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Evaluation of Serum Cartilage Oligomeric Matrix Protein in Egyptian Patients with Rheumatoid Arthritis

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Rheumatoid Arthritis (RA) is the most common form of chronic inflammatory joint disease. The diagnosis of RA may be a challenge in certain patients where the clinical presentation is equivocal and serum Rheumatoid Factor (RF) is negative. The evaluation of joint damage and the disease activity is usually done by radiological scoring and the assessment of Disease Activity Score (DAS). Cartilage Oligomeric Matrix Protein (COMP) is a pentameric glycoprotein that was initially found in articular cartilage. The serum levels of COMP in a group of Egyptian patients with RA were measured and the diagnostic performance of serum COMP was compared to quantitative serum Rheumatoid Factor (RF) and C-Reactive Protein (CRP) values. The current study included 2 groups: a control group, comprised 20 healthy subjects (16 women and 4 men) aged (mean±SD) 43.0±15.22 years and a patients group, comprised 30 rheumatoid arthritis patients (24 women and 6 men) aged 48.4±12.39 years. Serum COMP was significantly higher in patients with rheumatoid arthritis when compared to the controls ($p<0.01$). The median range of serum COMP was 7.49 (4.95-9.56) and 8.78(6.41-27.3) U L^{-1} in controls and patients with rheumatoid arthritis respectively. When patients with RA were classified into a seronegative and a seropositive subgroups, serum COMP showed a superior diagnostic value in seronegative patients compared to quantitative RF. The Area Under the Curve (AUC) for the COMP was 0.771 (p value 0.011 and the 95% Confidence Interval (CI) was 0.602-0.940), while the AUC for the quantitative RF was 0.673 (p value: 0.106 and the 95% CI was 0.465-0.88). Using Youden index the best cutoff value for serum COMP in seronegative patients was 8.9 U L^{-1}, which had a sensitivity of 58%. On the other hand using the same index the best cutoff value for RF was 7.35 IU mL^{-1}, which had a sensitivity of only 42%. When both COMP and quantitative RF were combined, a higher sensitivity of 83% was achieved. The current study has found a significantly elevated serum COMP in Egyptian patients with RA compared to controls. Furthermore serum COMP has a higher diagnostic performance in RA with low serum quantitative RF titer (seronegative patients). When both serum COMP and quantitative RF values were combined a better diagnostic sensitivity was achieved.

Key words: Cartilage oligomeric matrix protein (COMP), Rheumatoid arthritis (RA), C reactive protein (CRP), Rheumatoid factor (RF)

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INTRODUCTION

Rheumatoid Arthritis (RA) is the most common form of chronic inflammatory joint disease (Kiss *et al*., 2005). It is widely accepted that early detection of RA and therapeutic intervention are key elements in the prevention of joint damage (Shmerlig, 2005). The diagnosis of RA as well as evaluating its activity and severity can be made using various clinical, radiological and laboratory approaches (Khanna *et al*., 2005). The most commonly used clinical approaches are, the revised American College of Rheumatology (ACR) criteria for diagnoses of RA and the Disease Activity Score (DAS) for evaluating the activity of RA (Arnett *et al*., 1988). However, some of these criteria are frequently observed in diseases other than RA, such as infections and other rheumatic diseases (Mies Richie and Francis, 2003). Thus, the differential diagnosis of RA in a patient presenting with polyarthritis and fever can be a challenge (Khanna *et al*., 2005).

Rheumatoid factor (s) are naturally occurring autoantibodies with specificity for the Fc region of immunoglobulin (Jonsson *et al*., 1998) Rheumatoid Factor (RF) is commonly used to support the diagnosis of RA. However, several patients test negative for rheumatoid factor (Eggelmeijer *et al*., 1990). This together with a non classical clinical picture may represent a challenge for the diagnosis of RA (Mies Richie and Francis, 2003). Several acute-phase reactants such as C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR) have been evaluated previously as indicators for RA disease activity and progression (Wolfe, 1997). However, it is uncertain whether these markers are useful in predicting disease course in patients with early RA (Jonsson *et al*., 1998) On the other hand, quantification of radiographically detectable joint destruction is a prerequisite to measure damage progression in RA (Ory, 2003).

Cartilage Oligomeric Matrix Protein (COMP) is a 524-kDa pentameric glycoprotein, that was initially found in articular cartilage (Mörgelin *et al*., 1992),where also the corresponding mRNA was demonstrated (Wolfe, 1997). COMP is primarily observed in the proliferative region of the growth plate, where it is prominent pericellularly indicating a role in cell growth and matrix development (Hedbom *et al*., 1992). The function of COMP is not yet clear (Di Cesare *et al*., 2000), but its clinical importance is suggested by the finding that COMP was found elevated in patients with rapidly destructive RA and could be a predicting factor for the outcome of the disease (Wollheim *et al*., 1997). Furthermore it is a marker for early destruction of cartilage (Hedbom *et al*., 1992) and is claimed to be more sensitive than magnetic resonance imaging (MRI) or radiographs in the early stages (Nakamura., 2000). A recent study (Lindqvist *et al*., 2005) has found that serum levels of cartilage oligomeric matrix protein are elevated in RA, but not in inflammatory rheumatic diseases such as psoriatic arthritis, reactive arthritis, Raynaud's syndrome, scleroderma, systemic lupus erythematosus, vasculitis and Sjögren's syndrome. It was suggested that serum COMP may be useful as a prognostic marker of cartilage degradation in patients with established RA (Wollheim *et al*., 1997).

No data is available about the level of COMP in the RA patients in the Egyptian population. The present study aimed for measuring serum levels of COMP in the Egyptian patients with RA and evaluating the diagnostic performance of this test in comparison to serum quantitative rheumatoid factor and CRP values.

MATERIALS AND METHODS

Subjects included in this study were examined in the rheumatology department of Al-Amiry Alexandria University Teaching Hospital in the period between September 2004 and December 2005. A written informed consent was taken from all participants in the study. The current study included 2 groups: a control group, comprised 20 healthy subjects (16 women and 4 men) aged (mean±SD) 43.0±15.22 years and a group of patients, comprised of 30 rheumatoid arthritis patients (24 women and 6 men) aged 48.4±12.39 years. All subjects participating in the study had a detailed history taken with stress on the symptoms of RA especially, duration of disease, the number and the type of swollen joints. Both patients and subjects were weighed and their heights were recorded. For all patients included in the study, A Ritchie's Articular Index (RAI) and Disease Activity Scores (DAS) were calculated (Van der Heijde *et al*., 1993; Ritchie *et al*., 1968). Ritchie's articular index is a numerical measurement of joint tenderness in patients with rheumatoid arthritis. DAS was calculated using the RAI, Swollen Joint Count (SJC), ESR at first hour and Visual Analogue Scale (VAS).

$$DAS = 0.54*\text{sqrt}(RAI)+0.065*(SJC)+0.33*\text{Ln}(ESR) + 0.0072*(VAS)$$ [16]

An X ray on the hands was done for all patients and the Scott's modified Larsen score of disease activity was taken as a gold radiological standard for evaluation of the severity of joint damage (Scott *et al*., 1995). Larsen score was graded as follows; Grade 0: no changes found, grade 1 changed to include erosions/cysts<1 mm in diameter and grade 2 modified to include one or more erosions >1 mm, with a break in the cortical margin. Patients with acute infections, systemic lupus erythromatosus, mixed

connective tissue diseases, other collagenic diseases and patients with liver, heart or renal diseases were excluded from the study.

After 12 h fast, blood samples were taken for estimating serum levels of fasting blood glucose, creatinine, urea, uric acid, calcium, phosphorous and the activities of Serum Alkaline Phosphatase (SAP), alanine and aspartate transaminases (ALT and AST). These were measured using a Konelab auto-analyzer (Thermoelectron Corporation, Finland) (Burtis and Ashwood, 1999). Another blood samples were taken for complete blood count and erythrocyte sedimentation rate. Serum aliquots were also taken for quantitative determination of rheumatoid factor, C- reactive protein and serum COMP. Serum COMP was determined according to the manufacturer instructions using ELISA kit AnaMar Medical, Uppsala Sweden (Cat. Number 14-1006-71). The assay has a detection limit of 0.1 U L^{-1}. The intra assay CV was 1.8% and inter assay CV was 3% at a serum COMP level of 6.9 U L^{-1}, while at a serum COMP level of 18 U L^{-1} the intra assay CV was 1.7% and inter assay CV was 4.2%.

Statistical analysis: Comparison among the groups was conducted with the nonparametric Mann-Whitney U test. Data were analyzed for sensitivity and specificity derived from the Receiver Operating Characteristics (ROC) curve. For the choice of the optimal cutoff, receiver-operating curve analysis was constructed and the Youden index was calculated (Youden, 1950). The Youden index is defined as follows: (sensitivity+specificity)- 1. The best cutoff has the highest Youden index. Combining the serum COMP and quantitative rheumatoid factor was done where any sample was considered positive if its result for COMP and/or RF exceeded their best cutoff values. Normally distributed variables were expressed as Mean±SD while variables with non Gaussian distribution were expressed as median, range and 25 to 75 percentiles. The commercial statistical software package used was SPSS 11.0 (SPSS, Inc., Chicago, IL)

RESULTS

There was no significant age difference between patients with RA and the controls. The percentage of females was the same in the two groups. There were no significant differences between patients with rheumatoid arthritis and the controls regarding fasting serum glucose, urea, creatinine, uric acid, phosphorous or calcium and the activities of serum alkaline phosphatase and aminotransferases ($p>0.05$). As expected, patients with rheumatoid arthritis had a significantly higher reading of the first hour of ESR compared to the controls ($p<0.05$) (Table 1).

Table 1: Some clinical and biochemical characteristics of the groups enrolled in the study

Parameters	Controls (n:20)	Patients (n:32)
ESR mm(First hour)	17.6±7.53	35.67±20.27*
Hb (gm dL^{-1})	12±0.5	11.2±0.3
AGE (years)	43.0±15.22	48.4±12.39
Female percentage	80%	80.6%
Disease duration (years)	--------	8.30 ±8.45
DAS Score	--------	5.79±1.34
Ritchie Articular index (RAI)		37.17±16.59
BMI (Kg m^{-2})	27.3±3.71	29.90±4.57
Fasting plasma glucose (mmol L^{-1})	5.94±1.33	6.62±3.65
Creatinine (µmol L^{-1})	83.1±12.4	92.8±24.8
Urea (mmol L^{-1})	4.7±1.4	4.9±2.9
Uric acid (µmol L^{-1})	217.2±81.5	233.2±77
Calcium (mmol L^{-1})	2.33±0.1	2.29±0.11
Phosphorous (mmol L^{-1})	1.22±0.26	1.17±0.22
Serum Alkaline phosphatase (U L^{-1})	195.4±43.3	191.13±62.07
AST (U L^{-1})	16.50±4.55	27.267±22.44
ALT (U L^{-1})	20.15±9.01	29.30±25.06*

ESR: Erythrocyte sedimentation rate. Hb: haemoglobin. BMI: Body mass index. RAI: Ritchie Articular index. DAS: Disease activity score. AST: Aspartate aminotransferase, ALT: Alanine aminotransferase. Data are presented as mean±SD*: Significant difference versus the control group. $p<0.05$ was considered significant

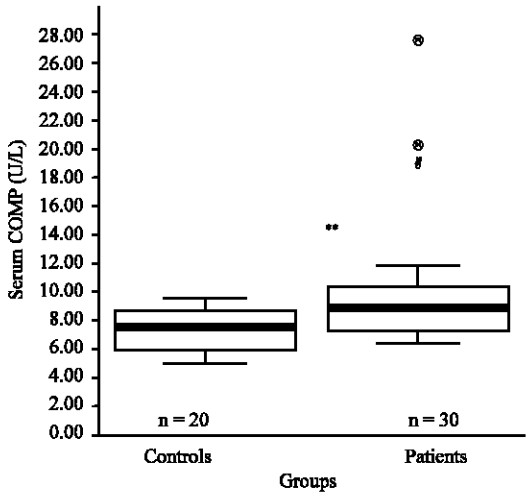

Fig. 1: Serum COMP in the studied groups Boxplots illustrate serum Cartilage Oligo Meric Protein (COMP U L^{-1}) in the control subjects and patients with Rheumatoid arthritis. The boxplots represent the interquartile range from the 25th to the 75th percentiles. The whiskers below and above the boxes represent the minimum and maximum values, respectively. The line across each box represents the median value. n = number of subjects included in each group. ** = Significant difference versus the healthy control group, $p<0.001$ ✌ = outliers (values larger than the upper quartile plus 1.5 times the interquartile range) ☹ = Extreme (values larger than the upper quartile plus 3 times the interquartile range)

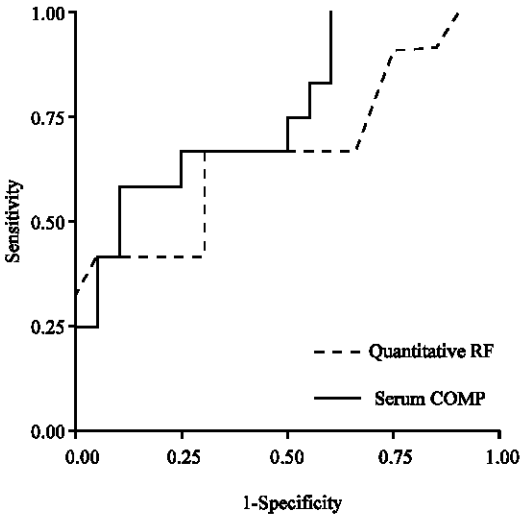

Fig. 2: Receiver operating characteristic curves (ROC) for serum COMP and quantitative Rheumatoid factor. Receiver operating characteristic curves were constructed by plotting the sensitivity versus 1-specificity at different cut off values for serum COMP and quantitative Rheumatoid factor in seronegative patients. Serum COMP showed a higher specificity and sensitivity compared to RF. The area under the curve (AUC) for the COMP was 0.771 (p-value: 0.011), while the AUC for the quantitative RF was 0.673 (p-value: 0.106).

Serum values of quantitative RF and quantitative CRP were significantly higher in patients with RA compared to the control group. The median (range) of quantitative RF was 5.45 (4.7-7.6) IU mL^{-1} in controls and 23.65 (4.9-638.4) IU mL^{-1} in RA patients. The median (range) of quantitative CRP was 3.65 (1.1-9.1) mg L^{-1} in controls and 5.8 (0.9-71.7) mg L^{-1} in patients with rheumatoid arthritis.

Serum COMP was significantly higher in RA patients than the control group ($p<0.01$). The median (range) of serum COMP was 7.49 (4.95-9.56) U/L in controls and 8.78 (6.41-27.3) U/L in RA patients (Fig. 1). Serum COMP did not correlate with neither modified Larsen scoring nor DAS.

To evaluate the diagnostic use of serum COMP compared with quantitative RF in patients with low serum RF values (seronegative for RF), ROC curves were constructed. Serum COMP has a superior diagnostic value in seronegative patients compared to quantitative RF. The Area Under the Curve (AUC) for the COMP was 0.771 (p-value 0.011 and the 95% Confidence Interval (CI) was 0.602-0.940), while the AUC for the quantitative RF was 0.673 (value: 0.106 and the 95% CI was 0.465 - 0.88) (Fig. 2). Using Youden index, the best cutoff value for COMP in seronegative patients was 8.9 U L^{-1}, which had a sensitivity of 58%. On the other hand using the same index the best cutoff value for RF was 7.35 IU mL^{-1}, which had a sensitivity of only 42%. When both serum COMP and quantitative RF were combined, a higher sensitivity of 83% was achieved.

DISCUSSION

Rheumatoid Arthritis (RA) is a potentially severe and crippling disease, early aggressive therapy is now widely advocated in the hope of improving the long-term outcome for patients (Gonzalez-Gay *et al*., 2005) This strategy carries the risk of exposure to toxic therapies in cases that may have a benign prognosis even without such therapy. The need for reliable early predictors of the course of disease is therefore increasing. Clinical features, early radiological changes and CRP are commonly used predictors (Ropes *et al*., 1958). In addition, the diagnosis of RA relies on certain clinical criteria and on the presence of positive serum RF (Wollheim, 2000). However, in certain patients seronegativity for the RF and the presence of equivocal clinical picture and history may delay the diagnosis of RA. Serum COPM is considered a unique marker that reflects the state of cartilaginous joints, which are the first to be affected in cases of RA (Schmidt-Rohlfing *et al*., 2002). The current study found a significantly elevated serum COMP in Egyptian patients affected with rheumatoid arthritis compared to control subjects. This finding is in keeping with other previous studies that evaluated serum COMP in rheumatoid patients from different ethnic populations. The high serum COMP may reflect an increased breakdown of joint COPM in rheumatoid arthritis by the effect of MMP (matrix metalloproteinases) enzymes (Stracke *et al*., 2000). Previous studies have found high level of MMP in the synovial fluid and serum of patients with RA (Andereya *et al*., 2005; Wislowska and Jablonska., 2005). Murphy *et al*., (2002) had found a significantly raised serum COMP in patients with chondromalacia and suggested that it could be used as a prognostic marker of the disease activity. Furthermore, the elevated serum COMP may reflect a state of synovitis in RA patients (Vilim *et al*., 2001), as synovial membrane is considered an important tissue source of COMP and may contribute to either synovial fluid or serum COMP levels (Di Cesare *et al*., 1997).

Currently clinical evaluation of patients with RA is performed by assessing the pain and mobility problems caused by the joint destruction and by quantifying measures of systemic inflammation in RA patients. Even though a number of standardized rating systems have

been introduced, it is difficult to quantify these parameters (Stucki and Langenegger 1997; Scott and Houssien 1996). At present radiological examination is the method of choice for obtaining information about joint-status and especially the progression of articular cartilage destruction in diseased joints of RA patients (Skoumal *et al*., 2003; Jansen *et al*., 2001). In the current study when seronegative patients were studied, serum COMP showed a superior diagnostic performance compared to RF. This may be attributed to the early release of COMP from the inflamed joint cartilages with subsequent increase in its level irrespective of the seropostivity for RF. Also it may be due to methodological limitation, as most assays for the determination of quantitative RF rely on the detection of anti-IgM antibodies in serum, thus it may possible that those patients with other types of RF (anti-IgA, anti-IgG) in serum may go missed and were classified as seronegative. On the other hand, the used assay for determination of COMP has a detection limit of 0.1 U L^{-1} and detects most of the isoforms of COMP in serum.

An important observation in this study is the lack of correlation between serum levels of COMP and serum levels of CRP, which indicates that serum COMP does not reflect the inflammatory component of the disease. Thus, generalized systemic inflammation do not influence COMP turnover to the extent that can affects serum concentrations. These results are concordant with those of Roux-Lombard *et al.* (2001) who conducted a study aiming to investigate the relationship between COMP and variables reflecting generalized inflammation as CRP, IL-6, IL-10, the IL-1 receptor antagonist IL-1Ra and others, the results showed lack of correlation between serum levels of COMP and the other variables. They concluded that COMP did not reflect the inflammatory CRP-related component of the disease and that COMP is a measure of tissue processes that are distinct from the acute-phase reaction. On the other hand treating patients solely with anti-inflammatories and following them up both clinically and by measuring conventional markers of inflammation, may be somehow miss leading as the signs and symptoms of inflammation may decrease together with laboratory markers of inflammation but still the under going process of joint destruction is taking place. Thus serum COMP may provide a distinguished marker that reflects cartilage structural without being biased by the anti-inflammatory given to nearly all patients.

Although the current study shed some light on the status of serum COMP in the Egyptian patients, still more studies are required to follow up our patients regarding the status of serum COMP and the degree of radiological damage over a long period of time. Furthermore the original COMP assay and the one used in the present study measure both intact and fragmented COMP, which limits the possibility of discriminating between increased COMP synthesis and thus cartilage turnover, from increased COMP degradation from destroyed cartilage. Refinement of the technology enabling specific measurement of select fragments will most probably increase the value of COMP as an early prognostic marker in RA.

Moreover, a recent study found a significant association between vitamin D gene polymorphism and the development of arthritis, thus evaluation of serum COMP and vitamin D gene polymorphism may be an important point to be investigated (Maalej *et al*., 2005).

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