Diagnostic Accuracy of Cartilage Oligomeric Matrix Protein (COMP), for Cartilage Damage in Rheumatoid Arthritis

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Authors’ contributions

This work was carried out in collaboration among all authors. Authors SQ and FS designed the study, wrote the protocol and wrote the first draft of the manuscript. Authors AIM and MA supported and supervised the data collection, data analysis and interpretation. Author SK performed the statistical analysis. Author MAS managed the analyses of the study. All authors read and approved the final manuscript.

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ABSTRACT

Background: Cartilage oligomeric matrix protein (COMP), is an extracellular matrix (ECM) non-collagenous glycoprotein that is mainly localized within the cartilage, and also be found in tendon and synovium. Recent studies in west and Asia Pacific region has shown that COMP, is a prognostic marker in Rheumatoid arthritis (RA).

Objective: To correlate serum COMP levels with disease severity and cartilage destruction in rheumatoid arthritis.

Methods: The study was conducted in Department of Pathology and Rheumatology, Ziauddin University Hospital, Karachi from June 2018 to May 2019. Patients were recruited as per American
1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune joint disease that prevail virtually 0.5–1.0% of the adult population worldwide [1]. The approximate prevalence of RA in developing countries is variable [2-4]. The prevalence of RA in Pakistan is 0.5% where it is 0.2–1% in India for both male and female [5]. The prevalence of RA in southern areas of Pakistan such as city of Karachi is 0.142%, where as in northern areas it is reported to be 0.55% [6]. The precise etiology of Rheumatoid joint inflammation is obscure, it might be hereditary and natural components appear to be associated with its pathogenesis [7]. The most common reported symptoms in patients with RA are joint pain and stiffness particularly severe in the morning [8].

RA preferentially involves symmetrical small joints [9]. Joint destruction in rheumatoid arthritis brought about by infiltration of synovial fibroblasts and inflammatory cells, for example, macrophages and T cells in the subchondral bone and cartilage, which brings about irreversible harm to involved joint that may lead joint disfigurement and stiffness [10].

Diagnosis of RA can be made by various antibodies such as rheumatoid factor (RF) and Anti-cyclic citrullinated peptide (anti-CCP) [11]. As per literature anti-CCP is considered as gold standard for RA diagnosis. Anti-CCP may be embroiled in the disease pathophysiology and joint disintegrations yet it does not tell us about the extent of cartilage damage [12]. Cartilage oligomeric matrix protein (COMP) is biological marker that can identify the extent of cartilage damage quantitatively. It is an ECM non-collagenous glycoprotein that is mainly localized within the cartilage, but can also be found in tendon and synovium. It is homopentameric multidomain protein that interacts with number of ECM proteins, cells as well as growth factors and act as adaptor molecule to guide ECM synthesis and tissue remodeling in various physiological and pathological conditions [13]. There is proof about the connection between COMP level and radiologic indications of RA [14]. This biomarker emphatically correlates with cartilage debasement [15,16]. However the outcomes of all studies are not compatible. Consequently we investigate the diagnostic accuracy of this biomarker in separating RA patients from healthy persons and to set up whether serum COMP can be utilized to analyze cartilage harm in RA characterized by radiographic findings.

2. MATERIALS AND METHODS

2.1 Study Setting

This study was conducted at Department of Pathology and Rheumatology, Ziauddin University Hospital, Karachi from June 2018 to May 2019. Three groups were established consisting of 44 RA patients with high DAS, 44 RA patients with moderate DAS and 88 controls having same age and sex.

2.2 Patients and Methods

This research enrolled 88 recently diagnosed RA patients and 88 age and sex matched controls. All patients fulfilled the ACR Criteria 2010. The inclusion criteria were as under:

College of Rheumatology (ACR) 2010 classification criteria. The study population consists of 88 healthy subjects and 88 RA patients. Sandwich ELISA technique was used to assess serum COMP level. Other inflammatory markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) antibodies like rheumatoid factor, and anti-cyclic citrullinated protein (anti-CCP) were also assessed. Results were analyzed using SPSS-20 and P-value ≤0.05 was considered as significant.

**Results:** Serum COMP levels were significantly higher in RA patients 51.35 ng/ml than controls 21.454 ng/ml with significant p value=<0.0001. There was strong positive correlation between COMP level and disease severity in RA patients with moderate as well as high disease activity score (DAS) with significant p value. Serum COMP showed 96% sensitivity and 83% specificity at level of 27.01 ng/ml for diagnosis of RA.

**Conclusions:** COMP has significant positive correlation with severity of RA. Serum COMP can be utilized as a biomarker to quantify cartilage destruction in RA patients.

Keywords: Diagnostic accuracy; Cartilage Oligomeric Matrix Protein (COMP); cartilage damage; rheumatoid arthritis.
Investigations were carried out for all means of venipuncture. The following laboratory In addition, venous blood was collected by Patients with low disease activity have DAS From this, the disease activity of the patient was number of swollen joints is performed. Examination of joints is performed on fol joints such as shoulder, elbow, wrist, knee joint. are bilateral proximal and distal inter phalangeal tments. The joints evalated through DAS score can be classified as Patients with low disease activity have DAS <3.2, patients with moderate disease activity have DAS -3.2 - <5.1, patients with high disease activity have DAS -5.1 and patients in remission have DAS -2.6. In addition, venous blood was collected by means of venipuncture. The following laboratory investigations were carried out for all participants(a) ESR using the westergren method (b) CRP using nephelometry (c) Serum rheumatoid factor (RF) using nephelometry (d) Serum Anti-CCP antibody using high sensitive ELISA kit (e) COMP assay using Human (COMP) ELISA kit (Cloud Clone CO, USA, catalog no. SEB197Hu).

- plain x-rays of the hands and feet were taken at radiology department of Ziauddin Hospital and assessed for radiological changes by Van der Heijde modified Sharp score [18].

2.3 Statistical Analysis

SPSS-20 was used to analyze the data. The quantitative data like age were presented as mean ± S.D. Paired data of continuous variables like DAS28, CRP were calculated using paired t-test. Pearson correlation was used to measure the correlation between quantitative variables like DAS28, CRP, RF, Anti-CCP and COMP levels. Receiver-operating characteristic (ROC) curve was used to check the sensitivity, specificity of the potential biomarker. P-value ≤0.05 was considered significant

3. RESULTS

Our study included 88 controls and 88 RA patients. There was no significant difference in the mean age of the both groups. Mean SD of disease duration, morning stiffness in hours, joint tenderness index score and joint swelling index score was 2.68±6.43 years, 2.01±0.32 hours, 12.11±9.52, and 9.97±13.43 respectively. Figs.1 and 2 shows some radiological findings of the involved joints in our study.

Fig. 1. X-ray of patient no 8 showing erosion and decrease in joint space and matting of carpal bones at wrist joints in both hand
Table 1 compares the mean values of variables in both groups, which shows significant difference in value of ESR, CRP, RF and Anti-CCP between patients and controls group P<0.0001. As it can be observed in Table 2 serum COMP levels are significantly higher in RA patients 51.35 ng/ml than controls 21.45 ng/ml and Table 3 shows serum COMP with high DAS 63.386 ng/ml is higher than COMP levels with moderate DAS 39.34 ng/ml in RA patients with in RA patients significant p value of <0.0001.

Table 4 and Figs. 3 & 4 shows the correlation between biomarkers and radiological damage severity (sharp scores). Serum COMP level shows strong positive correlation with Moderate DAS RA (r=0.932, p<0.001) and High DAS RA (r=0.952, p<0.001).

To check the diagnostic ability of COMP for cartilage damage we plot ROC curve. The ROC curve clearly shows strong sensitivity and specificity of COMP levels with increased severity of disease.

Fig. 5 & Table 5 shows the receiver operating characteristic curve analysis for COMP in differentiating 88 Controls and 88 RA patients. Table 5 shows at level of 27.01 ng/ml serum COMP level had 96% sensitivity and 83% specificity to differentiate control from RA with AUC= 99%.

4. DISCUSSION

RA can be presented as a mellow and non-ruinous illness to a genuine and rapidly
dangerous joint sickness. Distinctive new proposed biomarkers are used to pick the best treatment procedure and anticipate RA prognosis [19,20]. These biomarkers could be applied in clinical practice and exploration settings to supervise accommodating response and joint harm and turnover movement. Taking into account the procured results, serum COMP level was essentially higher among RA patients stood out from control subjects. In the subset of RA patients, COMP not solely was higher in those with serious ailment, yet what's more had a satisfactory affectability and particularity to decide RA patients to have late-stage disease [15]. There is likewise proof that COMP has role in initiating complement cascade that adds to pathogenesis of disease. According to finding of Andersson et al in 2013 COMP is discharged because of catabolic response and when there is high damage of cartilage in RA [13]. Repair systems can’t repay joint damage in late stages of disease [21,22]. In concurrence with our outcomes, a recent research led by Sakthiswary et al in 2017 which included RA patients and healthy individuals, revealed high levels of serum COMP in RA in contrast with healthy individuals [24]. In the view of this proof, serum COMP seems a specific test for RA. Our outcomes propose that serum COMP not exclusively can be utilized for diagnosis of RA, yet in addition, high levels recommend severe cartilage destruction. Additionally along with other clinical tools that are currently used to monitor the disease progression like DAS-28 and radiologic scores serum COMP levels can be objectively measured to check the disease progression in RA patients. Estimating biological markers to calculate cartilage development and breakdown disparity is an established practice to decide disease progress and treatment response [25]. Andersson et al. uncovered that at the time of diagnosis if levels of COMP are high they are associated with cartilage damage in RA patients over the next five years. This highlights that COMP is a good prognostic marker in RA [13].

**Table 1.** The Means (SD) of the variable in the studied groups.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Controls N=88</th>
<th>Patients N=88</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age years (mean SD)</td>
<td>42.44 ± 6.88</td>
<td>43.43 ± 9.4</td>
<td>0.429</td>
</tr>
<tr>
<td>ESR mm/h (mean SD)</td>
<td>7.55 ± 2.76</td>
<td>59.62 ± 28.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP mg/l (mean SD)</td>
<td>1.53 ± .48</td>
<td>27.02 ± 25.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RF U/ml (mean SD)</td>
<td>6.95 ± 3.12</td>
<td>59.84 ± 65.72</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anti-CCP U/ml (mean SD)</td>
<td>6.69 ± 2.5</td>
<td>103.38 ± 98.95</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Table 2.** Means (SD) of COMP between control and patients

<table>
<thead>
<tr>
<th>COMP ng/ml</th>
<th>CONTROL(n=88) mean ± SD</th>
<th>PATINTS(n=88) mean ± SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>21.454±(5.208)</td>
<td>51.35 ± 15.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Table 3.** Means (SD) of COMP between moderate DAS and High DAS in RA patients

<table>
<thead>
<tr>
<th>COMP ng/ml</th>
<th>LOW DAS(n=44) mean ± SD</th>
<th>HIGH DAS(n=44) mean ± SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>39.34(±6.258)</td>
<td>63.38(±12.675)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

COMP=Cartilage Oligomeric matrix Protein, CRP=C-Reactive Proteins, RF=Rheumatoid factor, Anti CCP=Anticyclic citrullinated Protein, DAS=disease activity score.
Table 4. Correlation between the radiological sharp scores in rheumatoid arthritis and the measured markers

<table>
<thead>
<tr>
<th>Sharp Scores</th>
<th>Correlation coefficient and significance</th>
<th>COMP</th>
<th>CRP</th>
<th>RF</th>
<th>Anti CCP</th>
</tr>
</thead>
<tbody>
<tr>
<td>High DAS</td>
<td>R</td>
<td>.952</td>
<td>.508</td>
<td>.055</td>
<td>.049</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>.000</td>
<td>.000</td>
<td>.721</td>
<td>.753</td>
</tr>
<tr>
<td>Moderate DAS</td>
<td>R</td>
<td>.932</td>
<td>.566</td>
<td>.182</td>
<td>.010</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>.000</td>
<td>.000</td>
<td>.238</td>
<td>.950</td>
</tr>
</tbody>
</table>

Table 5. Diagnostic accuracy of serum COMP

<table>
<thead>
<tr>
<th>Area under curve</th>
<th>Cut-off point</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.994</td>
<td>COMP=27.01 ng/ml</td>
<td>96%</td>
<td>83%</td>
</tr>
</tbody>
</table>

Fig. 5. Receiver operating characteristic curve analysis for COMP in differentiating 88 Controls and 88 RA patients

As our research was case control, so we were unable to find how serum COMP level can anticipate RA exacerbation and its relationship with radiographic scoring declining. A research led in 2013 described COMP as characteristic marker in RA and exhibited that patients with established RA will undoubtedly have progressively raised degrees of COMP [22]. Different studies showed that other biologic therapies and anti-TNF could prevent joint damage and reduce COMP levels in RA [26,27]. In addition to that serum COMP level shows significant correlation with extensively used clinical tools like DAS-28 and radiographic scoring systems [15,28]. The present results are compatible with this reality, as the joint involvement increased the serum COMP levels became elevated. The ROC curve demonstrated that COMP, have acceptable sensitivity and specificity and can be utilized as diagnostic marker. This shows COMP didn't just mirror the cartilage damage, yet additionally it was related with disease seriousness. Utilizing COMP for diagnosis, prognosis and anticipating destruction of cartilage in patients with RA can unite a restorative manual for distinguish who may respond significantly to a particular treatment and for abatement of treatment related aftereffects.

5. CONCLUSIONS

Our results showed that serum COMP has significant positive correlation with severity of RA. Serum COMP can be utilized as a biomarker
to quantitatively measure cartilage destruction in RA patients. Further studies are recommended to see correlation between synovial thickness on ultrasound and COMP levels, and furthermore to decide prognostic value of serum COMP level by following participants over time.

6. LIMITATIONS

Firstly as study was case control so we cannot observe the patients to see the prognostic capability of COMP, secondly due to budget limitation we were unable to measure cytokines like IL and TNF which may show association with serum COMP levels and disease severity.

CONSENT AND ETHIC APPROVAL

Written and informed consents were taken from all participants.

Research approval was taken from Ethics Review Committee of Ziauddin Medical University (Ref.no:01604SKPATH).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES


