Serum Levels of Hyaluronic Acid (HA) and Cartilage Oligomeric Matrix Protein (COMP). Predictors of Disease Progression in Rheumatoid Arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is a disease characterized by destruction of joint structures such as articular cartilage and bone. The pathogenic mechanisms responsible for tissue destruction are not well understood. The aim of the present study was to measure the serum concentrations of specific cartilage and bone molecules reflecting tissue turnover to investigate disease activity. The study included 30 rheumatoid arthritis (RA) patients with age range 42 – 66 years, sixteen patients were rapid erosive patients and fourteen were slow erosive, compared with 20 matched normal population with age range 40 – 63 years. All studied individuals were subjected to full history taking clinical examination and laboratory investigations including measurement of serum levels of cartilage oligomeric matrix protein (COMP), hyaluronic acid (HA), high sensitive C- reactive protein (CRP), erythrocyte sedimentation rate (ESR) and RF concentration, measurement of activity of RA by disease activity score (DAS) 28 joint counts. The study showed a significantly higher values of COMP, HA, CRP and ESR in slow erosive (P < 0.001) and rapid erosive (P <0.0001) RA patients when compared to controls. There were significantly higher values of COMP, HA, CRP and ESR in rapid erosive RA patients compared to slow erosive RA patients. A significant positive correlation between serum levels of COMP and HA and age, disease duration, Larsen score, DAS and CRP and ESR was found. Also, there was a significant positive correlation between serum levels of COMP and HA (r = 0.674, P <0.01). It could be concluded that the measurement of some serological biomarkers that reflect bone and cartilage destruction in RA patients, could be used to investigate disease activity and increase the knowledge of the basic pathophysiology of joint disease.

INTRODUCTION

Arthritis is a longstanding, debilitating disease that results in serious sequel on the population. It causes pain, impairment, and disability in patients with increasing injury to the cartilage, synovium and bone of the affected joints [1].

Existing methods to diagnose and to monitor the disease are based on late clinical manifestations of arthritis. However, with recent development of successful treatments for rheumatoid arthritis and osteoarthritis, it becomes important to identify prognostic factors that can predict the evolution of arthritis. This would be of most

value in the early phases of the disease so that treatments could be started rapidly to help slow down progression of the disease [1].

A possible approach to monitor arthritis is the measurement of biological markers of cartilage repair and degradation to reflect variations in joint remodeling. One such potential biological marker of arthritis is cartilage oligomeric matrix protein (COMP)[2].

COMP is also known as thrombospondin 5. It is a 524 kDa homopentameric extracellular matrix glycoprotein member of the thrombospondin family of calcium-binding proteins with five identical subunits [3&4].

The function of COMP remains unclear, but it may have a structural role in endochondral ossification and in the assembly and stabilization of the extracellular matrix by its interaction with collagen fibrils and matrix components [5&6].

COMP was first detected in the serum and the synovial fluid of patients suffering from rheumatoid disorders, such as RA, reactive arthritis, juvenile chronic arthritis, and osteoarthritis (OA)[7]. Serum concentrations of COMP are initially elevated in patients with early RA who later develop extensive joint destruction. This suggested that disease pathogenesis is characterized by abnormal turnover of that protein in these patients [8].

Hyaluronic acid (HA), is a glycosaminoglycan formed from alternating units of N- acetyl glucosamine and glucuronic acid[9]. It is a constituent of synovium and cartilage and is thought to contribute to the lubricating mechanisms of synovial fluid. Local increased production of HA has been demonstrated in inflamed synovium from patients with RA, osteoarthritis (OA), ankylosing spondylitis, and reactive arthritis[10].

Serum levels of HA have been shown to be increased in individuals with liver disease[11], cancer[12], hypothyroidism[13], amyloid-associated arthropathy[14], OA[15], and psoriasis with or without arthropathy[16].

The aim of the present study was to measure the serum concentrations of specific cartilage and bone molecules reflecting tissue turnover to investigate disease activity.

SUBJECTS & METHODS

The study included 50 subjects; they were classified into 2 main groups:
Group A:

It included 30 rheumatoid arthritis patients, who all fulfilled the American College of Rheumatology (formerly, the American Rheumatism Association) 1987 Criteria for RA [17], with age range 42–66 years, it included 18 females and 12 males. The median disease duration is 1.4 years (range 0.2-2.7 years), disease onset was defined as the time of onset of joint symptoms according to history at the initial visit to the department. It is subdivided into 2 subgroups according to radiographic examination using the Larsen method according to **Petterson**[18]

Group IA:

It included sixteen patients who developed significant erosive disease

of the knee joints (rapid erosive group)

Group IIA:

It included fourteen patients without rapidly progressive disease (slow erosive group).

Group B (control group):

It included 20 age and sex matched healthy volunteers. It included 11 females and 9 males with age range 40–63 years.

All patients were attendants of the Rheumatology Department of Minoufia University Hospital in the period from February 2008 to May 2009.

Patients with liver diseases, hypothyroidism, chronic renal diseases, OA and psoriasis were excluded from the study.

The following measures were recorded for RA patients: number of swollen joints, number of tender joints, patient's assessment of pain on a visual analogue scale (VAS) and patient's assessment of disease activity on a VAS. Disease activity score (DAS) were calculated with assessment of swollen and tender joints using 28-joint counts [19].

Radiographic examination:

Hands, wrists and feet of the 30 RA patients were examined radiographically. The radiographs were graded by the same radiologist without knowledge of clinical data using the Larsen method modified according to **Pettersson** [18&20]. That method is based on comparisons with standard radiographs, where 0 denotes a radiographically normal joint and 5 denotes the one with maximum degree of joint destruction. A theoretical range of values from 0 to 200 were used to grade these joints.

All patients and controls were subjected to full history taking, clinical examination and laboratory investigations including measurement of serum levels of COMP, HA, ultrasensitive C- reactive protein (CRP), erythrocyte sedimentation rate (ESR) and determination of rheumatoid factor titer.

Sample collection and assay:

5 ml of venous blood were collected from all fasting subjects into a plain tube, let to stand to clot and serum was separated in aliquots after centrifugation and stored at -70° until analysis of the following parameters: HA using an enzyme-linked binding protein assay that uses a capture molecule known as hyaluronic acid binding protein (HABP) [21]. Serum COMP levels was measured by enzyme-linked immunosorbent assay (ELISA)[22].

Erythrocyte sedimentation rate (ESR) was determined according to Westergreen method and ultrasensitive CRP assay by using latex enhanced immunoturbidimetric assay. Serum CRP causes agglutination of the latex particles coated antihuman CRP, the agglutination of the latex particles is proportional to CRP concentration [23]. Rheumatoid factor titer was determined using RF-latex which is a slide agglutination test for the qualitative and semiquantitative detection of RF in human serum. Latex particles coated with human gamma globulin are agglutinated when mixed with samples containing RF[24].

Statistical analysis:

The data were statistically analyzed by SPSS 14 software

package. Differences between groups were calculated using Mann-Whitney's test for unpaired variables. Differences between three groups were compared by means of ANOVA test. Correlations between variables were calculated by spearman's correlation coefficient. P values <0.05 were considered significant. Assessment of optimal cut off points was done by using receiver operating characteristic (ROC) curve analysis[25].

RESULTS

Table (1): Serum levels of HA, COMP, CRP and ESR in RA patients (group A) and controls(group B)

Parameters	RA patients (group A) X± SD	Control (group B) X± SD	P
HA**(ng/ml)**	142± 5.6	30.7±4.5	**<0.001**
COMP**(µg/ml)**	28± 4.6	11.7±1.1	**<0.001**
CRP**(mg/l)**	40.6 ± 5.6	2.6 ±0.1	**<0.001**
ESR**(mm/1h)**	18 ±3.4	10.9±1.87	**<0.001**

hyaluronic acid (HA), cartilage oligomeric matrix protein (COMP), erythrocyte sedimentation rate (ESR), ultrasensitive CRP.

There are significantly higher values of HA, COMP, CRP and ESR in RA patients when compared to controls.

Table (2): Characteristics of patients

	Slow erosive group Group11A X± SD	Rapid erosive group Group 1A X± SD	P
Number of patients (female/ male)	14 (8/6)	16 (10/6)	>0.05*
Age at disease onset (years)	59 ±5.6	47 ± 6.7	**< 0.001**
Duration of disease (years)	2.9± 0.96	2.3± 0.75	>0.05
RF positivity no. (%)	9 (64.3%)	12 (75%)	>0.05*
Radiographic index (Larsen score: 0-200))	6.9± 1.7	30.8± 3.6	**< 0.001**
disease activity score (**DAS) (0-10)**	3 ± 0.2	3.2± 0.5	>0.05

* by Chi square test

There are no significant differences in the number of patients, gender, duration of RA disease, DAS and RF status. However, there is a significant difference as

regarding the age of the patients, also the patients who had rapid erosion have a significant higher Larsen score than those with slow erosion.

Table (3): Serum levels of HA, COMP, CRP and ESR in the slow erosive RA patients and controls.

	Control group (n=20) X± SD	Slow erosive group (n=14) X± SD	P
HA (ng/ml)	30.7± 4.5	45.3±5.6	**< 0.001**
COMP (µg/ml)	11.7±1.1	16.83±1.5	**< 0.001**
CRP (mg/l)	2.6±0.1	8.5±**0.3**	**< 0.001**
ESR (mm/1h)	10.9 ± **1.87**	20.41±**2.18**	**< 0.001**

There are significantly higher values of HA, COMP, CRP and ESR in slow erosive RA patients compared to controls.

Table (4): Serum levels of HA, COMP, CRP and ESR in the rapid erosive RA patients and controls.

	Control group (n=20) X± SD	Rapid erosive group (n=16) X± SD	P
HA (ng/ml)	30.7± 4.5	175.7± 25.2	**<0.0001**
COMP (µg/ml)	11.7±1.1	32.8 ±3.1	**<0.0001**
CRP (mg/l)	2.6±0.1	58 ±6.2	**<0.0001**
ESR (mm/1h)	10.9 ± **1.87**	52±**4.1**	**<0.0001**

There are significantly higher values of HA, COMP, CRP and ESR in rapid erosive RA patients compared to controls.

Table (5): Serum levels of HA, COMP, CRP and ESR in the rapid erosive and slow erosive RA patients group.

	Slow erosive group (n=14) X± SD	Rapid erosive group (n=16) X± SD	P
HA (ng/ml)	45.3±5.6	175.7± 25.2	**<0.01**
COMP (µg/ml)	16.83±1.5	32.8 ±3.1	**<0.0001**
CRP (mg/l)	8.5±**0.3**.	58 ±6.2	**<0.001**
ESR (mm/1h)	20.41±**2.18**	52±**4.1**	**<0.001**

There are significantly higher values of HA, COMP, CRP and ESR in rapid erosive compared to slow erosive RA patients

Table (6): Relationship between serum levels of COMP and HA and disease-related characteristics.

	HA(ng/ml)		COMP(µg/ml)	
	X± SD	P	X± SD	P
Duration of disease:				
- less than 2 years	43±**4.1**	< 0.001	15±**1.1**	<0.001
- more than 2 years	145±12.1		25.6±2.2	
Larsen score:				
- least erosive disease	52.3±**6.1**	< 0.001	16.3±**2.1**	
- more erosive disease	163.6±**20.3**		27.6±**2.3**	<0.001
DAS:				
- mild	15.6±0.3	F value	12.8±**1.2**	F value
- moderate	36.4±1.9	(21.4)	20.4±2.1	(9.3)
- high	156.7±**12.3**	<0.001*	30.3±3.4	<0.01*
RF status:				
- RF seropositive	57.3±**8.8**	>0.05	18.5±4.7	>0.05
- RF seronegative	52.7±**7.9**		16.3±4.1	

***** *By ANOVA test, disease activity score (**DAS**), rheumatoid factor (RF)*

There are significantly higher values of COMP and HA in RA patients with disease duration more than 2 years, in more erosive Larsen patients group and in high more than moderate and mild DAS. However, There are no significant differences in the serum levels of COMP and HA in RF seropositive and RF seronegative patient groups.

Table (7): Correlations between serum concentration of COMP, HA and patient characters, CRP and ESR.

	HA (ng/ml)		COMP (µg/ml)	
	r	P	R	P
Age of patients (years)	0.524	< 0.05	0.542	< 0.05
Disease duration (years)	0.546	< 0.05	0.283	< 0.01
Larsen score	0.526	< 0.05	0.591	< 0.01
DAS	0.627	<0.01	0.563	< 0.01
CRP **(mg/l)**	0.537	< 0.05	0.272	< 0.01
ESR **(mm/1h)**	0.614	<0.01	0.524	< 0.05

There are significant positive correlations between serum levels of COMP and HA with age, disease duration, Larsen score, DAS, CRP and ESR.

Table (8): Correlation between serum concentrations of COMP and HA in the patients group.
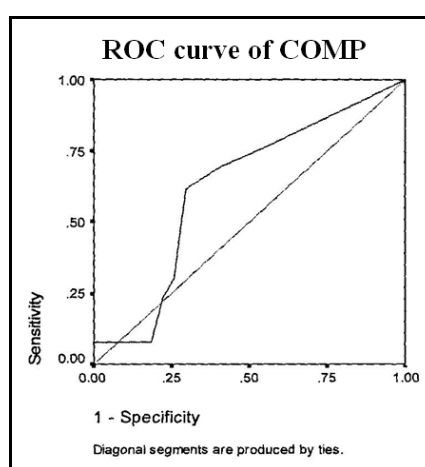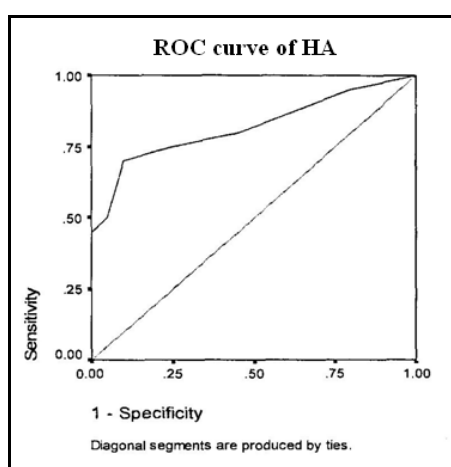
HA (ng/ml)		
	R	**P**
COMP (µg/ml)	0.674	<0.01

correlation coefficient (r)

There is significant positive correlation between serum levels of COMP and HA.

Table (9): Cutoff values, specificity and sensitivity of COMP and HA in RA patients.

	COMP(µg/ml)	HA(ng/ml)
Cutoff	15.17	60
Sensitivity	72.6%	42.6%
Specificity	79%	71.1%

DISCUSSION

Rheumatoid arthritis (RA) is a disease characterized by destruction of joint structures such as articular cartilage and bone[2]. The pathogenic mechanisms responsible for tissue destruction are not well understood[26]. Furthermore, it is not clear why joint destruction progresses very slowly in some patients and causes little tissue derangement, whereas in others extensive destruction occurs within a few years after disease onset [27&2].

The use of immunoassays for the quantification of cartilage and bone molecules which enter the circulation as part of tissue turnover that occur in RA, has reflected the changes in the metabolism of extracellular matrix in these tissues [27].

The present study demonstrated that there are no significant differences in the number of patients, gender, duration of RA, DAS and RF status in the rapid erosive and the slow erosive patient groups. However, there is a significant difference as regard the age of the patients, also the patients who had rapid erosion have a significant higher Larsen score than those with slow erosion.

Majeed et al. and Young et al.[28&29], have reported that there were no significant differences in gender, age of patients, disease duration, RF positivity and DAS. However, the patients with radiographic progression had a higher Larsen score.

The present study demonstrated a significant increase in serum levels of HA in RA patients compared with control group, using cut off point of 60 ng/ml, test sensitivity was 42.6% and specificity was 71.1%. The levels of HA were higher in the rapid erosive group than in the slow erosive group, these results agreed with those of **Santos et al. and Majeed et al.** [30&28] who suggested that an increased systemic level might act as an early indicator of structural damage and hence provide a useful prognostic marker.

Elliott et al. [15] have reported that HA is produced locally by cells of the ECM, degradation and turnover of the ECM result in release of HA and HA fragments into the systemic circulation. Increased production and release of HA from arthritis joints are thought to reflect the localized inflammation of synovial lining and, to a lesser extent, to cartilage degradation.

Chubinskaya et al. [30] have postulated that levels of HA were higher in RA patients than in asymptomatic donors. These results, also, go with those of **Pothacharoen et al.** [32] who suggested that RA may be detected systemically according to these results.

In the current study, RA patients showed a significant increase of COMP compared with the control group, using a cut off value of 15.17 μg/ml, test sensitivity was 72.6% and specificity was 79%.

The levels of COMP were higher in the rapid erosive group than in the slow erosive group, these results agreed with those of **Poole et al.** and **Bengt et al.** [33&27]

Galeotti et al. [34] have reported that there is a significant increase in COMP serum levels in adult RA compared to age- and gender-matched controls having no inflammatory disease.

Morozzi et al. [7] demonstrated that increased levels of COMP in RA could be used as a potential marker for measuring articular cartilage damage. These results were similar to those reported by **Skoumal et al. and Posey and Hecht** [35&6], who found that increased serum levels of COMP in RA patients reflect increased cartilage turnover.

Also, **Syversen et al.** [2] have reported that COMP and other cartilage and bone biomarkers will serve as more useful prognostic markers than current predictors such as anti-cyclic citrullinated peptide (ACCP), radiographic damage early in the disease course, and signs of inflammation.

The present study demonstrated a significant increase in serum levels of CRP and ESR in RA patients compared with control group. The levels of CRP and ESR were higher in the rapid erosive group than in the slow erosive group, these results agreed with those of **Bengt et al. and Majeed et al.** [27&28]

In the current study, significant positive correlations between serum levels of HA and age of the patients at disease onset, disease duration, DAS and Larsen score were detected, in accordance to results reported by **Emlen et al.**[36]

In the current study, a significant positive correlation was detected between serum levels of HA and ESR and CRP as recorded by **Bengt et al.**[27], a finding which supports a connection between joint and systemic inflammation.

Majeed et al.[28] demonstrated that HA serum levels are correlated with measures of disease activity including swollen joint count, tender joint count and pain VAS. However, there is a strong positive correlation with laboratory indices of disease activity (ESR and CRP) rather than with the clinical indices of the disease.

In the current study, significant positive correlations between serum levels of COMP and age of the patients at disease onset, disease duration, DAS and Larsen score were detected. These results agreed with those of **Wislowska and Jablonska,** [37] who reported that serum COMP levels were correlated to the age of RA patients and DAS value.

Marti et al. [38] have reported that a high clinical disease activity (DAS) was correlated with high COMP

values in serum and synovial fluid and with increasing proteolytic activity. An increased turnover of cartilage matrix in joint inflammation might explain that correlation.

These results agreed also with those of **Skoumal et al. and De Jong et al.**[35&39] who found positive correlations between serum levels of COMP and Larsen score and DAS. These results, also, paralleled those of **Lindqvist et al.** [40] who reported that serum levels of COMP were significantly elevated in patients whose RA progressed radiographically compared with those whose disease remained radiographically stable, and levels correlated with radiographic progression.

In the current study, significant positive correlations between COMP and ESR and CRP were detected. These results, also, go with those of **Momohara et al.; Soderlin et al. and Fujikawa et al.** [41,42&43] who reported that serum COMP levels correlated with ESR and CRP, which are indicators of the acute-phase response, these findings suggest that serum COMP levels may reflect cartilage destruction..

In the current study, There are significantly higher values of COMP and HA in RA patients with disease duration more than 2 years, in more erosive Larsen group patients and in high more than moderate and mild DAS. However, there are no significant differences in the serum levels of COMP and HA in RF seropositive and RF seronegative patient groups.

Momohara et al.[41] have postulated that COMP serum levels of

the patients with least erosive disease (LES) group were significantly lower than those of the patients with more erosive disease (MES) group. **Young-Min et al.[29]** have reported that increased COMP serum levels in RA patients are correlated significantly with radiographic progression of the disease, which indicate that COMP is a useful predictor of radiographic progression in RA.

Majeed et al. [28] found that no significant difference was found in HA serum levels between RF seropositive and RF seronegative patients.

A significant positive correlation between serum levels of HA and COMP was found in the present study, a similar result was reported by **Bengt et al.[27]**

Serum COMP was found to be a specific marker for the cartilage degradation in RA and not related to the nonspecific inflammatory process, as there was a significant difference in levels when compared to patients with other inflammatory rheumatic diseases with less cartilage-destructive arthritis [44].

Consequently, it could be concluded that the measurement of some serological biomarkers that reflect bone and cartilage destruction in RA patients (COMP and HA) could be used to investigate disease activity and increase the knowledge of the basic pathophysiology of joint disease. These observations draw attention to the fact that the measurement of cartilage derived macromolecules could be used for prognostic purposes and in therapeutic studies.

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حامض الهيالورنيك و بروتين النسيج الغضروفى كمؤشرات لتطور مرض الروماتويد المفصلى

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يعتبـر مـرض الروماتويـد المفصـلى واحدا مـن أهـم الأسـباب التـى تـؤدى الـى تلـف المفاصـل و الغضاريف و حتى الأن لم يتم التوصل الي التغيرات المرضية المصاحبة له.

يهدف هذا البحث لتقييم مستوى بعض نـواتج التكسير النـاتجة مـن الغضـروف واستخدامها كمؤشر لتحديد مدى تطور المرض فى مرضى الروماتويد المفصلى ومدى علاقتهم بنشاط المرض ومقارنتهم بأناس طبيعيين .

أجريت هـذه الدراسـة علـى خمسـين شـخص تـم اختيـارهم فـى أعمـار متقاربـه وتـم تقسيمهم إلـى مجمـوعتين المجموعـة الأولـى (أ) وتشمل ٣٠ مريضـا مصـابا بالروماتويد المفصلى وتـم تقسيمها إلـى مجمـوعتين- الأولى (١أ) : شملت ١٦ مريضـا مصـابين بمرض الروماتويد المفصلى ذو تأكل سـريع- المجموعة (٢أ) : شملت١٤ مريضا مصـابين بمرض الروماتويد المفصلى ذو تأكل بطئ . والمجموعـة الثانية: شملت ٢٠ شخصا طبيعيين كمجموعة ضابطة .

وقـد أظهـرت نتـائج الدراسـة وجـود زيـادة ذات دلالـه إحصـائية فـى نسـبة حـامض الهيالورونيك وبروتين النسيج الغضروفى وبروتين سى المنـاعى النشط وسرعة الترسيب فى مجموعـة المرضـى مقارنه بالمجموعة الضابطة وكذلك وجود زيادة ذات دلاله إحصائية فى هذه الدلائل فى مرضـى التآكل السريع مقارنه بمرضى التآكل البطئ .

ويمكن الاستنتاج بـأن قيـاس هـذه الـدلائل يمكـن أن تسـتخدم كمؤشـر لتـدهور مـرض الروماتويـد المفصلى وأيضا استخدامها كمؤشرات للاستجابة العلاجية .