ORIGINAL ARTICLE

Diagnostic and prognostic value of some biochemical markers in early knee osteoarthritis

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Received 18 August 2011; accepted 13 September 2011
Available online 2 November 2011

Abstract  Background: Osteoarthritis (OA); the most common joint disease, is not only characterized by cartilage destruction; but also by alteration of bone and synovial tissue metabolism, though their relative importance in the initiation and progression of OA is still debated. To identify patients with a high risk for destructive OA, more sensitive techniques than plain X-rays are needed.

Aim of the work: To study the diagnostic and prognostic value of some biochemical markers serum hyaluronic acid (HA) and serum cartilage oligomeric matrix protein (COMP), high sensitive C-reactive protein (hs-CRP) in the included patients had early OA knees and their relation to disease progression.

Patients and methods: Sixty patients had early knee OA and 20 control subjects were included. WOMAC index, laboratory investigations (COMP, HA, hs-CRP) and radiological evaluation (Kellgren and Lawrence grading scale and Thomas compartmental score) were performed for each patient at baseline and after one year.

Results: HA was significantly higher in patients than controls ($p > 0.001$) with the highest specificity and positive predictive value. It was significantly correlated with COMP at baseline and after one year ($p = 0.01$). The levels of HA at baseline correlated with its levels after one year ($p > 0.001$). It also correlated with K–L grading score ($p = 0.02$). COMP was significantly higher in patients than controls ($p > 0.001$). It was significantly correlated with Thomas score after one year.

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Peer review under responsibility of Egyptian Society for Joint Diseases and Arthritis.
doi:10.1016/j.ejr.2011.09.001
1. Introduction

Osteoarthritis (OA) is defined by focal lesions of the articular cartilage, combined with a hypertrophic reaction (sclerosis) in the subchondral bone and new bone formation (osteophytes) at the joint margins. More recently, OA has been relabelled as a whole organ disease because pathological abnormalities such as periarticular muscle weakness, lax ligaments, low grade synovitis, meniscal degeneration and neurosensory system alteration are frequently present in these patients [1].

To identify patients with a high risk for destructive OA and to monitor drug efficacy, more sensitive techniques than plain X-rays are needed. Specific and sensitive biochemical markers reflecting abnormalities of the turnover of bone, cartilage, and synovial tissues may be useful for the investigation and monitoring of OA [2].

Good approaches in the treatment of OA increase the need for measurable standard for disease progression. One or two years are needed to observe changes in plain radiographs whereas few months are sufficient to observe changes in biochemical markers [3]. Early diagnosis of OA and assessment of disease severity are other potential uses for these markers [4]. Serum cartilage oligomeric matrix protein (COMP) and serum levels of HA have the potential to be a prognostic marker of disease progression [5,6].

COMP was the foremost biomarker among investigated biomarkers. It could be continuously expressed and predicted knee OA progression. [26]. Serum levels of HA had a predictive value for further development of knee OA in that further joint space narrowing was detected in patients with knee OA [6].

We aimed to study the diagnostic and prognostic value of some biochemical markers; HA and COMP, hs-CRP in the included patients had early OA knees and their relation to disease progression.

2. Patients and methods

Sixty OA patients diagnosed by the American College of Rheumatology (ACR) clinical and radiographic criteria for knee OA [7], and 20 control subjects matched for age and sex were included in the present study. The patients were recruited over 6 months at the Rheumatology and Rehabilitation Outpatient Clinic, Minia University Hospital. Follow-up was done after one year for each patient from finishing the recruitment.

year ($p = 0.007$). Baseline levels of COMP correlated significantly with its levels after one year ($p = 0.005$). The differences of the serum levels of hs-CRP at the baseline evaluation and after one year between patients and controls were not statistically significant ($p = 0.4, 0.5$, respectively).

Conclusions: The measurements of HA and COMP may be of diagnostic and prognostic value in differentiating patients with early joint destruction and in determining disease progression. A single biochemical marker has definitive diagnostic value and the combination with other biochemical markers as well as with clinical and radiographic data would most likely help to improve the clinical assessment of patients. Serum hs-CRP is not a good predictor of individual patient progression and has a poor sensitivity and specificity.

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2.1. Inclusion criteria

Patients with primary knee OA unilateral or bilateral.

Patients less than 50 years with chronic knee pain more than three months and radiological evidence of early OA.

2.2. Exclusion criteria

Patients with secondary OA, e.g. post-traumatic or post-inflammatory, e.g. rheumatoid arthritis (RA).

Patients with systemic diseases as renal or hepatic failure.

Patients with generalized OA or patients with concomitant knee and hip OA.

Patients with cervical or lumbar spondylosis.

All patients were subjected to: full history, clinical examination, laboratory investigations and radiological examination at the start of the study and after one year according to the following.

2.3. Clinical evaluation

Assessment of pain was done using Numerical Rating Scale of Pain [8].

2.4. Functional evaluation

Functional evaluation of the patient was done using Arabic translated and validated version of Western Ontario and McMaster University (WOMAC) index [9].

2.5. Radiological evaluation

Anteroposterior radiographs were taken to the patients in the supine position, in standing (weight bearing position) with the knee flexed by 20°, and a skyline view was taken for assessment of patellofemoral compartment. Radiological evaluation was done to all patients by two methods: Kellgren–Lawrence grading scale (1957). For categorization of the patients to four categories at baseline and for correlating it with clinical and laboratory parameters, as it is the gold standard in all clinical trials. It was not done after one year as for a patient to progress by one grade K–L it needs two or more years [10].

Thomas grading scale (1975): It is compartmental evaluation for knee OA used as a scoring system for joint space narrowing, subchondral sclerosis, subchondral cysts and osteophyte. Each
item has four grades from 0 to 3. The score was calculated for each compartment, e.g. right and left medial compartment, right and left lateral compartment, right and left patellofemoral compartment. Then the total score was calculated by summation of the three compartments. This score was used for sensitive correlations with clinical and laboratory parameters, for compartmental evaluation, and for detection of disease progression. It was done at baseline and after one year. Remodeling, intra-articular calcification, periarticular calcification, subluxation and femoral cortical erosion were recorded as present or absent. X-rays were evaluated by three observers two of them were fixed, two of the observers were blinded to the condition of the patients and whether it is the baseline or the follow-up examination [11].

2.6. Laboratory evaluation

The following routine and special laboratory tests were done for all patients and control subjects at baseline and after one year. Complete blood count, erythrocyte sedimentation rate (ESR) (by Westergren method), liver and renal function tests were done for exclusion of renal or hepatic patients.

2.7. Synovial inflammation markers

Synovial inflammation markers: serum hyaluronic acid (HA) by ELISA: The HA test kit is an enzyme-linked binding protein assay that uses a capture molecule known as hyaluronic acid binding protein (HABP) [12]. Normal range = 0–75 ng/mL. Values more than 75 ng/mL were reported to be positive. Hs-C reactive protein (CRP) was done using the high sensitivity enzyme immunoassay (hs-CRP ELISA) for quantitative determination of CRP concentration. Values more than 8.2 mg/L were reported to be positive.

2.8. Cartilage marker

Serum cartilage oligomeric matrix protein (COMP). COMP ELISA is a solid-phase, two-site enzyme immunoassay. Value <12 U/L lower risk of aggressive joint destruction (negative), or >12 U/L increasing risk of aggressive joint destruction (positive).

Data were coded, entered and analyzed by the statistical Package for the Social Sciences (SPSS for windows version 11.0) SPSS Inc., 2001. Two-tailed tests were used throughout and statistical significance was set at the conventional 0.05 level. Group comparisons were done by Student’s t-test to compare the means of two groups of cases and chi-squared ($\chi^2$) test, to test the significance of the differences between the two groups in categorical variables. Correlations was done by the bivariate Spearman correlation coefficient. Positive and negative predictive values were calculated and reported.

3. Results

3.1. Demographic data and clinical features

This study included 60 OA patients underwent clinical assessment, radiological examination and laboratory evaluation at baseline and after one year. It also included 20 control subjects. The age of the patients ranged from 44 to 79 years with a mean of 58.9 ± 7.7 years. Male patients were 48.3% while female patients were 51.7%. The control group was age and sex matched. The disease duration ranged from 0.5 to 20 years with a mean of 4 ± 3.8 years. Age of onset ranged from 42 to 70 years with a mean of 54.9 ± 6.8 years. Morning stiffness ranged from 0 to 15 min with a mean of 9.7 ± 5.4 min while inactivity stiffness ranged from 0 to 10 min with a mean of 5.8 ± 2.9 min. BMI of the patients ranged from 20.7 to 55.8 with a mean of 28.6 ± 8. Numerical Rating Scale of Pain (NRSP) at baseline ranged from 3 to 10 with a mean of 6.8 ± 1.7. WOMAC index at baseline ranged from 6 to 88 with a mean of 52.2 ± 17.8, the prevalence of other clinical findings obtained by history taking, other than pain at baseline evaluation were reported in Table 1. Physical findings in knee examination at baseline evaluation and after one year for each knee are shown in Table 2.

Fig. 1 and Table 3 show radiological evaluation of patients at baseline.

3.2. Compartmental evaluation at baseline and after one year by Thomas score

Thomas score at baseline ranged from 8 to 45 with a mean of 28.3 ± 7.7. After one year it ranged from 10 to 58 with a mean of 31.5 ± 9.4. The difference was very highly significant ($p > 0.001$) Fig. 2. Patients who had increased Thomas score after one year were defined as radiological progressors were 40 patients (66.7%), and the non-progressors were 20 patients (33.3%).

Biochemical and inflammatory markers difference between patients group and control group at the baseline and after one year. Qualitative hs-CRP, ESR (first hour), quantitative and qualitative HA, quantitative and qualitative serum COMP levels at the baseline were highly significant in patients than control ($p = 0.009$, $p = 0.03$, $p > 0.001$, $p > 0.001$, $p > 0.001$ and $p > 0.001$, respectively), Tables 4 and 5.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical data of patients at baseline evaluation.</th>
</tr>
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<tbody>
<tr>
<td>Range</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>0.5–20</td>
</tr>
<tr>
<td>Age at onset (years)</td>
<td>42–70</td>
</tr>
<tr>
<td>Morning stiffness (minutes)</td>
<td>0–15</td>
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<tr>
<td>Inactivity stiffness</td>
<td>0–10</td>
</tr>
<tr>
<td>BMI</td>
<td>20.7–55.8</td>
</tr>
<tr>
<td>NRSP</td>
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<tr>
<td>WOMAC</td>
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</table>

<table>
<thead>
<tr>
<th>Number</th>
<th>Percent</th>
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<tbody>
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<tr>
<td>Muscle wasting</td>
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<td>Knee instability</td>
<td>44</td>
</tr>
<tr>
<td>Knee swelling</td>
<td>32</td>
</tr>
<tr>
<td>Deformity</td>
<td>15</td>
</tr>
</tbody>
</table>

BMI = Body Mass Index, NRSP = Numerical Rating Scale of Pain, WOMAC = Western Ontario and McMaster University.
Table 6 shows the comparison between quantitative serum HA, hs-CRP and serum COMP in patients at baseline and after one year. It didn’t show significant difference regarding serum HA \((p = 0.5)\) and hs-CRP \((p = 0.3)\), while the difference of serum COMP was very highly significant \((p > 0.001)\).

Table 7 shows no statistically significant differences of the serum levels of hs-CRP at the baseline evaluation and after one year between patients and controls \((p = 0.4\) and 0.5, respectively).

### 3.3. Correlations

The correlations between serum COMP levels qualitatively and quantitatively, at baseline and after one year showed significance with variable degrees and serum HA titers at baseline were highly significantly correlated with HA titers after one year \((p > 0.001)\).

COMP at baseline correlated significantly with qualitative CRP at baseline \((p = 0.005)\), with HA titer at baseline and after one year \((p = 0.01)\), with qualitative HA at baseline \((p = 0.05)\) and after one year \((p = 0.004)\). COMP after one year correlated only with qualitative HA after one year \((p = 0.01)\).

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3.4. Sensitivity and specificity

Sensitivity and specificity of CRP at baseline was 65% and 70%, respectively. Positive predictive value and negative predictive value was 0.1 and 0.4, respectively. While sensitivity and specificity of CRP, after one year, was 50% and 70%, respectively. Positive predictive value and negative predictive value was 0.8 and 0.3, respectively.

Sensitivity and specificity of HA at baseline was 42% and 100%, respectively. Positive predictive value and negative predictive value was 1 and 0.7, respectively. While sensitivity and specificity of HA, after one year, was 38% and 100%, respectively. Positive predictive value and negative predictive value was 1 and 0.4, respectively.

Sensitivity and specificity of COMP at baseline was 70% and 80%, respectively. Positive predictive value and negative predictive value was 0.9 and 0.5, respectively. While sensitivity and specificity of COMP, after one year, was 57% and 80%, respectively. Positive predictive value and negative predictive value was 0.9 and 0.8, respectively.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Quantitative and qualitative serum COMP and serum HA in patients and control group at baseline.</th>
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<tbody>
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<td>Serum COMP</td>
<td>Serum HA</td>
</tr>
<tr>
<td>Quantitative</td>
<td>Range</td>
</tr>
<tr>
<td>Patients</td>
<td>4–32</td>
</tr>
<tr>
<td>Control</td>
<td>1–17.8</td>
</tr>
<tr>
<td>Qualitative</td>
<td>Number</td>
</tr>
<tr>
<td>Patients</td>
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<tr>
<td>Control</td>
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<table>
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<tr>
<th>Table 5</th>
<th>Quantitative and qualitative serum COMP and serum HA in patients and control group after one year.</th>
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<tbody>
<tr>
<td>Serum COMP</td>
<td>Serum HA</td>
</tr>
<tr>
<td>Quantitative</td>
<td>Range</td>
</tr>
<tr>
<td>Patients</td>
<td>1–32</td>
</tr>
<tr>
<td>Control</td>
<td>1–17.8</td>
</tr>
<tr>
<td>Qualitative</td>
<td>Number</td>
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<td>Patients</td>
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<td>Control</td>
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<table>
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<tr>
<th>Table 6</th>
<th>Comparison between quantitative serum HA, hs-CRP and serum COMP in patients at baseline and after one year.</th>
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<tbody>
<tr>
<td>Range</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Quantitative HA Baseline</td>
<td>5–800</td>
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<tr>
<td>After one year</td>
<td>15–800</td>
</tr>
<tr>
<td>Quantitative COMP Baseline</td>
<td>4–32</td>
</tr>
<tr>
<td>After one year</td>
<td>1–32</td>
</tr>
<tr>
<td>Quantitative hs-CRP Baseline</td>
<td>3–450</td>
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<tr>
<td>After one year</td>
<td>3–200</td>
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<table>
<thead>
<tr>
<th>Table 7</th>
<th>Quantitative hs-CRP in patients and controls at baseline evaluation and after one year.</th>
</tr>
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<tbody>
<tr>
<td>Range</td>
<td>Mean ± SD</td>
</tr>
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<td>Hc-CRP at baseline Patients</td>
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</tr>
<tr>
<td>Control</td>
<td>3–100</td>
</tr>
<tr>
<td>Hc-CRP after one year Patients</td>
<td>3–200</td>
</tr>
<tr>
<td>Control</td>
<td>3–100</td>
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</table>

Figure 3 Correlation between K–L grade and HA at baseline.
4. Discussion

A diagnosis of knee OA is traditionally based upon weight-bearing radiographs and pain. The diagnosis is usually made by the time joint tissue degeneration is already advanced. Therefore, much attention has been focused on developing assays for molecular markers, namely cartilage derived macromolecules or their fragments whose release into the circulation from the joint may reflect disturbances in joint tissue turnover [13]. A particular need has been to develop markers to sensitively predict early initiation and progression of OA [5].

There have been a number of reports demonstrating associations between biochemical markers measured in serum and disease severity and outcome in OA [14–16].

So this study was designed to evaluate diagnostic and prognostic value of some biochemical markers; hs-CRP, HA and COMP, in the included patients with early OA knees and their relation to disease severity and progression.

As regards the radiological evaluation K–L grading score was done at baseline evaluation but not after one year as for one patient to progress from one grade K–L to another it needs more than two years. Thomas score was used at baseline and after one year as it can detect minute changes that may progress in one year follow-up. One of the potential uses of biochemical markers would be to identify patients at high risk of rapidly progressive joint destruction.

Initial results showed that the older the patient, the higher the frequency of synovitis and the higher the radiological grade.

Traditionally CRP has been seen as normal in OA. Sensitive assays show that it is raised in many OA patients, but is below the level usually detected in hospital clinical pathology departments [17,15,16]. This agrees with our results as qualitative hs-CRP was significantly higher in patients compared to controls (p = 0.009).

Sharif et al. [18] found that sensitivity and specificity for CRP was 38% and 85%, respectively, this is close to the figures obtained in our results as sensitivity and specificity of CRP at baseline was 65% and 70%, while sensitivity and specificity of CRP, after one year, was 50% and 70%. So, serum CRP is not a good predictor of individual patient progression and has a poor sensitivity and specificity.

HA is a marker of synthesis activity of synovium. As a major product of synovial cells, HA is considered a marker of synovitis [13]. Our results support that HA at baseline was significantly correlated with morning stiffness and joint swelling (p = 0.1, 0.2), respectively. So HA can be considered a marker of synovial inflammation as it is correlated with joint synovitis and morning stiffness which reflects joint inflammation too. Sharif et al. [18] found that sensitivity and specificity for HA was 80% and 89%, respectively. Our results showed that sensitivity of HA is poor (42% at baseline and 38% after one year), but on contrary it showed high specificity 100%. This may be attributed to small number of controls who didn’t show any elevation of serum HA. But we can say that HA is a unique marker for joint disease difficult to be detected in healthy population.

Turan et al. [19] found significant difference between HA levels in patients and controls (p = 0.02), and this agrees with our results, as serum levels of HA at baseline and after one year were significantly higher than those of control group (p = 0.001).

Also, there was a significant correlation between HA level and disease duration (p = 0.04), ESR (p = 0.001), and CRP level (p < 0.001), but these items were not correlated in our study.

Turan et al. [19] found significant correlation with radiological grade (p > 0.05). Elliott et al. [20] came to the same results that levels of serum HA were positively associated with all definitions of radiographic OA (p < 0.0001). Pavelka et al. [6] found that the patients with higher basic serum levels of HA had a faster radiological progression (r = 0.56, p < 0.005), which agrees with our study as the qualitative HA at baseline was correlated with K–L grading (p = 0.02). We can consider HA marker of joint destruction and disease progression.

Pavelka et al. [6] found that higher serum levels of COMP (p = 0.05) were detected compared with healthy control subjects, indicating increased cartilage turnover in OA patients. That result coincides with ours. Comparing COMP levels at baseline and after one year in patients and controls revealed significantly higher levels in patients (p < 0.001). These findings support the role of COMP as joint marker which is difficult to be elevated in healthy subjects.

Wisowska and Jabonśka [21] found that the average value of COMP in OA patients was 10.4 ± 2.7 U/l. This agrees with our study in which the mean was 16.2 ± 6.3. They found no correlation between the serum COMP level and patients’ age and disease duration, and this also agrees with our results. Because some patients have cartilage destruction early in the disease and those patients who will progress radiologically, and others have stationary course that are called non-progressors. This occurs independent of age or disease duration.

Vilim et al. [5] studied COMP levels in a group of OA patients; their results didn’t show correlation of COMP levels with any demographic, clinical, radiological or other laboratory parameters at baseline evaluation.

Vilim et al. [5] found a significant correlation of serum COMP levels with a change in JSW over three years. The association was significant for COMP level at the study end (p > 0.001), but not for COMP level at baseline. Clark et al. [22] observed an association between serum COMP level and knee OA disease severity assessed by Kellgren and Lawrence grading. Both are in agreement with our results, as COMP titers after one year correlated with lateral compartment affection (p = 0.05) and with Thomas score after one year (p = 0.007). In some studies, the progression of joint space narrowing seems to be positively correlated with markers of degeneration of type I and type II collagen, COMP corresponding to degradation of non-agreca and non-collagen proteins [23]. So, serum COMP has the potential to be a prognostic marker of disease progression. Although COMP is expressed by other tissues within a joint [24], it prevails in the articular cartilage and it has been demonstrated that serum levels are representative of cartilage catabolism [25].

Most studies in recent years could draw the conclusion that COMP was associated with OA. COMP was the foremost biomarker among investigated biomarkers. It could be continuously expressed and predicted knee OA progression early [26]. Thus, the correlation of serum COMP level with Thomas score as a measure of radiological destruction which reflects cartilage catabolism is accepted.

In the present study, COMP level at baseline were significantly correlated with synovitis after one year (p = 0.02) which was consistent with the results of Vilim et al. [27].
who found that COMP levels are correlated with joint swelling. COMP is known as cartilage marker and its correlation with synovitis may reflect its role in synovial inflammation. Because of the complex involvement of bone, cartilage, synovium and systemic inflammation, only a combination of several biochemical markers will adequately predict disease progression [28].

In our study we found no correlation of serum COMP level at baseline and at the study end with NRSP or with WOMAC index, this was consistent with that of Vilim et al. [5]. So we can say that COMP levels are not a reflection to the clinical or functional status of patients in time of assay, as it may reflect ongoing early cartilage destruction not detectable by functional parameters. Bruyere et al. [29] could not find correlation between baseline levels of COMP and WOMAC index and that agrees with our results.

On contrary, Wisowska and Jabońska [21] found correlation between the serum COMP level and WOMAC index ($p < 0.005$), but these parameters were not correlated in our study at baseline or after one year.

In general it was found from this study and the previous studies that the best correlation between COMP level and radiological progression when both knees were included in the analysis. This result is expected for a marker, such as COMP, whose potential release from all joints in the body contributes to the serum level [5].

Indeed, clinical indices such as pain and physical function scores are poorly related to the destruction of joint structure, as confirmed in our study by the absence of a correlation between the total WOMAC index and radiological parameters.

To obtain an accurate estimation of the rate of joint progression of joint destruction in individual patients with early knee OA, long-term studies are required because of low rate of progression in patients with established OA.

In this follow-up study we correlated the levels of biochemical markers with radiological destruction using the compartmental evaluation of Thomas score. To our knowledge, we could not find other studies using this score with biochemical markers.

Most previous reports, including the most recent ones, correlating levels of biochemical markers with the degree of joint destruction, were evaluated by a composite index such as K–L grading system.

Although the number of patients was small owing to the cost of biochemical markers; however, this is probably one of the largest studies performed including both a panel of recently developed biochemical markers and sensitive radiological measure. To our knowledge this may be the first follow-up study done on Egyptian OA patient with this design.

In conclusion, the measurements of serum HA and COMP may be of diagnostic and prognostic value in differentiating patients with early joint destruction and in determining disease progression. A single biochemical marker has definitive diagnostic value and the combination with other biochemical markers as well as with clinical and radiographic data would most likely help to improve the clinical assessment of patients affected early with this common disorder. Serum HA was the most specific markers with the highest positive predictive value. Serum hs-CRP is not a good predictor of individual patient progression and has a poor sensitivity and specificity. Using the compartmental evaluation of Thomas score with biochemical markers is better than K–L grading system especially with short durations of follow-up.

References


