Early Diagnostic and Prognostic values of Anti-Cyclic Citrullinated Peptide Antibody and Cartilage Oligomeric Matrix Protein in Rheumatoid Arthritis

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This study aimed to evaluate the role of Anti-Cyclic Citrullinated Peptide (anti-CCP) antibody in comparison to Cartilage oligomeric matrix protein (COMP) in Rheumatoid Arthritis (RA) patients as predictors of the disease activity and cartilage destruction. The study included 60 patients &10 apparently healthy subjects. They were divided into 4 groups. Group I*:* consisted of 20 patients with established rheumatoid arthritis(and positive rheumatoid factor)Group 2: 20 suspected (rheumatoid factor negative) patients Group 3: 20 patients with other autoimmune inflammatory diseases (15 with psoaritic arthritis, 5 with systemic lupus erthromatosis).and Group 4: 10 age and sex matched controls. For each patient medical examination and disease activity evaluation using Disease Activity Score (DAS) was performed Anti cyclic citrullinated peptide (anti CCP) level was measured by ELISA method and cartilage oligomeric matrix protein (COMP) was determined by indirect immune fluorescent method. Serum level of anti CCP antibodies and COMP were Significantly related to DAS (disease activity score) and cartilage destruction, the serum presence of COMP was highly significant in rheumatoid arthritis patients than those with other autoimmune disease, the sensitivity of anti CCP in diagnosis of RA was 77.5 % and specificity was96.6%. It is concluded that anti CCP, and COMP may be a useful noninvasive markers for disease activity and cartilage destruction.

Rheumatoid arthritis (RA), the most commonly occurring form of inflammatory polyarthritis, and inflammation can affect any organ or area of the body other than joints including pericarditis and pleuritis. Sjogren's syndrome (Inflammation of the gland of the eye and mouth cause dryness of these areas) Felty's syndrome (Enlarged spleen, decrease white cell) and vasculitis (Inflammation of blood vessel). It is prevalent in approximately 0.8% of adults worldwide. Approximately 1.3 million adults in the United States have been diagnosed with RA. If untreated, 20%–30% of RA patients become so severely debilitated within the first three years following initial diagnosis that they become permanently disabled (Rindfleisch & Muller, 2005).

Autoantibodies are common and characteristic feature of rheumatic autoimmune disease and it have proven to be extremely useful as diagnostic tool and indicator of the disease activity (Staikova *et al.,* 2003).

Rheumatoid factor (RF) is an autoantibody that react with Fc portion of IgG. It can be detected in 60-80% of patient with rheumatoid arthritis however the specificity of RF is inferior to that of other auto antibody used in diagnosis (Sharif *et al.,* 2005).

Anti cyclic citrullinated peptide (Anti CCP) is an auto antibody that is proven to be highly specific and sensitive autoantibody in rheumatoid arthritis. Citrulline is nonstandard amino acid created by deamination of arginine residue in several protein by the action of peptidyl arginine deaminase (PAD) enzyme. There are several isotype of this enzyme. In inflammatory rheumatoid arthritis PAD2, PAD4 are abundant. These enzymes cause local citrullination of synovial protein. Interestingly citrullinated peptide fit better in

(HLA-DR4) antigen binding groove than the corresponding arginine containing peptide. Citrullinated extra cellular fibrin in the rheumatoid arthritis synovium is one of the autoantigens driving immune response suggesting discovery of local production of anti CCP then diffuse into the patient serum (Van Gaalen *et al.,* 2004).

IgM RF is the best known serological marker, Sensitivity of anti-CCP is close to that of RF with a higher specificity for distinguishing RA from other rheumatic diseases (Avouac *et al.,* 2006).

Cartilage oligomeric matrix protein (COMP) is a new serum marker for assessing degree of muscle and joint destruction. It is glycoprotein component of articular cartilaginous matrix degraded by the disease Protein filament are produced and diffuse into the joint fluid then subsequently appear in the circulation (Carl *et al.,* 2010). Numerous studies in human and experimental arthritis clearly indicate that the assessment of COMP levels both in serum and synovial fluid, provide important information about metabolic changes occurring in the cartilage matrix in joint disease that permits early establishment of the degree of cartilage damage and destruction in RA (Skoumal *et al.,* 2003).

The aim of the work is to assess the diagnostic and prognostic values of anti CCP and COMP in RA patients. We compared serum presence of circulating COMP, and anti-CCP levels in relation to imaging and clinical findings in rheumatoid arthritis patients and inflammatory arthritis.

Subjects and Methods

This study was carried out at Microbiology and Immunology Department, Benha Faculty of medicine and Rheumatology Department, at Benha University Hospital, in the period between April 2011 and February 2012. A written informed consent (in Arabic language) was obtained from the patients before participation

This study included 70 individuals, 60 patients from those attending the outpatient clinic and inpatient of Rheumatology Department at Benha University Hospital, they include 54 females and 6 males. Their ages ranged from 35-55 years and, 10 apparently healthy subjects as a control group (7 females, 3males) The ages of the control group ranged between 35-45 years. The studied individuals were divided into 4 groups. Group I*:* consisted of 20 patients with established rheumatoid arthritis (and positive rheumatoid factor) Arnett, *et al,* 1988 they were 18 females and 2 males. Group 2: 20 suspected (rheumatoid factor negative) patients they were 18 females and 2 males. Group 3*:* 20 patients with other autoimmune inflammatory diseases (15 with psoaritic arthritis *(*Helliwell & Taylor 2005), 5 with systemic lupus erthromatosis) (Hochberg, 1997) they were 18 females and 2 males. Group 4: (control group) 10 age and sex matched controls they were 7 females and 3 males. For each patient complete history was taken (family, present and past), complete examination was done (general and rheumatologic), disease activity evaluation using Disease Activity Score (DAS) was performed (Heijde *et al.,* 1990) and Radiological investigation: plain x-ray for all patients to detect destruction and erosion (Larsen, 1995).

Specimens

Three ml of blood was withdrawn from the patients and controls under complete aseptic condition. They were divided to detect levels of anti-cyclic citrullinated peptide (anti CCP) and cartilage oligomeric matrix protein (COMP).

Detection of serum level of anti CCP

The detection of anti-CCP antibody was done by ELISA method. The test utilizes microtitre plate wells coated with citrullinated synthetic peptides (antigen). lmmunoscan CCPlus® test kit EURO-DIAGNOSTICA. Sweden. The diluted patient serum (10 µL of patient serum is added to 490 µL of dilution buffer) is applied to the wells and incubated. In presence of specific antibodies, they would bind to the antigen in the wells. Unbound material was washed away and any bound antibody was detected by adding horse radish peroxidase (HRP) labeled anti-human IgG, followed by a second washing step and incubation with substrate. The presence of reacting antibodies would result in the development of color, which was proportional to the quantity of bound antibody, and this was determined photometrically at 450 nm (Vossenaar & Venrooij, 2004).

Detection of serum presence of COMP

Test System is based on the indirect fluorescent antibody technique. Primary polyclonal anti-COMP antibodies (Abcam Plc 330 Cambridge science park, Cambridge, UK) overlaid onto HEp-2 cells grown on a microscope slide (ANAFLOUR, DiaSorin, USA), then patient serum samples diluted in buffer were added. If specific protein antigens were present in the serum, stable antigen-antibody complexes would form. These complexes bind fluorescein labeled antihuman immunoglobulin. The resultant positive reaction was observed as apple-green fluorescence of the nuclei when viewed with a properly equipped fluorescence microscope (LEITZ Germany) (Lui *et al.,* 2006).

Statistical Analysis

The collected data were tabulated and analyzed using SPSS version 16 soft ware. Categorical data were presented as number and percentages while quantitative data were expressed as mean and standard deviation. Chi square (X^2), student "t", Mann Whitney U test, ANOVA and spearman's correlation coefficient were used for correlation studies. Levels of anti CCP were found to be non-parametric so, non parametric tests are used for any analysis involving it. (P <0.05 is considered significant).

Results

There was no significant difference in age and sex distribution among the studied patients. But there was significant difference in family history of RA (Table 1).

Table 1. Description of the studied groups according to age, sex and family history of RA

		Group 1 established rheumatoid arthritis (RF+)		Group 2 suspected rheumatoid arthritis (RF-)		Group 3 patients with other autoimmune diseases		Group 4 control group		*P* value
		No	%	No	%	No	%	No	%	
Male		2	10	2	10	2	10	3	30	NS
Female		18	90	18	90	18	90	7	70	
Family history of RA	negative	4	20	7	35	20	100	10	100	<0.001
	Positive	16	80	13	65	0	0	0	0	
Age		Mean ± SD		Mean ± SD		Mean ± SD		Mean ± SD		ANOVA
		45.4±8.617		42.7±7.4417		40.95±7.33		40±6.1464		NS

P>0.05 is not significant (NS).

According to clinical rheumatologic examination all patients(100%) in group 1,2(RF+, RF-) had morning stiffness, 10% of patients in group 3 had morning stiffness, 95% of Patients in group 1(RF+) and 90% of patient in group 2 (RF-) had joint swelling, all patients in group 1,2 (RF+, RF-) had Limited movement (100%) and only 40% of patients in group 1(RF+) had Rh nodule, 35% of Patient in group 1(RF+)and 10% of patients in group 2(RF-) had deformity (Table 2).

RF was positive in 24 patients, including all patients of group 1 (20 patients), 3 patients in group3 (2 patients with psoriasis & one SLE patient and one of the control group was RF+

Table 2. Distribution of the studied groups according to clinical data

Clinical data		Group 1 established rheumatoid arthritis (RF+)		Group 2 suspected rheumatoid arthritis (RF-)		Group 3 patients with other autoimmune diseases		Group 4 control group		*P* value
		No	%	No	%	No	%	No	%	
Morning stiffness	Absent	0	0	0	0	18	90	10	100	<0.001
	Present	20	100	20	100	2	10	0	0	
Swelling	Absent	1	5	2	10	20	100	10	100	<0.001
	Present	19	95	18	90	0	0	0	0	
Limited movement	Absent	0	0	0	0	20	100	10	100	<0.001
	Present	20	100	20	100	0	0	0	0	
Rh nodule	absent	12	60	20	100	20	100	10	100	<0.001
	Present	8	40	0	0	0	0	0	0	
Deformity	Absent	13	65	18	90	20	100	10	100	<0.001
	Present	7	35	2	10	0	0	0	0	

P<0.05 is significant.

To study the relation between serum level of anti CCP and DAS among the patients of (group 1,2), patients in group 1,2 were divided according to DAS in to three groups low, moderate and high & there were Significant relation between DAS (disease activity score) and serum level of anti CCP antibodies (Table 3).

Comparison between serum presence of COMP in of patients of group 1 and group 3 was performed & it we found that there was significant difference between serum presence of COMP between group 1 and group 3 (Table 4).

To study the relation between COMP and DAS among the patients of (group 1,2), patients in group 1,2 were divided according to DAS in to three groups low, moderate and high & there were Significant relation between DAS (disease activity score) and presence of COMP (Table 5).

Table 3. Relation between anti CCP and DAS among the studied sample group 1(established rheumatoid arthritis (RF+) group 2 suspected rheumatoid arthritis (RF-)

DAS	N	Anti CCP (Mean±SD)	*P value
Low	12	100.2±161.5	<0.001
moderate	17	281.4±423.3	
High	11	2117.3±1505.2	
Total	40	731.9±1189.3	

Disease activity evaluation using Disease Activity Score (DAS) (Heijde et al., 1990). The DAS includes the following:- □ Richie articular index (RAI). □ Number of swollen joints out of 44 joints (NSJ44). □ Erythrocyte sedimentation rate (ESR). □ Pain severity determination on a visual analogue scale (VAS). The DAS is calculated using the following formula:-DAS= 0.54 (vRAI) + 0.065 (NSJ44) + 0.33 (in ESR) + 0.0072 (VAS).The DAS has a continous scale ranging from 0-10. The level of disease activity can be interpreted as follows:- Low = 2.4, Moderate > 2.4- 3.7, High > 3.7 *P<0.05 is significant

Table 4. Comparison between presence of COMP in group 1 and group 3.

COMP		groups		Total
		Group 1 established rheumatoid arthritis (RF+)	Group 3 patients with other autoimmune diseases	
negative	Count	8	15	23
	% within groups	45.0%	75.0%	57.5%
positive	Count	12	5	23
	% within groups	60.0%	25.0%	42.5%
Total	Count	20	20	40
	% within groups	100.0%	100.0%	100.0%
*P value		0.025		

*P< 0.05 is significant

Table 5. Relation between COMP and DAS among the studied sample group 1(established rheumatoid arthritis (RF+), group 2 (suspected rheumatoid arthritis (RF-).

DAS		COMP		Total
		Negative	Positive	
Low	Count	8	1	9
	% within COMP	47. %	4.4%	22.5%
Moderate	Count	7	10	17
	% within COMP	41.1%	43.5%	42.5%
high	Count	2	12	14
	% within COMP	11.7%	52.1%	35.0%
Total	Count	17	23	40
	% within COMP	100.0%	100.0%	100.0%

The mean & SD of serum level of anti CCP in patients of (group 1, 2) with negative cartilage destruction were 72.17 & 179.96 respectively, while the mean ± SD of serum level of anti CCP in patients of (group 1, 2) with positive cartilage destruction were 1719.88 & 1385.36 respectively, so there is significant relation between serum level of anti CCP antibodies and cartilage destruction among the studied groups 1, 2 (Table 6).

There is significant relation between COMP and cartilage destruction among the studied groups 1, 2 (Table 7).

Table 6. Relation between anti CCP and cartilage destruction among the studied groups (group 1,2)

Variable	Cartilage destruction –VE (Mean±SD) (N= 24)	Cartilage destruction +VE (Mean±SD) (N= 16)	*P value
anti CCP	72.17±179.96	1719.88±1385.36	<0.001

group 1 (established rheumatoid arthritis(RF+), group 2 (suspected rheumatoid arthritis (RF-) *P<0.05 is significant

Table 7. Relation between COMP and cartilage destruction among patients with of group 1 (established rheumatoid arthritis (RF+), group 2 (suspected rheumatoid arthritis (RF-)

Cartilage destruction		COMP		Total
		Negative	Positive	
Negative	Count	14	10	24
	% within COMP	93.6%	43.5%	77.1%
positive	Count	3	13	16
	% within COMP	6.4%	56.5%	22.9%
Total	Count	17	23	40
	% within COMP	100.0%	100.0%	100.0%

The relation between serum level of anti CCP and RF among the studied groups were studied and it was found that there is significant relation between serum level of anti CCP antibodies and serum level of RF among the studied groups this was shown in Table (8)

Table 8. Relation between anti CCP and RF among the studied sample

Variable	RF–VE (Mean±SD) (N= 46)	RF+VE (Mean±SD) (N= 24)	*P value
anti CCP	202.97±645.24	1063.36±1318.67	<0.001

P<0.05 is significant.

Bone erosion was present only in group 1 with percentage (40%) Cartilage destruction were present in group 1 with percentage (60%) but in group 2 with percentage (20%), group 3,4 Show no Cartilage destruction (Figure 1).

The sensitivity of anti CCP in diagnosis of RA was (31/40) 77.5% however the Sensitivity of RF in diagnosis of RA was (20/40) 50% specificity of anti CCP (29/30) 96.6% and that of RF was (26/30) 86%.

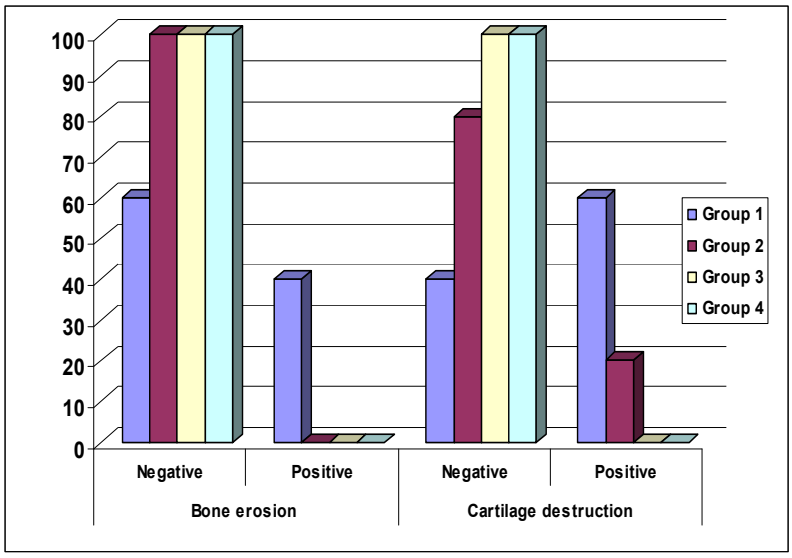

Figure 1. Distribution of the studied groups according to radiological finding.

Discussion

Rheumatoid arthritis (RA) is a systemic inflammatory disease characterized by chronic and erosive polyarthritis caused by abnormal growth of synovial tissue or pannus, and causes irreversible joint disability (Lee & Weinblatt; 2001).

The utility of anti-cyclic citrullinated peptide (anti-CCP) antibodies is well-established as a diagnostic and prognostic tool in rheumatoid arthritis and as a predictor of RA risk in established undifferentiated arthritis (UA). The 2010 RA classification criteria include anti-CCP as a key item. A new two-year study from Italy finds that the presence of anti-CCP positivity has value in recent-onset UA, predicting the development of future RA and even predicting the interval between first symptoms and RA onset (Bizzaro *et al.,* 2013). Also numerous studies in human and experimental arthritis clearly indicate that the assessment of COMP levels in serum provide important information about metabolic changes occurring in the cartilage matrix in joint disease that permits early establishment of the degree of cartilage damage and destruction in RA (Skoumal *et al.,* 2003).

The modern trend of RA treatment has been changed to start treatment as early as possible, based on the concept that early control of inflammation results in reduced

joint damage (Emery, 1994). Therefore is important to differentiate between RA and other forms of arthritis early after the onset of symptoms (Visser, 2005). So specific and sensitive serological marker which is present very early in the disease, is needed. Rheumatologists need to be able to target the use of potentially toxic and expensive drugs to those patients, where the benefits clearly outweigh the risk (Kirwan & Quilty; 1997).
(Smith *et al.,* 2006) reported that rheumatoid arthritis is 2-3 times more common in females than males and the frequency of RA increases with age \ aged 35-50 years which came in agreement with our study.

In our study we found that there is a significant relation between anti-CCP antibody levels and DAS this comes in agreement with other studies (Kamal *et al.,* 2012) who reported that there is significant relation between serum anti-CCP and DAS. On the other hand (Alexio *et al.,* 2007) reported no significant relation between anti-CCP antibody titer and DAS. This discrepancy can be explained that patients in that study may be under treatment with DMARDs that definitely improve the functional outcome (Kastbom *et al.,* 2004).

In the present study it was found that there is a significant relation between COMP ,anti CCP and DAS, cartilage destruction which comes in agreement with another two studies (Anne *et al.,* 2011) who reported a significant relation between COMP, anti CCP antibodies and, cartilage destruction and (Skoumal *et al.,* 2003) who reported a positive correlation between serum and synovial levels of COMP, anti CCP and Disease Activity Score (DAS). This can be explained that high serum COMP may reflect an increased breakdown of joint 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.,* 2006; Wislowska & Jablonska, 2005).

Murphy *et al.,* (2002) found a significantly increase in the percentage of positive serum COMP in patients with chondromalacia and suggested that it could be used as a prognostic marker of the disease activity. Furthermore, the serum presence of 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 presence of synovial fluid or serum COMP (Di Cesare *et al.,* 1997).

In our study, we found a significant difference between serum presence of COMP in rheumatoid arthritis patients and patients with other auto immune disease this come in agreement with (Martin *et al* 2004) who found that serum presence of COMP is elevated in rheumatoid arthritis, but not in inflammatory rheumatic diseases such as psoriatic arthritis, reactive arthritis, Raynaud's syndrome, scleroderma, systemic lupus erythematosus.

In the present study the Sensitivity of anti CCP in diagnosis of RA was77.5 % and the specificity was 96.6% however the Sensitivity of RF in diagnosis of RA was 50% and the specificity was 86% while (Münevver *et al.,* 2008) reported that the anti-CCP test demonstrated a specificity of 100% and sensitivity of 50% for RA also (Bas *et al.,* 2003) reported that the anti-CCP test demonstrated sensitivity for diagnosis of RA ranged from 50% - 80% and its specificity was 70% - 80%. These data confirmed the data of (Stikova and his collegues, 2003), who reported the superiority of anti CCP antibodies to RF in the diagnosis of RA.

Based on the previous finding, it could be concluded that, the serum level of anti CCP antibodies and COMP were significantly related to DAS (disease activity score) and cartilage destruction, the sensitivity of anti CCP in diagnosis of RA was77.5% while the

sensitivity of RF in diagnosis of RA was 50%. So, anti CCP, COMP could be a useful non invasive marker for estimation of disease activity and cartilage destruction. Anti CCP is more diagnostic and applicable for early detection of disease than COMP, also anti CCP is more sensitive than RF in diagnosis of RA, which help in early aggressive therapy in the hope of improving the long-term outcome for patients

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