

The study of temporomandibular joint disorders and anti-cyclic citrullinated peptide antibodies in serum and saliva of patients with rheumatoid arthritis

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ABSTRACT

Background: Rheumatoid arthritis is an autoimmune disease that affects mainly the synovial membranes and articular structures and is characterized by chronic, systemic inflammation involving multiple joints. Being a synovial joint, the Temporomandibular Joint is subject to the same disorders affecting other synovial joints, including RA. Beside it was considered as a specific serological marker for diagnosing RA disease, antibodies to cyclic citrullinated peptide have proven to be associated with joints destruction, though; it may play a potential role in the prediction of the disease severity.

Materials and Methods: Sixty nine individuals (69) were enrolled in this study, forty nine (49) were patients diagnosed with Rheumatoid Arthritis, and twenty (20) were healthy control subjects. Blood and saliva samples were taken from each subject for immunological analysis of Anti-Cyclic Citrullinated Peptides antibodies by ELISA. Each patient with Rheumatoid Arthritis disease was examined by means of Research Diagnostic Criteria for Temporomandibular Disorders for the assessment of temporomandibular joint involvement.

Results: Frequency of positive serum Anti-CCP antibodies was higher in rheumatoid arthritis patients compared to healthy controls ($p=0.000$). Temporomandibular joint clinical findings were bilaterally involved except joint sounds, sometimes; it was unilateral. Chronic rheumatoid arthritis patients associated with higher prevalence of temporomandibular joint disorders than newly diagnosed RA, except limited mouth opening which were prevalent in newly diagnosed RA patients, ($p=0.012$) was significant. Positive serum Anti-CCP rheumatoid arthritis patients were associated with higher frequency of temporomandibular joint disorders compared with RA patients with negative serum Anti-CCP, a non-significant difference was found.

Conclusions: Anti-Cyclic Citrullinated Peptide antibodies are considered as a biomarker of inflammation and disease activity. Temporomandibular joint disorders are frequently involved in rheumatoid arthritis patients. Rheumatoid arthritis patients with positive serum Anti-Cyclic Citrullinated Peptides antibodies associated with higher frequency of temporomandibular joint disorders.

Keywords: Rheumatoid arthritis, Temporomandibular joint, Anti-Cyclic Citrullinated Peptide antibody. (J Bagh Coll Dentistry 2013; 25(Special Issue 1):67-71).

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease that may affect many tissues and organs, but is mainly characterized by chronic inflammation of the joints. The inflammation leads to joint destruction, joint deformity with loss of function and increased mortality ⁽¹⁾.

Rheumatoid arthritis causes chronic inflammation in joint tissues; it is usually seen in other joints prior to temporomandibular joint involvement. The common clinical TMJ findings in rheumatoid arthritis are tenderness, pain, clicking, crepitation, stiffness, and limitation in jaw movements ⁽²⁾.

The publication in 1992 of the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) provided clinicians and investigators with a precise and reliable tool for diagnosing the most common alterations of the TMJ. Group III of axis I of this classification includes the sub-categories arthralgia, osteoarthritis and osteoarthrosis ⁽³⁾.

Until recently, assays detecting rheumatoid factor (RF), antibodies directed against the Fc portion of the IgG molecule, have been the primary serologic test in diagnosis of RA. However, RF antibodies are not very specific for this disease and can also be detected in other rheumatic disorders, infections, and in 3-5% of apparently healthy individuals ⁽⁴⁾. Recently, antibodies directed to citrulline-containing proteins, which appear to be a promising alternative of RF in the diagnosis of RA. Anti-CCP antibodies is specific for RA and appear early in the disease, often even preceding the symptoms of RA. Moreover, Anti-CCP is a reliable predictor of a progressive and erosive course of RA ^(5,6). The aims of the study were:

1. Assessment of Anti-cyclic Citrullinated Peptide (anti-CCP) antibodies in serum and saliva of patients with Rheumatoid Arthritis and compare the results with those of healthy control subjects.
2. Study the prevalence of Temporomandibular Joint disorders in Rheumatoid Arthritis patients.

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MATERIALS AND METHODS

The study was conducted in Al-kindi teaching hospital and Baghdad teaching hospital. The study samples consist of forty nine rheumatoid arthritis patients sub grouped into fifteen newly diagnosed rheumatoid arthritis of a duration less than one year, and thirty four chronic rheumatoid arthritis patients. Apparently healthy controls group were twenty subjects. Temporomandibular joint disorders were evaluated according to the RDC/TMD⁽³⁾, and the examination included: Range of mouth opening (limitation), Joint sounds, Palpation of masticatory muscles, Palpation of TMJ sites. Determination of serum and saliva Anti-Cyclic Citrullinated Peptide antibodies was done by means of Enzyme Linked Immunosorbent Assay, using IgG ELISA (AESKULISA)2-kits.

Statistical analysis

Graphical presentation by using: Cluster Bar Charts. Inferential data analysis by using Chi-Square statistic, likelihood ratio test, Fisher Exact Probability test, Contingency Coefficients test for the cause's correlation ship of the association tables and Odds Ratio.

RESULTS

Laboratory results of Anti-Cyclic Citrullinated Peptide antibodies

Results in table (1) reveal that from overall 49 RA patients, 35 (71.4%) were with serum positive Anti-CCP antibodies and the remainder RA patients were 14 (28.6%) with serum negative Anti-CCP antibodies. Healthy controls have had non results of serum Anti-CCP (0.00%), thus, a highly significant differences was found ($P=0.000$). Results in table(2) reveal that eleven (73.3%) of the newly diagnosed RA patients were with serum positive Anti-CCP and remainder were with serum negative Anti-CCP 4 (26.7%). Twenty four (70.6%) of the chronic RA patients were with serum positive Anti-CCP and remainder were with serum negative Anti-CCP 10 (29.4%), though, a non-significant differences was found ($P=0.845$).

The prevalence of temporomandibular joint disorders among newly diagnosed and chronic rheumatoid arthritis patients

Figure (1) illustrates the prevalence of TMJ clinical findings among the two groups of RA. Temporalis muscle's tenderness was found in 12(80.0%) of newly diagnosed RA patients, and in 24(66.7%) of chronic RA patients. Masseter muscle's tenderness was found in 2(13.3%) of newly diagnosed RA patients, and in 12 (35.3%) of chronic RA patients. Lateral poles of TMJ was found tender in 13 (86.7%) of newly diagnosed

RA patients, and in 22 (64.7%) of chronic RA patients. Posterior attachments was found tender in 7(46.7%) of newly diagnosed RA patients, and in 19(55.9%) of chronic RA patients, non-significant differences was found when $p>0.05$ regarding muscles and joint tenderness between newly diagnosed and chronic RA patients. Limited mouth opening was significantly prevalent in 12(80.0%) of newly diagnosed RA patients compared with 14 (41.2%) of chronic RA patients, a significant differences was found $p=0.013$ between newly and chronic RA patients. Joint sounds was the only TMJ clinical finding that was detected unilateral in some RA patients 11(22.4%), they were 8 (23.5%) in chronic RA patients and 3 (20%) in newly diagnosed RA patients. Bilateral joint sounds among RA patients was detected in 9 (18.45%), they were 8 (23.5%) in chronic RA patients and 1 (6.7%) in newly RA patients. Statistically, a non-significant difference was found $p=0.259$ between newly diagnosed and chronic RA patients.

The prevalence of temporomandibular joint disorders among RA patients with serum positive and negative Anti-CCP antibodies

Figure (2) illustrates the prevalence of TMJ clinical findings among serum positive and negative RA patients. The frequency of temporalis muscle's tenderness was found in 25 (71.4%) of serum positive Anti-CCP compared with 11 (78.6%) of serum negative RA patients. Frequency of masseter muscle's tenderness was found in 10 (28.6%) of serum positive compared with 4 (28.6%) of serum negative Anti-CCP RA patients. Frequency of tenderness of TMJ's lateral poles was found in 25 (71.4%) of positive serum Anti-CCP compared with 10 (71.4%) of negative serum Anti-CCP RA patients. Frequency of tenderness of TMJ's posterior attachments was found in 20 (57.1%) of positive serum Anti-CCP compared with 6 (42.9%) of negative serum Anti-CCP RA patients. Frequency of limited mouth opening was found in 20 (57.1%) of positive serum Anti-CCP compared with 6 (42.9%) of negative serum Anti-CCP RA patients. Frequency of joint sounds was found in 17(48.6%) of positive serum Anti-CCP compared with 3 (21.4%) of negative serum Anti-CCP RA patients, a non-significant differences was found regarding all those findings between serum positive and negative RA patients when $p>0.05$.

DISCUSSION

Positive Serum Anti-CCP antibodies among the studied groups

High frequency of positive serum Anti-CCP test was significantly found among RA groups

71.4% compared with 0.00% in healthy controls, these findings correlates with ⁽⁷⁾, who reported relatively similar results with a positive serum Anti-CCP 79% among RA patients, and none of the healthy controls' sera were positive for anti-CCP. On the other hand, the current study results are inconsistent with studies of ⁽⁸⁾, who reported that 58% of RA patients were positive for anti-CCP and ⁽⁹⁾ who suggested that citrullinated collagen-II results in 40% positivity for Anti-CCP, which is too low in comparison with results of the current study. In addition, results revealed high frequency of Anti-CCP positivity among newly diagnosed RA 73.3% compared with 70.6% for chronic RA. A non-significant difference was found statistically. An Iraqi study carried by ⁽¹⁰⁾ proposed 70% positivity for early RA and 95% for chronic RA patients compared with 0.0% for healthy controls.

Prevalence of temporomandibular joint disorders among the two groups of rheumatoid arthritis patients

Bilateral TMJ findings were detected among the RA patients frequent muscle tenderness including the temporalis and masseter muscle was found prevalent in chronic RA more than newly diagnosed RA patients. Ardic et al. reported muscle tenderness in RA patients secondary to temporomandibular joint involvement, and stated that if a joint is not functioning normally a patient will often develop muscle tenderness that can be experienced as facial pain ⁽¹¹⁾. Frequent joint tenderness in the area of lateral pole and posterior attachment was found prevalent in chronic more than newly diagnosed RA patients. This is in agreement with studies ^(12, 13, 14) they found bilateral TMJ pain in patients with rheumatoid arthritis which might be due to increase in pressure within the joint capsule as the pannus extrudes itself into the inter bony spaces but before any significant bone resorption has taken place. Mouth opening was reduced in 53.1% of RA patients, and furthermore it was prevalent in the newly diagnosed RA patients compared with chronic RA patients. Previous studies report that complains of limitation in mouth opening is common in more than half of RA patients ^(15, 16, 17) and could be as a result of intra-articular fibrous adhesions or due to displacement of the disc ⁽¹⁸⁾. Joint sounds was the only TMJ finding that was sometimes detected unilateral, however it was frequently detected in the chronic more often than newly diagnosed RA patients, agreed with ⁽¹⁸⁾, they reported somehow similar findings and stated that a disturbance in the normal anatomic relationship between the disc and condyle that interferes with smooth movement of the joint and

causes momentary catching, clicking or popping ⁽¹⁹⁾.

The prevalence of temporomandibular joint disorders among RA patients with serum positive and negative Anti-CCP antibodies

Results revealed that RA patients with positive serum Anti-CCP have been found to exhibit clinical TMJ disorders more often than RA patients with negative serum Anti-CCP after evaluating TMJ findings by RDC/TMD which suggests that positive serum Anti-CCP RA patients associated with significant prevalence of TMJ disorders. Correlation of positive Anti-CCP and the degree of joints involvement, including TMJ in RA disease, have been previously investigated by ⁽²⁰⁾. They stated that RA patients with positive serum Anti-CCP develop more progressive and significant disease course than RA patients with negative Anti-CCP, and interestingly; TMJ was the last joint with its prevalence rate among Anti-CCP positive patients compared with joints such as Meta Carpophalangeal (MCP) or Proximal Interphalangeal (PIP). For the best of knowledge this is the first study that proposed TMJ clinical findings in relation to Anti-CCP antibody status by means of RDC/TMD.

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Table 1: Distribution of the studied samples according to positive serum Anti-CCP with Comparisons Significant

Serum Anti-CCP	Freq.'s & Percents	The Studied Groups		Total	C.S. (*) P-value
		Healthy control	Rheumatoid Arthritis		
Negative	Freq.	20	14	34	C.C.=0.544 P=0.000 HS
	% Serum Anti-CCP	58.8%	41.2%	100%	
	% The Studied Groups	100%	28.6%	49.3%	
Positive	Freq.	0	35	35	
	% Serum Anti-CCP	0.0%	100%	100%	
	% The Studied Groups	0.0%	71.4%	50.7%	

(*) HS: Highly Significant at P<0.01

Table 2: Distribution of the RA groups according to positive serum Anti-CCP with Comparisons Significant

Serum Anti-CCP	Freq.'s & Percents	The Studied Groups		Total	C.S. (*) P-value
		Newly Diagnosed RA	Chronic RA		
Negative	Freq.	4	10	14	C.C.=0.028 P=0.845 NS
	% Serum Anti-CCP	28.6%	71.4%	100%	
	% The Studied Groups	26.7%	29.4%	28.6%	
Positive	Freq.	11	24	35	
	% Serum Anti-CCP	31.4%	68.6%	100%	
	% The Studied Groups	73.3%	70.6%	71.4%	

(*) NS : Non Significant at P >0.05

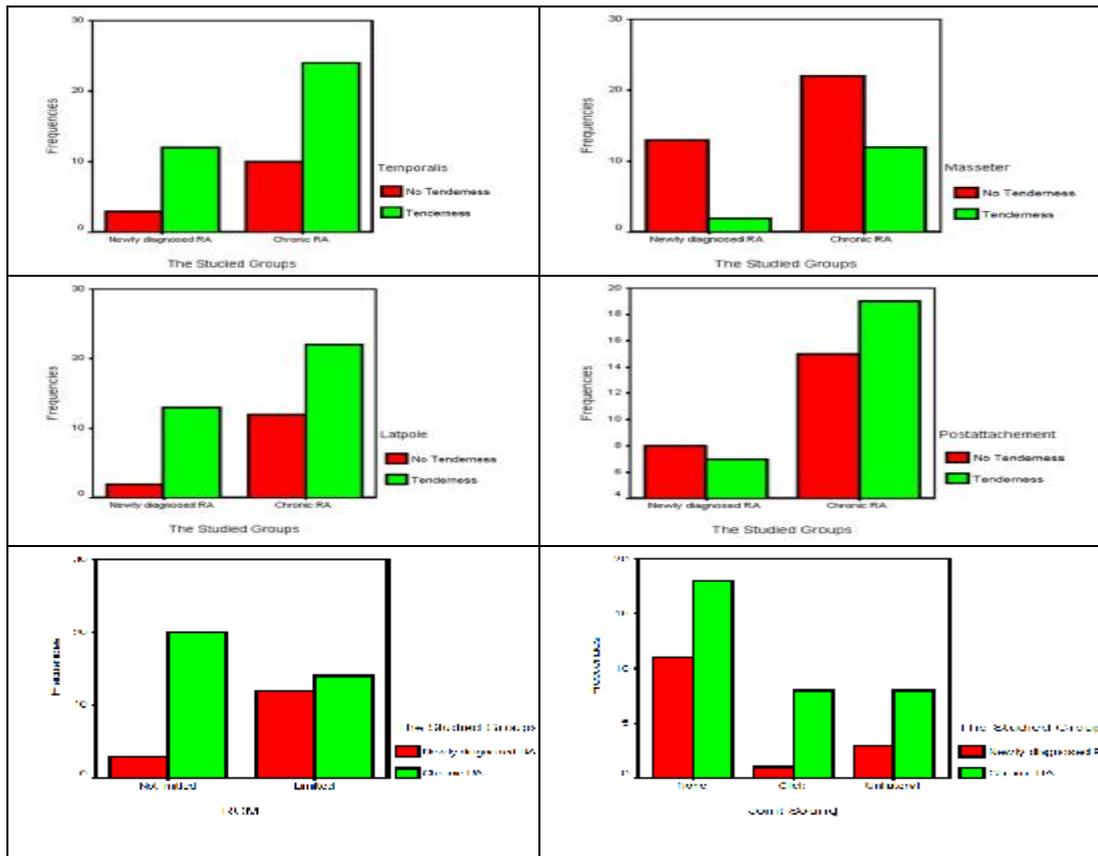


Figure 1: TMJ clinical findings among RA patient group

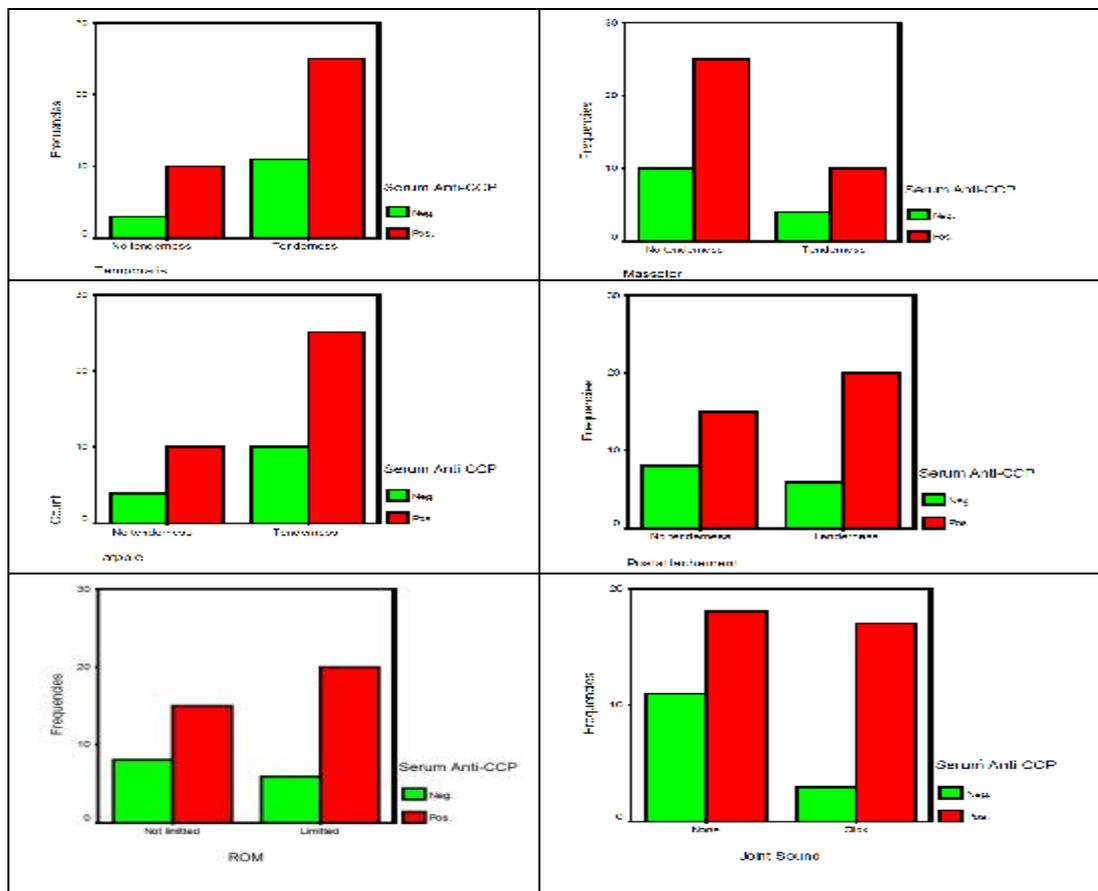


Figure 2: TMJ clinical findings among positive and negative serum Anti-CCP RA Patients