ORIGINAL ARTICLE

Serum COMP and their correlations with various disease parameters in patients with systemic lupus erythematosus and osteoarthritis

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Systemic lupus erythematosus;
Osteoarthritis

Abstract  Introduction: The cartilage oligomeric matrix protein (COMP) is a glycoprotein, which occurs mainly in an articular cartilage. The amount of this protein increases under the influence of cytokines and growth factors. As a result of various diseases that cause damage to cartilage, fragments of matrix protein are released into synovial fluid and then into blood. The assessment of matrix protein level in serum, for example COMP, permits the establishment of the degree of cartilage damage in inflammatory joint diseases, and permits observation of the effectiveness of the treatment.

Aim of the work: To assess serum COMP level, as a marker for cartilage degradation, in SLE and OA patients and to find a correlation between serum COMP level and other markers as well as activity of disease, disease duration and the age of the patients.

Patients and methods: Blood was collected from 40 systemic lupus erythematosus (SLE) patients group I, [the patients were further subdivided into two subgroups, group (Ia) comprised 20 SLE patients received 1 g IV methylprednisolone (MP) daily for three successive days, group (Ib) comprised 20 SLE patients did not receive IV methylprednisolone (MP)], and from 20 patients with...
1. Introduction

Cartilage oligomeric matrix protein (COMP)/thrombospondin-5, a non-collagenous extra cellular matrix (ECM) glycoprotein distributed abundantly in cartilage [1], appears to catalyze fibril formation by promoting early association of collagen molecules, leading to an increased rate of fibrilogenesis and more distinct fibril organization [2]. COMP might function to support matrix interactions in ECM of cartilage [3]. Association of COMP with granulin-epithelin precursor, which promotes chondrocyte proliferation [4], also suggests that COMP is a key molecule in the interplay between cells and ECM in cartilage [5]. This protein has a complete molecular mass of 524 kD, the structure of a pentamer and consists of five arms containing a peripheral globular domain, a flexible strand and a central assembly domain where the five arms are connected in a cylindrical structure [6–9]. COMP can be found in human articular cartilage, meniscus, cruciate ligament, tendon and synovial membranes [10]. The amount of this protein increases under the influence of cytokines and growth factors (such as transforming growth factor-b1-TGFb1). As a result of various diseases which damage articular cartilage, fragments of matrix protein are released into synovial fluid and then into blood. The assessment of the matrix protein level in serum, for example COMP, permits the establishment of the degree of cartilage damage in inflammatory joint diseases such as rheumatoid arthritis [11–15] or OA [16,17] and permits observation of the effectiveness of the treatment of these diseases [18–21]. It is interesting how COMP functions in SLE patients under steroid treatment over years. Over time, this treatment may be destructive to cartilage in SLE patients, causing degenerative changes in joints. The degree of destruction of cartilage can be measured with the new cartilage marker COMP [22]. The aim of this study was to assess serum COMP level, as a marker for cartilage degradation, in SLE and OA patients and to find a correlation between serum COMP level and other markers as well as activity of disease, disease duration and the age of the patients.

2. Patients and methods

2.1. Subjects

A total of 40 consecutive SLE patients (group I) were included in the present study all fulfilling the updated American College of Rheumatology (ACR) revised criteria for the classification of SLE [23]. The patients were further subdivided into two subgroups, group (Ia) comprised 20 SLE patients received 1 g IV methylprednisolone (MP) daily for three successive days, group (Ib) comprised 20 SLE patients who did not receive IV methylprednisolone (MP). All Patients were recruited from the Rheumatology department and outpatient clinic of Cairo University Hospitals. After taking their informed consent, full history, thorough general and locomotor system examination, laboratory and relevant radiological investigations were done for all the patients. Disease activity was assessed for all the patients using the SLAM index [24].

Twenty age matched patients with knee OA who fulfilled the ARA Classification Criteria for Osteoarthritis [25] were considered as a control group (group II). The selected patients had unilateral or bilateral knee effusion with exclusion of patients with suggestive history of secondary OA.

The patients were assessed by Western Ontario and McMaster universities osteoarthritis index (WOMAC) questionnaires for the lower limbs and antero-posterior knee X ray assessed by Kellgren and Lawrence (K/L) grading scale to classify the degree of OA [26,27].

For all patients venous samples were obtained for routine laboratory investigations (CBC, liver and kidney function and urine analysis), the blood sample of group (Ia) patients was obtained 2–10 days after the first treatment with IV steroid.
Part of the blood sample was allowed to clot for 2 h at room temperature and was then centrifuged and stored at 
−80°C until analysed following a standardized protocol using the commercially available kits. The COMP level was determined using an inhibition enzyme-linked immunosorbent assay (ELISA), polyclonal antibodies raised in a rabbit against the bovine protein were used. The blood serum is diluted four times before applying it to a plate that contains COMP antigens, the plate was washed to remove all the other components of the blood serum then a secondary antibody that binds to the COMP antibodies to the plate was applied and the plate was washed again. This secondary antibody is chemically linked to an enzyme which the plate now contains in proportion to the amount of secondary antibody. Then a substrate was applied to make the enzyme detectable. This typically causes the enzyme to change color or fluorescence. The results of an ELISA were reported as a number so that the color change was quantified in some way. The threshold for a positive result was established. This is the most difficult part of the ELISA because the result can cover a wide range. A minimum value must, therefore, be selected to identify a positive result. An ELISA was performed on a control sample with a known concentration of the analyte and the signal that this sample produces was set as the standard. Any test sample that produces a stronger signal than the control sample is a positive result.

In SLE patients, serological examinations were made to discover the presence of:

1. Anti-nuclear antibody and anti-ds DNA tests were carried out by indirect Immunofluorescence (IIF) technique.
2. Anti cardiolipin antibodies (IgG and IgM) and Anti Ro (SSA) and AntiLa (SSB) were detected by ELISA.

### 2.2. Statistics

The data were coded and entered using the statistical package SPSS version 15. The data were summarized using descriptive statistics: mean ± standard deviation (±SD), or frequencies (n) and percentages (%). Statistical differences between groups were tested using Chi Square test ($\chi^2$) for qualitative variables, Independent sample t-test and ANOVA (analysis of variance) for quantitative normally distributed variables and non-parametric Mann Whitney test and Kruskal Wallis test for not normally distributed quantitative variables. Correlations were done to test for linear relations between variables. A probability value ($p$ value) $\leq 0.05$ was considered statistically significant.

### 3. Results

Demographic, clinical and laboratory characteristics of the study SLE group are shown in Tables 1 and 2, while demographic and clinical data of OA group are shown in Table 3. The measured values of the serum COMP level in SLE patients ranged from 1.32 to 1.71 μg/ml with a mean of 1.51 ± 0.13 μg/ml in group (Ia), and ranged from 2.43 to 3.56 μg/ml with a mean of 2.86 ± 0.31 μg/ml in group (Ib).

While in OA group (II) the value of serum COMP ranged from 0.97 to 2.65 μg/ml with a mean of 1.25 ± 0.37 μg/ml. We found significantly elevated COMP levels in the SLE group (Ib) compared to the SLE group (Ia) patients and OA group (II) ($p < 0.001$) (Table 4 and Fig. 1).

According to the Pearson’s correlation coefficient, in SLE patients the serum COMP level showed statistically significant positive correlations with the number of tender joints (correlation coefficient Pearson’s: $r = 0.45$, $p < 0.01$), the number of swollen joints ($r = 0.55$, $p < 0.001$), SLAM value ($r = 0.56$, $p < 0.001$) in Table 5. A significant positive correlation was found between serum COMP level and the ESR value in the 1st hour ($r = 0.35$, $p < 0.001$) (Fig. 2). While the serum

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**Table 1** Shows demographic and clinical characteristics of the SLE group I ($n =$ 40).

<table>
<thead>
<tr>
<th>Feature</th>
<th>Group Ia ($n = 20$)</th>
<th>Group Ib ($n = 20$)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex M/F</strong></td>
<td>3/17</td>
<td>3/17</td>
</tr>
<tr>
<td><strong>Age (y)</strong></td>
<td>38 ± 14.0</td>
<td>38 ± 14.0</td>
</tr>
<tr>
<td><strong>Disease duration (y)</strong></td>
<td>1–19</td>
<td>1–17</td>
</tr>
<tr>
<td><strong>Mean ± SD</strong></td>
<td>6.004 ± 0.66</td>
<td>6.805 ± 0.24</td>
</tr>
<tr>
<td><strong>No. of tender joints</strong></td>
<td>0–13</td>
<td>0–13</td>
</tr>
<tr>
<td><strong>Mean ± SD</strong></td>
<td>6.354 ± 0.31</td>
<td>5.634 ± 0.17</td>
</tr>
<tr>
<td><strong>No. of swollen joints</strong></td>
<td>0–5.00</td>
<td>0–10.00</td>
</tr>
<tr>
<td><strong>Mean ± SD</strong></td>
<td>2.101 ± 0.92</td>
<td>2.052 ± 0.58</td>
</tr>
<tr>
<td><strong>Morning stiffness (min)</strong></td>
<td>0–120</td>
<td>0–180</td>
</tr>
<tr>
<td><strong>Mean ± SD</strong></td>
<td>44.25 ± 28.99</td>
<td>49.254 ± 5.69</td>
</tr>
<tr>
<td><strong>ANA</strong></td>
<td>Seropositive</td>
<td>20 (100%)</td>
</tr>
<tr>
<td><strong>Seronegative</strong></td>
<td>0</td>
<td>3 (15%)</td>
</tr>
<tr>
<td><strong>SLAM</strong></td>
<td>Range</td>
<td>18–35</td>
</tr>
<tr>
<td><strong>Mean ± SD</strong></td>
<td>27.054 ± 0.67</td>
<td>15.053 ± 0.91</td>
</tr>
<tr>
<td><strong>Mild disease activity (1–28)</strong></td>
<td>31 (77.5%)</td>
<td>26 (65%)</td>
</tr>
<tr>
<td><strong>Moderate disease act (29–50)</strong></td>
<td>9 (22.5%)</td>
<td>3 (7.5%)</td>
</tr>
<tr>
<td><strong>Sever disease activity &gt;51</strong></td>
<td>0</td>
<td>1 (2.5%)</td>
</tr>
</tbody>
</table>

Data are the mean ± SD; SLAM = systemic lupus activity.

**Table 2** Shows the laboratory data of the SLE group ($n =$ 40).

<table>
<thead>
<tr>
<th>Items</th>
<th>Group Ia</th>
<th>Group Ib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hb (gm/dl)</strong></td>
<td>4.50–11.40</td>
<td>6.90–15.70</td>
</tr>
<tr>
<td><strong>WBC (dl)</strong></td>
<td>3.10–26.30</td>
<td>4.40–21.10</td>
</tr>
<tr>
<td><strong>PLT (dl)</strong></td>
<td>7.14 ± 4.97</td>
<td>8.97 ± 3.93</td>
</tr>
<tr>
<td><strong>Mean ± SD</strong></td>
<td>298.50 ± 128.41</td>
<td>303.40 ± 115.64</td>
</tr>
<tr>
<td><strong>ESR first (mm/h)</strong></td>
<td>15–150.00</td>
<td>6.00–140.00</td>
</tr>
<tr>
<td><strong>Mean ± SD</strong></td>
<td>78.70 ± 44.48</td>
<td>54.60 ± 40.65</td>
</tr>
<tr>
<td><strong>Twenty-four hours urinary prot. in gram</strong></td>
<td>0–59</td>
<td>0–2.10</td>
</tr>
<tr>
<td><strong>Mean ± SD</strong></td>
<td>6.06 ± 15.11</td>
<td>0.42 ± .54</td>
</tr>
</tbody>
</table>
COMP level was independent of the patients’ age ($r = 0.04$, $p = NS$), disease duration ($r = -0.03$, $p = NS$) and morning stiffness duration ($r = -0.05$, $p = NS$).

Decreased haemoglobin level below 11.0 g/dl was considered as an abnormal value. We found that in patients with decreased haemoglobin level the average serum COMP level was higher than in patients with normal haemoglobin level, Table 5. So a negative correlation was found between the serum COMP level and haemoglobin value ($r = -0.11$, $p = NS$) (Fig. 3).

Particular interest was shown on arthritis presence, 16 patients (80%) had arthritis of hands without degenerative changes, at disease flare in group Ia and fifteen patients (75%) had arthritis in group Ib. We found that serum COMP level was independent of arthritis presence ($r = 0.04$, $p = NS$).
level was higher in group Ib (were not on MP) than in group Ia (on MP). However, no significant differences were found between the serum COMP level and arthritis presence in both groups, \( p = \text{NS} \) (see Table 6).

As regards to the OA group, no correlation was found between the serum COMP level and patients’ age \( (r = -0.05, \ p = \text{NS}) \) and disease duration \( (r = 0.24, \ p = \text{NS}) \). There were positive correlations between serum COMP and WOMAC index score for the lower limbs \( (r = 0.64, \ p < 0.05) \).

4. Discussion

The cartilage oligomeric matrix protein (COMP), also known as thrombospondins (TSP-5), is expressed in cartilage, tendon, vitreous, and vascular smooth muscle cells [28]. Serum COMP may predict joint damage in rheumatoid arthritis (RA) [29,30] and in systemic lupus erythematosus (SLE) [22]. Increased serum COMP was reported in osteoarthritis (OA) and after cartilage injury [31,32]. Recently, cartilage oligomeric matrix protein (COMP), which is an important constituent of the non-collagenous matrix within the hyaline cartilage needed to maintain the properties and integrity of collagen network [33], has been suggested as a biomarker for increased cartilage damage and/or metabolism arising from exercise [34–37]. It consists of five identical glycoprotein subunits. The presence of COMP in synovial fluid and serum is lower than COMP purified from cartilage [38].

In this study, serum concentrations of antigenic fragments of a cartilage-specific component, COMP, were found to be increasing in SLE patients. Patients with arthritis had higher COMP concentration in comparison with patients without arthritis, and we found that serum COMP level was lower in arthritic patients who received IV MP than in arthritic patients who did not receive IV MP but not to a statistically-significant extent. No correlation was found between the serum COMP level and patient’s age, disease duration and morning stiffness duration. Forslind et al. [12] explain that this tissue-specific protein merely reflects generalised inflammation, and, therefore, that measurement of COMP in serum should provide information, which is not provided by conventionally used measures of inflammation. In our study, we found a significant positive correlation between serum COMP level and ESR value, number of tender joints, number of swollen joints and SLAM value as well as a negative correlation between serum COMP level and haemoglobin value. We assumed that COMP correlates positively with the inflammation marker ESR in SLE.

However in the study by Forslind et al. [12], the serum COMP level in their SLE patients did not correlate with disease activity. However, this study was carried out on a small group of only nine SLE patients and only three of them had arthritis.

In SLE patients in Forslind’s study and in our own, the serum COMP level was increased. It is possible that the COMP, although it is in part related to type 2 collagen, may also be related to some components of synovial tissue, tendon, ligaments or even cardiac tissues, or for that matter types 4, 9 or 10 collagen or even fibrin.

Our results in this study, also investigating the changes in serum levels of COMP during the treatment regime, indicate that intravenous treatment with steroids in SLE patients may have a rapid chondroprotective effect within 10 days. COMP seems to be a valuable parameter for monitoring the therapy response in patients with RA and is useful for the long-term control of cartilage turnover and the chondroprotective effect of different treatment modalities.

In conclusion, we found that the SLE patients had an increased serum COMP level and that serum levels of COMP can be used as a parameter for monitoring the therapy response in SLE patients. It is possible that in inflammatory joint diseases there is not only a higher cartilage breakdown, but also an elevated synthesis of COMP.

In a few studies, serum COMP level in knee osteoarthritis was examined [16,17]. Peterson et al. [15] examined the concentration of serum COMP in 38 patients with chronic knee pain (duration > 3 months) with or without changes in radiographs of both knee joints typical for osteoarthritis of the knee at the 3-year follow-up. The authors proved that in patients with chronic knee pain, increased concentration of COMP in serum can be found early as markers of early serious knee osteoarthritis. Vilim et al. [16], at the 3-year follow-up observation of 48 patients with symptomatic primary knee osteoarthritis, examined the serum COMP level and correlation with changes in joint space width according to Kellgren–Lawrence, Lequesne and WOMAC indices over 3 years.

Changes in joint space width (summed for both knees) correlated positively with baseline as well as study end period serum COMP level. Serum COMP level can be a prognostic marker of disease progression. High COMP levels, persisting over a 3-year study period in the patients with radiographic progression, indicated differences in disease activity detectable throughout the entire follow-up.

In our study there was a positive correlation between COMP levels and WOMAC index pain scale for the lower limb of the affected patients. The laboratory tests were normal in knee osteoarthritis patients so we decided not to examine serum COMP correlation with markers of inflammation.

Increasing serum COMP level in both SLE and knee OA suggests that the serum concentration of this marker can reflect changes in the cartilage.

In conclusion, we noted the following points:

- Increased serum COMP level was found in both: SLE and knee OA.

<table>
<thead>
<tr>
<th>Table 6</th>
<th>Shows comparison between serum COMP level and arthritis in SLE sub groups.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>N</td>
</tr>
<tr>
<td>---------</td>
<td>----</td>
</tr>
<tr>
<td>Ia</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>16</td>
</tr>
<tr>
<td>Ib</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>15</td>
</tr>
</tbody>
</table>
– A positive correlation was found between the serum COMP level and such data as ESR value, number of tender joints, number of swollen joints and SLAM value, and a negative correlation was found between serum COMP level and haemoglobin value in SLE patients.

– SLE patients with arthritis had higher COMP concentration in comparison with patients without arthritis, and we found that serum COMP level was lower in arthritic patients who received IV MP than in arthritic patients who did not receive IV MP.

References


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