

# Correlation Between CCP Levels And Health Assessment Questionnaire In Rheumatoid Arthritis: A Single Center Analysis

M Mohd Shahrir, M Eishwary, S Shahid, H Hussein

## Citation

M Mohd Shahrir, M Eishwary, S Shahid, H Hussein. *Correlation Between CCP Levels And Health Assessment Questionnaire In Rheumatoid Arthritis: A Single Center Analysis*. The Internet Journal of Rheumatology. 2006 Volume 4 Number 1.

## Abstract

Introduction: This cross sectional study consisted of taking anti-Citrulinated Cyclic Peptide CCP levels and doing Health Assessment Questionnaire for Rheumatoid Arthritis patients. 52 rheumatoid arthritis patients were recruited.

Objective: To investigate the correlation between anti-Citrulinated Cyclic Peptide levels and Health Assessment Questionnaire severity among rheumatoid arthritis patients.

Results: 52 RA patients were recruited. 43(82.7%) patients were female and 9(17.3%) were male. 43(82.7%) patients were Malay, 2(3.8%) patients were Chinese, 6(11.5%) patients were Indian and 1(1.9%) patient was Sikh. Mean age was  $46.17 \pm 12.66$  years and the 41-60 age group has the most patients (30(47.1%)). Mean age of onset was  $43.24 \pm 12.72$  years and mean disease duration was  $3.08 \pm 4.49$  years.

30(58.8%) patients did not have any complications, 13(25.5%) had secondary osteoarthritis, 4(7.8%) had lungs complications, 2(3.9%) had hepatitis, 1(2.0%) had nephropathy and 1(2.0%) had Cushing's syndrome. 25(49.0%) of the patients had deformities. 33(67.4%) patients were still active with a mean DAS28 score of  $4.3 \pm 2.0$  and 16(32.7%) had complete remission with a mean DAS28 score of  $1.6 \pm 0.8$ .

The anti-Citrulinated Cyclic Peptide median value was  $10768.17 \pm 48342.30$  IU/ml and the median total Health Assessment Questionnaire score was  $1.50 \pm 1.25$ .

Pearson correlation analysis revealed statistical significant correlation between Health Assessment Questionnaire severity and anti-Citrulinated Cyclic Peptide levels ( $p=0.039$ ) and Health Assessment Questionnaire score and anti-Citrulinated Cyclic Peptide levels ( $p=0.016$ ).

Conclusion: There was significant correlation between Health Assessment Questionnaire severity and anti-Citrulinated Cyclic Peptide levels.

## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disorder of unknown etiology that involves not only the joints but also other extra-articular organs (1).

Many of the clinical features that are used in this study also serve as classification criteria for RA (1).

The following is a summary of clinical features that are useful for diagnostic and classification purposes.

- Morning stiffness for at least one hour and present for at least six weeks.
- Swelling of three or more joints for at least six weeks.
- Swelling of wrist, metacarpophalangeal, or proximal interphalangeal joints for at least six weeks.
- Symmetric joint swelling Hand X-ray changes typical of RA that must include erosions or

unequivocal bony decalcification.

- Rheumatoid subcutaneous nodules.
- Rheumatoid factors.

If the arthritis is uncontrolled it may lead to destruction of joints due to erosion of cartilage and bone which leads to deformity. The disease usually progresses from the periphery to more proximal joints, and in patients who do not fully respond to treatment, results in significant locomotor disability within 10 to 20 years (1).

Thus a suitable serologic marker is needed to predict the diagnosis of RA in cases of polyarthritis other than Rheumatoid factor (RF). This new marker is called anti-cyclic citrullinated antibodies (anti-CCP). The ELISA for anti-CCP can help in the differential diagnosis of early polyarthritis. Testing for the combination of anti-CCP antibodies and IgM RF may be better for excluding the diagnosis of RA than is achievable by testing for either antibody alone. In a study that compared the results of serologic testing in 196 patients with a clinical diagnosis of RA and 239 controls: Anti-CCP — sensitivity 56 percent, specificity 90 percent IgM RF — sensitivity 73 and specificity 82 percent IgM and anti-CCP — sensitivity 48 and specificity 96 percent (2).

In this study, the presence of these antibodies will be correlated with the functional status of the patient that is the Health Assessment Questionnaire (HAQ).

The Health Assessment Questionnaire (HAQ), was designed to represent a model of patient oriented outcome assessment and has played a major role in diverse areas such as prediction of successful aging, in rheumatoid arthritis (RA), quantification of non-steroidal anti-inflammatory drug gastropathy, development of risk factor models for osteoarthritis, and examination of mortality risks in RA. The HAQ has established itself as a valuable, effective, and sensitive tool for measurement of health status. It has increased the credibility and use of validated self-report measurement techniques as a quantifiable set of hard data endpoints and has contributed to a new appreciation of outcome assessment (3).

The main objective of this cross sectional study was to assess correlation of anti – CCP levels and HAQ severity among rheumatoid arthritis patients. The secondary objective was to assess characteristics of RA patients in

various severities of HAQ scores.

## **METHODS**

This cross sectional study consisted of taking anti-CCP levels and doing HAQ for RA patients. RA subjects were selected from the rheumatology clinic Putrajaya hospital for a total duration of 4 months.

Rheumatoid factor sera were analyzed in Putrajaya hospital using a commercially available kit and the anti-CCP antibodies sera were analyzed in Institute of Medical Research (IMR) using ELISA test.

HAQ interview was carried out independently on the day of recruitment. We also looked at disease complications and Disease Activity Score (DAS28).

All the patients' data was collected from Putrajaya hospital computers with permission from the head of department of medicine. Statistical analysis was done with SPSS 13.0. Firstly, the data was analyzed for normal distribution using Kolmogorov-Smirnov test. Then suitable parametric or non parametric tests were used to analyze the data.

## **RESULTS**

### **DEMOGRAPHIC DATA FOR RA PATIENTS**

51 RA patients were recruited. 43(82.7%) patients were female and 9(17.3%) were male. 43(82.7%) patients were Malay, 2(3.8%) patients were Chinese, 6(11.5%) patients were Indians and 1(1.9%) patient was a Sikh. Mean age was 46.17±12.66 years and the 41-60 age group has the most patients (30(47.1%)). Mean age of onset was 43.24±12.72 years and mean disease duration was 3.08±4.49 years. The median anti-CCP value was 10768.17±48342.30. IU/ml and the median total HAQ score was 1.50±1.25.

### **TREATMENT PATTERN OF RA PATIENTS**

39(76.5%) patients had 1 disease modifying anti – rheumatic drug (DMARDS), 7(13.7%) had 2 DMARDS, 3(5.9%) had 1 DMARDS and 2(3.9%) had no DMARDS. Meloxicam was the most widely used painkillers (26(26.3%)) followed by celecoxib (18(18.2%)), tramadol (3(3.0%)), etoricoxib (1(1.0%)), paracetamol (1(1.0%)) and combination of meloxicam and tramadol (1(1.0%)). 42(82.4%) patients were not put on steroids.

### **COMPLICATIONS OF RA PATIENTS**

30(58.8%) patients did not have any complications, 13(25.5%) had secondary osteoarthritis, 4(7.8%) had lungs

complications, 2(3.9%) had hepatitis, 1(2.0%) had nephropathy and 1(2.0%) had Cushing's syndrome. 25(49.0%) of the patients had deformities. 33(67.4%) patients were still active with a mean DAS28 score of  $4.3 \pm 2.0$  and 16(32.7%) had complete remission with a mean DAS28 score of  $1.6 \pm 0.8$ .

### **HAQ SCORE**

The severity of the HAQ score is divided into no activity, mild, moderate and severe.  $<0.25$  is no activity,  $0.25 - 0.50$  is mild,  $0.6 - 1.4$  is moderate and  $>1.4$  is severe.

### **NO ACTIVITY HAQ SCORE**

There were no patients in this category.

### **MILD HAQ SCORE**

Total of patients were 6(13.3%). 5(83.3%) respondents were Malay and 1(16.7%) respondent was Indian. 1(16.7%) patient was a male and 5(83.3%) patients were female. 2(33.3%) patients were above 60 years of age, 2(33.3%) patients were 51 – 60 years, 1(16.7%) patient was 41 – 50 years and 1(16.7%) patient was 21 – 30 years. 3(50.0%) patients had secondary osteoarthritis and 1(16.7%) patient had lung complication. 3(50.0%) patients had deformities. 3(50.0%) patients were in remission with a DAS28 score of  $1.4 \pm 0.3$ , and 3(50.0%) patients were still active at the time of study with a DAS28 score of  $4.0 \pm 2.0$ . 4(66.7%) patients had positive rheumatoid factor. 4(66.7%) patients were on 1 DMARDS, 2(33.3%) patients were not and no one was on steroids. Mean anti CCP levels was  $402.75 \pm 564.08$  IU/ml.

### **MODERATE HAQ SCORE**

Total of patients were 19(28.4%). 15(78.9%) respondents were Malay, 2(10.5%) were Chinese and 2(10.5%) were Indian. 3(15.8%) patient was a male and 16(84.2%) patients were female. 2(10.5%) patients were above 60 years of age, 4(21.1%) were 51 – 60 years, 6(31.6%) were 41 – 50 years, 3(15.8%) were 31 – 40 years, 3(15.8%) were 21 – 30 years and 1(5.3%) patient was 11 – 20 years. 4(21.1%) patients had secondary osteoarthritis, 1(5.3%) had lung complication, 1(5.3%) had nephropathy and 13(68.4%) had no complications. 6(31.6%) patients had deformities. 9(47.4%) patients were in remission with a DAS28 score of  $1.4 \pm 0.3$  and 9(47.3%) patients were still active at the time of study with a DAS28 score of  $4.3 \pm 1.8$ . 8(42.1%) patients had positive rheumatoid factor. 13(68.4%) patients were on 1 DMARDS and 5(26.3%) were on 2 DMARDS. 2(10.5%) patients were on steroids. Mean anti CCP levels

was  $150.21 \pm 326.61$  IU/ml. 12(63.2%) had negative anti – CCP.

### **SEVERE HAQ SCORE**

Total of patients were 24(58.3%). 20(83.3%) respondents were Malay, 3(12.5%) were Indian and 1(4.2%) was Sikh. 4(16.7%) patient was a male and 20(83.3%) patients were female. 4(16.7%) patients were above 60 years of age, 7(29.2%) were 51 – 60 years, 7(29.2%) were 41 – 50 years, 4(16.7%) were 31 – 40 years, 1(4.2%) were 21 – 30 years and 1(4.2%) patient was 11 – 20 years. 7(29.2%) patients had secondary osteoarthritis, 2(8.3%) had lung complication, 2(8.3%) had hepatitis and 13(54.2%) had no complications. 13(54.2%) patients had deformities. 6(25.0%) patients were in remission with a DAS28 score OF  $2.0 \pm 1.0$  and 18(75.0%) patients were still active at the time of study with a DAS28 score of  $4.4 \pm 2.0$ . 14(58.3%) patients had positive rheumatoid factor. 21(87.5%) patients were on 1 DMARDS, 2(8.3%) were on 2 DMARDS and 1(4.2%) were on 3 DMARDS. 5(20.8%) patients were on steroids. Mean anti CCP levels was  $23005.14 \pm 69939.46$  IU/ml. 7(36.8%) patients had negative anti CCP.

### **NEGATIVE ANTI – CCP LEVELS**

Total of patients were 21(43.8%). 17(81.0%) respondents were Malay, 1(4.8%) was a Chinese, 2(9.5%) were Indian and 1(4.8%) was a Sikh. 5(23.8%) patients were male and 16(76.2%) patients were female. 7(33.3%) were 51 – 60 years, 8(38.1%) were 41 – 50 years, 2(9.5%) were 31 – 40 years, 3(14.3%) were 21 – 30 years and 1(4.8%) were 11 – 20 years. 4(19.0%) patients had secondary osteoarthritis, 1(4.8%) had lung complication, 1(7.7%) had Cushing's and 15(71.4%) had no complications. 8(31.8%) patients had deformities. 11(52.4%) patients were in remission with DAS28 score of  $1.8 \pm 0.3$  and 10(47.6%) patients were still active at the time of study with a DAS28 score of  $4.0 \pm 2.0$ . 3(14.3%) patients had positive rheumatoid factor. 17(81.0%) patients were on 1 DMARDS and 4(19.0%) were on 2 DMARDS. 3(14.3%) of the patients were on steroids. 7(36.8%) patients had severe HAQ score and 12(63.2%) had moderate HAQ score.

### **CORRELATION BETWEEN HAQ SEVERITY AND SCORE WITH ANTI – CCP SEVERITY AND LEVELS**

Pearson correlation analysis revealed statistical significant correlation between HAQ severity and anti – CCP levels ( $p=0.039$ ) and HAQ scores and anti – CCP levels ( $p=0.016$ ).

There were no positive correlations with other indices.

## **DISCUSSION**

In this study, we tried to correlate between levels of anti – CCP antibodies level and HAQ score and severity. In another words, we were trying to correlate serology results and functional status. We also looked at demographic data, disease complications and deformities, activity status, rheumatoid factor and treatment.

51 RA patients were recruited from the outpatient clinic. 43(82.7%) patients were female and 8(17.3%) were male. 42(82.7%) patients were Malay, 2(3.8%) patients were Chinese, 6(11.5%) patients were Indians and 1(1.9%) patient was a Sikh. Mean age was 46.17±12.66 years and the 41-60 age group has the most patients (30(47.1%)). Mean age of onset was 43.24±12.72 years and mean disease duration was 3.08±4.49 years. The median anti-CCP value was 10768.17±48342.30. IU/ml and the median total HAQ score was 1.50±1.25.

The above study population had a short disease duration, high CCP and high HAQ scores. The racial distribution on the other hand did not resemble the Malaysian population.

Majority of the patients were in the moderate to severe group (43(86.7%)). As expected, disease severity and complications were mainly in the severe HAQ group. 7(29.2%) patients had secondary osteoarthritis, 2(8.3%) had lung complication, 2(8.3%) had hepatitis. 13(54.2%) patients were still active at the time of study, 14(58.3%) patients had positive rheumatoid factor, 21(87.5%) patients were on 1 DMARDS, 2(8.3%) were on 2 DMARDS, 1(4.2%) were on 3 DMARDS and 5(20.8%) patients were on steroids. Mean anti CCP levels was also the highest compared to mild and moderate group (23005.14±69939.46 IU/ml).

We also looked at the negative anti – CCP group. The major characteristics of the RA patients in the negative anti – CCP group they include: Malay 17(81.0%), 16(76.2%) female, 8(38.1%) 41 – 50 years, 15(71.4%) had no complications, 13(68.2%) patients had no deformities and 10(47.6%) patients were in remission. 18(85.7%) patients had negative rheumatoid factor, 17(81.0%) patients were on 1 DMARDS and 18(85.7%) of the patients were on steroids. 7(36.8%) patients had severe HAQ score and 12(63.2%) had moderate HAQ score. Despite having a negative assay this group consisted of patients who are very active and needing steroids as a mode of therapy.

J Ronnelid et al. found that 160/279 (57.3%) patients were anti-CCP positive at the first visit (mean 5 months after first symptoms). During follow up only 11/279 (3.9%) of the patients changed their anti-CCP status from negative to positive (4). Perhaps in the near future, this group of negative anti CCP patients will have a positive serology well correlated with their disease activity.

The HAQ has been significantly correlated with a wide variety of health status measures, and studies of mortality (5). Among the self-report measures that have been correlated with the HAQ since the review by Ramey and Fries in 1996 are the AIMS(6), AIMS2(7), global health status(8,9), VAS pain scale(8,10), Beck Depression Scale(11), Carstairs Index (12), Danish Nottingham Health Profile(13), Disease Activity Score(10,11,14), Dutch AIMS (14), EuroQol (15), Hollingshead Index(16), Life Event Interview(17), London Handicap Scale(50), Nottingham Health Profile(18), Medical Outcome Study Short Form-36 (SF-36)(15,19,20), Social Network Delineation Questionnaire(21), Trait Anxiety (22), and the WOMAC(15,23,24). Correlations with clinical measures have included the areas of joint and muscle activity (25,26,27,28,29,30,31,32,33,34,35, 36), bone health and radiographs (25,37,38,39,40), body fat(38,39,41), and health behaviors(42,43). Biochemical assessments have included C-reactive protein (44,45,46) and human leukocyte antigen (HLA) typing (47,48, 49).

However, in the Swedish TIRA studies (50), it was found that the time course of the patients' HAQ score showed no major differences between anti-CCP antibody seropositive or negative cases during the study. They found that this contradicted the findings related to the disease activity markers ESR, CRP, DAS28, and PGA and that HAQ reflects another aspect of the disease—that is, functional ability.

Our patients' DAS28 scores were found not reflective of their respective HAQ scores or severities. Therefore our results may suggest that respondents could be affected by racial, religion and socioeconomic background, especially in Malaysia. As expected the results are different from other studies involving HAQ.

Deformities were more in the severe HAQ group coincides with the high anti – CCP antibody levels with a high positivity of rheumatoid factor (RF). L De Rycke and his team had already proven this fact whereby they found that the presence of RF and anti-CCP2 antibodies yielded a 10 times higher average expectancy rate for a high radiological progression rate (51). No radiological scores were done in our

study but based on the deformities and secondary osteoarthritis this fact was true.

## CONCLUSION

We found in our study population there was statistical correlation between HAQ scores and severity and anti-CCP levels. We also found that in the negative CCP group the HAQ scores are both moderate to severe. The HAQ scores and severities were also not parallel with DAS28 scores.

## ACKNOWLEDGEMENTS

The authors would like to thank Dr Shahnaz Murad of the Medical Research Institute and her team for their cooperation for this study.

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**Author Information**

**MS Mohd Shahrir**

Faculty of Medicine UKM, Putrajaya Hospital

**M. Eishwary**

Faculty of Medicine UKM, Putrajaya Hospital

**S. Shahid**

Faculty of Medicine UKM, Putrajaya Hospital

**H. Hussein**

Faculty of Medicine UKM, Putrajaya Hospital