Serum cartilage biomarkers in late rheumatoid arthritis
Marcadores séricos de cartilagem na artrite reumatóide avançada

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ABSTRACT

Objectives: To evaluate the clinical value of two new cartilage serum markers in patients with rheumatoid arthritis of long duration. Methods: One hundred and forty patients followed for an average period of twelve years were evaluated for the presence of human cartilage glycoprotein-39 and cartilage serum oligomeric matrix protein and the respective coefficient correlation between markers and disease activity score. Results: The mean values of cartilage serum oligomeric matrix protein and human cartilage glycoprotein-39 were respectively 9 ± 6 ug/ml and 36 ± 16 mg/ml (p > 0.001) when compared to controls. A positive correlation was observed between disease activity score and the cartilage biomarkers (r = 0.67 for human cartilage glycoprotein-39 and r = 0.83 for cartilage serum oligomeric matrix protein). Conclusion: This study shows in a inequivocal form that patients with rheumatoid arthritis of long duration show higher values of serum biochemical markers of cartilage metabolism and a positive correlation with disease activity score.

Keywords: Arthritis rheumatoid; Biological markers/analysis; Cartilage/metabolism

RESUMO

Objetivos: Avaliar o valor clínico de dois novos marcadores séricos de cartilagem em pacientes com artrite reumatóide crônica. Métodos: Cento e quarenta pacientes foram seguidos por um período médio de 12 anos e avaliados para a presença de glicoproteína-39 de cartilagem humana e para matriz de proteína oligomérica sérica e seu respectivo coeficiente de correlação entre os marcadores e um escore de atividade da doença. Resultados: Os valores médios da matriz de proteína oligomérica sérica e glicoproteína-39 de cartilagem humana foram, respectivamente, 9 ± 6 ug/ml e 36 ± 16 ug/ml (p > 0,001) quando comparados aos controles. Uma correlação positiva foi observada entre os escores de atividade da doença e os biomarcadores (r = 0.67 para a glicoproteína-39 de cartilagem humana e r = 0.83 para a matriz de proteína oligomérica sérica). Conclusão: O presente estudo mostra de maneira inequívoca que pacientes com artrite reumatóide de longa duração mostram valores séricos mais elevados de marcadores bioquímicos do metabolismo da cartilagem e uma correlação positiva com o escore de atividade da doença.

Descritores: Artrite reumatóide; Marcadores biológicos/análise; Cartilagem/metabolismo

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic disease clinically leading to joint destruction as a consequence of a destructive inflammatory process¹-². Besides serum rheumatoid factor early predictors of joint destruction in recent onset rheumatoid arthritis are few including HLA DRB1, cartilage biomarkers and the novel anti-cyclic citrullinated peptide antibody³-⁵. In the present report we looked into a large number of patients with rheumatoid arthritis of long duration and the serum levels of two cartilage biochemical markers, YKLK-40 (also known as human cartilage glycoprotein-39) and cartilage serum oligomeric matrix protein (COMP) in an attempt to determine if patients with higher disease activity score (DAS) correlate with the serum levels of cartilage markers.

Study carried out at University Hospital from the Universidade Estadual do Rio de Janeiro, UERJ, Rio de Janeiro, (RJ) and Hospital Israelita Albert Einstein, São Paulo (SP), Brazil.

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METHODS

Patients

Hundred forty patients with long standing rheumatoid arthritis according to the ACR criteria attending the outpatient clinic of the University Hospital from the State University of Rio de Janeiro and Hospital Israelita Albert Einstein of São Paulo were studied: 128 women and 12 men with a mean age of 53 years and a mean duration of 12 years (table 1). The DAS was evaluated by the method of van der Heidje D and co-workers(6). According to the Eular criteria none of our patients were in remission or/and burned out disease (DAS less than 1). The drugs employed in the treatment of these patients are shown on table 2.

Table 1. Characteristics of patients and controls

<table>
<thead>
<tr>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>140</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>12.0</td>
</tr>
<tr>
<td>Mean age</td>
<td>53</td>
</tr>
<tr>
<td>Disease activity</td>
<td>2.5–7.0</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>3–15</td>
</tr>
</tbody>
</table>

Table 2. Patient therapy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprime</td>
<td>8</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>4</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>26</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>50</td>
</tr>
<tr>
<td>Anagelsic drugs</td>
<td>17</td>
</tr>
<tr>
<td>Steroids</td>
<td>39</td>
</tr>
<tr>
<td>NSAIDS</td>
<td>42</td>
</tr>
<tr>
<td>Gold salts</td>
<td>3</td>
</tr>
</tbody>
</table>

Laboratory analysis

The laboratory parameters used were COMP YKL-40 and C reactive protein performed as previously described(7-8).

Statistical Analysis

Spearman’s rank test and a linear multiple regression analysis were employed in our study.

RESULTS

Both cartilage markers were significantly elevated in patients with RA of long duration, when compared to a control population. The mean values of COMP and YKL-40 were respectively 9 + 6 and 36 + 16 (p > 0.001) (table 3). The scattered of COMP and YKL plotted agonist DAS are shown on figures 1 and 2. A positive correlation were observed between DAS and both cartilage biomarkers (r = 0.83 for COMP) and (r = 0.67 por YKL-40).

Table 3. Serum levels of COMP and YKL-40

<table>
<thead>
<tr>
<th>RA</th>
<th>Controls</th>
<th>Correlation (DAS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ug/ml COMP</td>
<td>9 +/6</td>
<td>1.2 +/3</td>
</tr>
<tr>
<td>mg/ml YKL-40</td>
<td>36 +/16</td>
<td>0.3 +/0.2</td>
</tr>
</tbody>
</table>

DISCUSSION

Our study shows that serum cartilage markers are elevated in patients with RA of long duration. Also both markers point to a strong correlation between DAS and biologic markers of cartilage turnover. The identification of blood markers that could identify patients with rheumatoid arthritis of the destructive type is important since now we have various new forms of therapy that could avoid joint destruction and functional impairment. Cartilage markers have been evaluated in patients with early onset RA and suggested to be a good predictor of aggressive disease even though correlation with inflammatory markers are somewhat controversial in some reports(9-12). Our study we believe is the first one looking in a large number of patients with elevated DAS. The correlation observed between cartilage markers and DAS confirms the notion that both YKL-40 and COMP are
good markers of outcome assessment and in some way similar to other proposed ones such as bone erosions, synovium activation and genetic susceptibility markers. In fact, treatment with DMARDs and biologicals are also shown to induce clinical response associated with reduction of the serum level of these markers in sera\(^\text{(13-16)}\). We have not attempted to look at correlations between inflammatory markers YKL-40 and COMP serum levels since in previous publications using the same patient population in disease of long duration we did not find a very good correlation between sedimentation rate, C reactive protein and DAS\(^\text{(15)}\).

In summary, in a population of patients with RA of long duration serum cartilage markers appear to reflect severe disease and maybe helpful as a routine tool in clinical practice where new therapeutic measures are gradually taking place in the treatment of rheumatoid arthritis\(^\text{(16)}\).

**CONCLUSION**

This study shows in an unequivocal form that patients with RA of long duration show higher values of serum biochemical markers of cartilage metabolism and a positive correlation with DAS.

**REFERENCES**