full history taking and thorough clinical examination. Assessment of RA disease activity state was done for all RA patients using the Disease Activity Score 28. Laboratory investigations included the measurement of complete blood cell count, erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, anticitrullinated peptide antibodies, kidney, liver functions; serum calprotectin levels were determined using enzyme-linked immunosorbent assay and radiological joint assessment was done using musculoskeletal ultrasound score.

Conflicts of interest: The authors declare they have no conflicts of interest.

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Results: There was a statistically significant elevation of serum calprotectin levels among RA patients when compared with healthy controls. Statistically significant correlations were also found between serum calprotectin and the ultrasound grading score, Disease Activity Score 28, and erythrocyte sedimentation rate, which reflect the degree of inflammatory activity in the affected joints in RA patients. Moreover, the study yielded a significant correlation between serum calprotectin levels and rheumatoid autoantibodies (rheumatoid factor and anticitrullinated peptide antibodies), which are strong predictors of the aggressiveness of the disease. Serum calprotectin at a cutoff level of 93.9 $\mu\text{g}/\text{dL}$ had 88.6% sensitivity and 100% specificity for diagnosis of RA.

Conclusion: Calprotectin was found to have high association with laboratory and ultrasonography markers of inflammation in RA patients, so it is recommended for use as a marker of inflammatory activity in RA patients especially for the follow-up of patients on biological therapy to assess its efficacy.

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterized by chronic synovitis and progressive joint destruction. There is synovial infiltration by inflammatory cells, activation of synovial fibroblasts, and production of a wide range of inflammatory cytokines [1].

Sustained high disease activity results in a poor disease outcome from the perspective of musculoskeletal health, cardiovascular atherosclerotic risk, and hence life expectancy [2].

Assessment of inflammatory activity in RA is of pivotal importance for the optimal treatment in these patients [3].

Calprotectin is a heterodimer of two calcium-binding proteins present in the cytoplasm of neutrophils and expressed on the membrane of monocytes. Upon neutrophil activation or endothelial adhesion of monocytes, calprotectin is released and may be detected in serum or body fluids as a potentially useful clinical inflammatory marker [4].

During the past 2 decades, there has been increasing interest in calprotectin. It has been found in the synovial tissue in RA patients, specifically in the lining layer adjacent to the cartilage–pannus junction. The sites where pannus meets the cartilage are the primary sites of cartilage destruction and bone erosions in RA [5].

Hammer et al [5] reported that a significant correlation was found between plasma calprotectin level and its level in the synovial fluid in a RA patient.

The aim of this study is to measure the serum calprotectin levels in RA patients and to assess its association—if there is any—with disease activity score and radiological findings using the musculoskeletal ultrasound (US).

Patients and methods

This case control study included 44 RA patients (Group I) who fulfilled the 2010 American College of Rheumatology/European League against Rheumatism classification criteria for RA [6]. In addition, 20 age- and sex-matched healthy volunteers were included as a control group (Group II). Patients were enrolled from the outpatient clinic of Ain Shams University Hospital. Written consent was obtained from all patients and controls after a full explanation of the study.

All patients were subjected to a series of procedures (discussed in the following subsection).

Full medical history taking and thorough clinical examination

Assessment of disease activity was carried out with Disease Activity Score 28 (DAS28) using the erythrocyte sedimentation rate (ESR) value. The DAS28 is an index similar to the original DAS, consisting of a 28-tender joint count (range, 0–28), a 28-swollen joint count (range, 0–28), ESR, and an optional general health assessment on a visual analogue scale (range, 0–100). The DAS28 has a continuous scale ranging from 0 to 9.4, and the level of disease activity can be interpreted as low ($\text{DAS28} \leq 3.2$), moderate ($3.2 < \text{DAS28} \leq 5.1$), or high ($\text{DAS28} > 5.1$) [7].

Laboratory investigations

The laboratory investigations included the following:

- Complete blood count
- ESR using the Westergren method
- C-reactive protein (CRP) by latex agglutination
- Detection of anticitrullinated peptide antibodies (ACPAs) in serum assessed by an enzyme-linked immunosorbent assay (ELISA) methodology using QUANTA Lite TM CCP3 IgG semiquantitative ELISA (INOVA Diagnostics, Inc. San Diego, CA, USA)
- Liver function tests and kidney function tests using Synchron CX9 (Beckman Instrument Inc., Brea, CA, USA)
- Measurement of plasma calprotectin levels using ELISA [5]

Radiological investigations

The radiological studies included the following:

- (1) Plain X-ray scan on hands, wrists, and feet.
- (2) Musculoskeletal US was performed at the radiocarpal, metacarpophalangeal joints, and proximal interphalangeal joints using the 13-MHz probe grayscale and

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