ORIGINAL ARTICLE

Anti-Cyclic Citrullinated Peptide and Rheumatoid Factor (Prevalence and Association) in Saudi Rheumatoid Arthritis Patients

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Abstract
To assess the prevalence and association of anti-cyclic citrullinated peptides and rheumatoid factor in Saudi rheumatoid arthritis patients. Over three years (February 2011 - February 2014). Demographic and clinical features, drugs, rheumatoid factor-positivity, and anti-cyclic citrullinated peptides-positivity were recorded for 205 Saudi rheumatoid arthritis patients (185 females; mean age was 45 years and mean disease duration was 5 years). Anti-cyclic citrullinated peptides and rheumatoid factor were assessed in serum. Disease activity scores for 28 joints was used. There were 36% rheumatoid factor+ve and 45% anti-cyclic citrullinated peptides+ve. 21.5% of the rheumatoid factor-ve subjects were anti-cyclic citrullinated peptides+ve. 13.3% of the rheumatoid factor positive patients were anti-cyclic citrullinated peptides-ve and 86.7% were anti-cyclic citrullinated peptides+ve. Significant association ($P < 0.05$) of anti-cyclic citrullinated peptides-positivity and rheumatoid factor-positivity with each other, and with gender, use of disease–modifying antirheumatic drugs, hydroxychloroquine and methotrexate. No direct impact of anti-cyclic citrullinated peptides status on the disease activity scores for 28 joints or its constituents ($P > 0.5$); nevertheless, anti-cyclic citrullinated peptides positive patients appear to represent a greater need for combination disease modifying drugs. Although anti-cyclic citrullinated peptides and rheumatoid factor were closely related, their divergence was sufficient to indicate that both should be measured in Saudi rheumatoid arthritis patients.

Keywords
Saudi Arabia; Anti-cyclic citrullinated peptides antibodies; Rheumatoid arthritis; Rheumatoid factor; Clinical association

Introduction

Rheumatoid arthritis (RA), which is a systemic autoimmune disease, affects around 1% of the general population worldwide[1]. An early intervention with RA is important for minimizing the consequences of the disease[2]. Rheumatoid factor (RF) was the only laboratory criterion among the seven criteria that were approved (for RA diagnosis) by the "American College of Rheumatology" ("ACR"; 1987)[3]. RF had become the primary laboratory diagnostic test for RA[4]. The positivity of RF among RA patients was about 50-80%, with incomplete sensitivity and specificity that limited its diagnostic value[5-8] .

More autoantibodies had been found in the sera of RA patients, that were specific but less sensitive with inconveniency for routine use from the technical point of view[9]. Recent assays have used peptides that contain citrulline but the sensitivity was low[10]. Cyclic variants of these peptides were used as antigen in the first generation of these assays and were called cyclic citrullinated peptides (CCP)[10,11]. However, second generation CCP (CCP2) tests[12,13] showed high sensitivity and specificity to RA[13]. Third-generation anti-CCP (CCP3) assays were developed that were more sensitive than those of the CCP2 assays[14,15].

Compared with RF testing, anti-CCP testing was better for disease prediction[16,17] and prognosis[18], while RF was better for the response to therapy[19]. Actually, anti-CCP can be detected at an early stage of RA, even prior to the onset of clinical symptoms[17], and considered for the early diagnosis of RA in high-risk groups, such as relatives from patients[20]. Recently (2010), anti-citrullinated protein antibodies (ACPA) testing was considered as substantial part of "*The 2010 ACR-EULAR Classification Criteria for Rheumatoid Arthritis*"[21].

Mostly, anti-CCP in general have been studied in European subjects ancestry[22], with few studies having been done in some developing counties: subjects from Egypt[23], from Iran[24], Thai subjects[25], from India[26], Black subjects from South Africans[27], and from Syria[28]. Among Saudi subjects were evaluated the prevalence of anti-CCP, together with their relationship to disease activity, in Saudi RF-ve RA patients seen (between February 2009 and February 2011) in a private centre for rheumatology in Jeddah[29]. In the current study we assess the prevalence and association of Anti-CCP and RF in a different cohort of Saudi RA patients seen (between February 2011 and February 2014) in the same private centre.

Patients and Methods

Patients

A retrospective review of consecutive patients seen over three years (February 2011-February 2014) was undertaken for RA patients seen on the first visit to Dr. Dhiya Centre for rheumatism, acupuncture and physiotherapy in Jeddah, Saudi Arabia. All of the patients met the 1978 classification criteria of ACR for RA[30].

Assessments

The recorded data consisted of demographic (gender, age, and nationality), clinical [disease duration/ per years, disease-modifying antirheumatic drugs (DMARDs) use and the starting date, early morning stiffness in minutes, 28 joint count for swelling (SJ) and for tenderness (TJ) and physician's global assessment (PGA) as 100 mm on scale] as well as laboratory data erythrocyte sedimentation rate (ESR) as mm/h, C-reactive protein, anti-CCP, RF, hemoglobin, and platelets count. The 28 joint Disease Activity Score (DAS28) was used for the assessment of the disease activity[31], that was calculated according to SJ, TJ, PGA, and ESR. Assessment of anti-CCP was by using electrochemiluminescence (Roche Elecsys Machine), that is a CE ("European Conformity") approved as anti-CCP2 and according to the manufacturer instructions the positivity starts when the concentration was ≥ 3 IU/ml. Latex agglutination was used for assessment of immunoglobulin M RF.

Prior Related Research

Prior related studies were checked by several methods including the Saudi Digital Library, Entrez-PubMed and Advanced search - PubMed - NCBI.

Statistical Analysis

The data were analysed using Statistical Package for Social Sciences, Version 14. (SPSS Inc., Chicago, IL USA). Significant results were indicated when the p-value was less than 0.05. The significant association was assessed by the chi-squared test and odds ratio with SPSS version 14. The predictive value of anti-CCP

positivity for the various DMARDs, was analyzed using the multivariate Linear Regression Analysis (Stepwise Model); with a confidence interval 95%.

Results

We studied 205 RA patients, of which 185 were females and 20 were males; the mean age was 45 years. All were Saudi Arabian who met the 1978 classification criteria of ACR for RA. Their features (the demographic, the clinical and the laboratorian) are summarized in Table 1.

Most of the patients (200/205, 98%) received DMARDs. These comprised hydroxychloroquine sulphate in 146 (71%) patients with 80 (39%) receiving it as a monotherapy, sulfasalazine in 29 (14%) with 8 (4%) as monotherapy, methotrexate in 85 (41%) with 21(10%) as monotherapy, leflunomide in 15 (7%) always as in combination and Adalimumab in 3 (2%) always in combination. Glucocorticoids (prednisolone) were received by 52 (25%) patients. Combination DMARDs were used in 90 (44%) patients.

Overall 75/205 (37%) patients were RF positive and 93/205 (45%) were anti-CCP positive (Table 2). There were strong associations between rheumatoid factor positivity and anti-CCP positivity in all patients and early and established RA (Table 2). 65/75 (87%) patients who were positive for rheumatoid factor were

Table 1. Patients' demographic and clinical characteristics.

Category	Variable	Mean (Standard Deviation) or Number (%)
Demographic	Age	45 years (SD13)
	Sex (Female/Male)	185/20 (90.25%/9.75%)
	Disease Duration	4.7 years (SD 6.3)
	Disease Duration ≤1 year.	80 (39.02%)
Disease Activity	Tender Joint Count	14.2 (SD 5.2)
	Swollen Joint Count	2.8 (SD 1.6)
	Patient Global Assessment	64 mm (SD 9)
	Erythrocyte Sedimentation Rate	39 mm/h (SD 24)
	28-joint Disease Activity Score	5.8 (SD 0.8)
Treatment	Disease-Modifying Antirheumatic Drugs	200 (97.56%)
	Hydroxychloroquine Sulphate	146 (71.22%)
	Sulfasalazine	29 (14.14%)
	Methotrexate	85 (41.46%)
	Leflunomide	15 (7.32%)
	Adalimumab	3 (1.45%)
	Combination DMARDs	90 (43.90%)
	Glucocorticoids (Prednisolone)	52 (25.36%)

DMARDs: Disease-modifying antirheumatic drugs

Table 2. Anti-cyclic citrullinated peptides positivity versus rheumatoid factor positivity.

Group			Rheumatoid Factor		Total	Significance
			Negative	*Positive*		
All	*Anti-CCP*	*Negative*	102 (78.46%)	10 (13.33%)	112 (54.63%)	Chi-Squared 82; DF=1; P<0.001
		Positive	28 (21.54%)	65 (86.67%)	93 (45.37%)	
	Total		130	75	205	
Early	*Anti-CCP*	*Negative*	43 (87.75%)	6 (18.75%)	49 (60.50%)	Chi-Squared 38; DF=1; P<0.001
		Positive	6 (12.25%)	26 (81.25%)	32 (39.50%)	
	Total		49	32	81	
Established	*Anti-CCP*	*Negative*	59 (72.84%)	4 (9.30%)	63 (50.80%)	Chi-Squared 45; DF=1; P<0.001
		Positive	22 (27.16%)	39 (90.70%)	61 (49.20%)	
	Total		81	43	124	

Anti-CCP: Anti-cyclic citrullinated peptides; Early RA: When the disease duration was equal or less than one year; Established RA: When the disease duration was more than one year
DF: Degrees of freedom

also positive for anti-CCP. However, 28/130 (22%) of patients negative for rheumatoid factor were positive for anti-CCP.

The prevalence of the anti-CCP was 93/205 (45.4) in total cohort; 28/130 (21.5%) in RF-ve patients (Table 2). 14/20 (70 %) in males and 79/185 (42.7%) in females (Table 3).

Men were more likely to be positive for anti-CCP and rheumatoid factor than women (Tables 3 and 4). Patients who were positive for anti-CCP and rheumatoid factor were also more likely to be receiving treatment with methotrexate and combination DMARDs (Tables 3 and 4). The Linear Regression Analysis (Stepwise) of different DMARDs related to the positivity of anti-CCP showed significant relationship with receiving methotrexate ($p < 0.001$), but not with other DMARDs, though R2 was 15% indicating this association was relatively weak (Table 5).

Comparing the frequencies of positive results for anti-CCP and rheumatoid factor (Table 6) showed this was most marked in patients aged 30-39, though there

Table 3. Associations of anti-cyclic citrullinated peptides positivity.

Variable		Anti-CCP		Total	Significance
		Positive	*Negative*		
Gender	*Female*	79	106	185	Chi-Squared 5.4; DF=1; P=0.02
	Male	14	6	20	
Hydroxychloroquine	*Receiving*	54	92	146	Chi-Squared 14.4; DF=1; P<0.001
	Not-Receiving	39	20	59	
Methotrexate	*Receiving*	58	27	85	Chi-Squared 30.6; DF=1; P<0.001
	Not-Receiving	35	85	120	
Combination DMARDs	*Receiving*	54	36	90	Chi-Squared 13.9; DF=1; P<0.001
	Not-Receiving	39	76	115	

Anti-CCP: Anti-cyclic citrullinated peptides positivity; DF: Degrees of freedom; DMARDs: Disease-modifying antirheumatic drugs

Table 4. Associations of rheumatoid factor positivity.

Variable		Rheumatoid Factor		Total	Significance
		Positive	*Negative*		
Gender	*Female*	61	124	185	Chi-Squared 10.7; DF=1; P=0.02
	Male	14	6	20	
Hydroxychloroquine	*Receiving*	42	104	146	Chi-Squared 13.4; DF=1; P<0.001
	Not-Receiving	33	26	59	
Methotrexate	*Receiving*	47	38	85	Chi-Squared 22; DF=1; P<0.001
	Not-Receiving	28	92	120	
Combination DMARDs	*Receiving*	42	48	90	Chi-Squared 7; DF=1; P<0.01
	Not-Receiving	33	82	115	

DMARDs: Disease-modifying antirheumatic drugs; DF: Degrees of freedom

Table 5. Linear regression analysis (stepwise) of disease-modifying antirheumatic drugs related to anti-cyclic citrullinated peptides positivity.

Model	Unstandardized Coefficients		Significance
	B	*Std. Error*	
Methotrexate	0.39	0.065	0.00

Dependent variable: anti-cyclic citrullinated peptides positivity
R^2=15%
Excluded variables: Hydroxychloroquine sulphate (Plaque), Sulfasalazine, Glucocorticoids(prednisolone), Leflunomide (Arava), Adalimumab (HUMIRA)

Table 6. Age groups, anti-cyclic citrullinated peptides positivity and rheumatoid factor positivity.

Age Group	Anti-CCP Positive	Rheumatoid Factor Positive	Total
20-29	10 (40.00%)	10 (40.00%)	25
30-39	34 (61.82%)	26 (47.27%)	55
40-49	21 (36.85%)	17 (39.82%)	57
50-59	16 (41.02%)	11 (28.20%)	39
60-69	7 (43.75%)	4 (25.00%)	16
≥70	5 (38.46%)	7 (53.85%)	13

Anti-CCP: Anti-cyclic citrullinated peptides

Table 7. The 28 joint Disease Activity Score groups, anti-cyclic citrullinated peptides, and rheumatoid factor positivity.

		DAS28 ≤ 5.1	DAS28 > 5.1	Total
Anti-CCP	*Negative*	15 (13.40%)	97 (86.60%)	112
	Positive	12 (12.90%)	81 (87.10%)	93
Rheumatoid Factor	*Negative*	16 (12.30%)	114 (87.70%)	130
	Positive	11 (14.66%)	64 (85.34%)	75
Total		27 (13.17%)	178 (86.83%)	205

Anti-CCP: Anti-cyclic citrullinated peptides; DAS28: 28 Joint Disease Activity Score

was also a minor increase in very elderly patients with rheumatoid factor positivity.

Finally, there was no relationship between positive findings with anti-CCP and rheumatoid factor (Table 7). 27/205 patients had moderate or low DAS28 scores and 178/205 had high DAS28 scores. The frequencies of positive and negative anti-CCP and rheumatoid factor measures were similar in both groups.

Discussion

We studied 205 Saudi RA patients on their first visit to a specialist centre. All patients met the ACR classification criteria for RA. The prevalence of anti-CCP antibodies in this cohort was 45% including 22% who were rheumatoid factor negative. A similar prevalence (22%) of anti-CCP in rheumatoid factor negative patients has been reported in Japanese patients by Matsui and co-workers[32]. A lower prevalence (20%) was reported for Thai rheumatoid factor negative subjects[25]. However, prevalences of 30%-43% have been seen in other groups of rheumatoid factor negative patients from Saudi Arabia and other populations. Safi *et al*.[29], in Saudi Arabia, reported a prevalence of 30.5%; this difference could be attributed to 1- the higher male percentage (double; 18% compared to 9.8% in the present study) accompanied with low anti-CCP antibodies in males (half; 38% compared to 70% in the present study) 2- and/or to the presence of higher proportion of comorbid diseases in the present study (41% compared with 25% in the previous study) which was found to decrease the prevalence of anti-CCP positivity[29] Additionally, among RF-ve RA subjects from Greece and from Germany the reported prevalence of anti-CCP antibodies was 34.9%[33] and 34.5%[34], respectively. The authors, accordingly, suggested its usefulness for the RF-ve subjects with suspected RA. In black subjects from South Africa with early RA, the report prevalence of anti-CCP antibodies was 36.4% among 22 patients of RF-ve RA[27]. Prevalence of 40% anti-CCP-positivity among RF-ve patients was reported from Finland by Sihvonen *et al*.[35], and from Swedin by Kastbom *et al*.[36], and 43.2% was reported by Kroot *et al*.[37] in Swedish RF-ve patients. And finally, positive anti-CCP was reported in 65.3% of Iranian seronegative RA patients[38]. However the low CCP antibodies in RF-ve patients (in this study = 22%) could be attributed to the low number of smokers among the RF-ve patients (24%), as smoking is a known risk factor for CCP antibodies[39-41].

The disease activity DAS28 (5.8) in these cohorts was similar to our previous report[29] (5.7) and fits within the ranges (3.1-6.0) in patients from 25 other communities[42]. The patients in these cohorts [178/205 (86.8%)] that had high DAS28 scores (> 5.1), was slightly higher than that Safi *et al*.[29] previously reported [80%; 160/200)] yet both studies revealed no significant differences (P > 0.10) between +ve and -ve anti-CCP for the disease activity as estimated by DAS28,

indicating that anti-CCP antibodies have limited value in predicting disease activity. This is compatible with Vanichapuntu and co-workers[25], Abdel-Nasser *et al.*[23] who found no correlation of anti-CCP antibodies with DAS 28 and Serdaroğlu *et al.*[43] who reported no correlation between anti-CCP antibody and the serological markers of disease activity (ESR, DAS28, CRP).

In Egypt, although Abdel-Nasser *et al.*[23] reported no significant correlations of anti-CCP titre with parameters of disease activity, they found correlations between anti-CCP titre and disease severity [rheumatoid nodules, rheumatoid factor (RF), and radiological damage] and HAQ-DI ($P < 0.05$). Other investigators found anti-CCP antibodies to be predictors of a severe disease course in RA, as judged by radiological joint outcome[37,44] or by swollen joint count and raised, 36 CRP[33].

Early RA (dd ≤ 1 year) was found in 81 (39.5%) patients, which was slightly higher than our previous finding[29] (63/200; 31.5%). Among the 81 patients with early RA (dd ≤ 1 year) 32/81 (39.5%) had positive anti-CCP antibodies which is comparable with what was previously reported 29 (22/63; 35%) and confirming that anti-CCP antibodies test can be considered as a precious predictor of the disease in the early RA when RF is still not detectable. In this respect, we are in concordance with Kastbom *et al.*[36] who concluded that anti-CCP positivity is a valuable disease predictor in Swedish early RA patients (dd ≤ 1 year).

Associations of anti-CCP positivity and RF positivity indicated that patients who were positive for anti-CCP and rheumatoid factor were more likely to be receiving treatment with combination DMARDs and methotrexate ($P < 0.001$). This is in concordance with our previous report[29] of significant correlation ($p \leq 0.01$) between anti-CCP and methotrexate and prednisolone, but not the other used DMARDs.

The current baseline cross-sectional study, assessed neither the sensitivity nor the specificity of anti-CCP antibodies. Such assessment in RA in Saudi population can be a plan for a future study, using a non-RA control group and a ROC curve analysis,

Sex ratio (F:M) for RA patients had been consistently found to be around 3:1[45]. However, according to the literature review of Almoallim and Alharbi[46], the only study for the rate of RA in SA was published in 1998[47] that involved a single Saudi region (Al-Qassim region), small sample size, and simple methodology. They reported a F:M ratio of 1.6:1 (4:1 for the age group of 30-39 years). The cohort of our study had nine times more females than males (9:1), representing the number of patients seen in the centre during the assigned period of this retrospective study (2/2011-2/2014), and does not address the epidemiological sex differences for the Saudi RA patients. Similarly, 9:1 male-to-female ratio was reported in the study group of a recent study about the association of HLA-DRB1with anti-CCP in Saudi RA patients[48]. However, examination of sex differences in epidemiological characteristics within a large number of RA patients should be considered for a future plan.

Conclusion and Recommendations

Although anti-CCP and RF were closely related, the divergence between them is sufficient to indicate that both should be measured in Saudi RA patients. Although anti-CCP antibodies are unrelated to immediate levels of disease activity, anti-CCP positive patients appear to represent a different clinical phenotype with a greater need for combination disease modifying drugs. More studies are needed in Saudi Arabia for the assessment of the test sensitivity and the test specificity of the anti-CCP assay in Saudi Arabian population. Further studies should be performed for the rate of RA in SA together with the sex ratio (F:M) for RA patients in Saudi Arabia and for the correlation between smoking and anti-CCP.

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Ethical Approval

As long as the collected data were part of a retrospective review, thus informed consent was not obtained; however, a written ethical approval was obtained before commencing the study.

Disclosures

Both authors have read and approved this manuscript. The current study was not funded or supported by any drug company. This paper is unique and is not under consideration by any other publication and has not been published elsewhere.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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أضداد الببتيد الستيروليني الحلقي وعامل الروماتويد أر - إف (مدى الإنتشار والترابط) في مرضى إلتهاب المفاصل الروماتيزمي السعوديين

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المستخلص. تقييم انتشار وترابط أضداد الببتيد-الستير وليني-الحلقي (أضدادCCP) وعامل الروماتويد (RF) في مرضى إلتهاب المفاصل الروماتيزمي ((RA السعوديين. الديموغرافيا، والسمات السريرية، الأدوية، وإيجابية كلا RF وأضدادCCP، سجلت على مدى ثلاث سنوات (فب راير ٢٠١١ - فبراي ر ٢٠١٤) في ٢٠٥ مرضى RA سعوديين. قيمنا أضدادCCP باللمعان الكهروكيميائيelectrochemiluminescence وعامل الروماتويد بتراص اللاتكس. واستخدمنا تقييم درجات نشاط المرض لـ ٢٨ مفصل (DAS28) والمكونات المكونة لها. المرضى شملوا ١٨٥ أنثى و ٢٠ ذكرا؛ متوسط أعمارهم ٤٥ سنة (بانحراف معياري ١٣) ومدة المرض ٥ سنوات (بانحراف معياري ٦). إيجابيين RF يمثلون ٤٥٪ من إيجابيي ضدادCCP. إيجابيي أضدادCCP يمثلون ٢١,٥٪ من سلبيي RF، بينما ١٣,٣٪ من إيجابيي RF كانوا سلبيين لأضدادCCP و ٨٦,٧٪ كانوا إيجابيين لأضدادCCP. ارتبطت إيجابية أضدادCCP بشكل كبير (P < ٠,٠٥) مع إيجابية RF، والجنس، واستخدام أدوية DMARDs، هيدروكسي كلوروكوين والميثوتريكسات. لم يكن لحالة أضدادCCP أي تأثير مباشر على مستويات نشاط المرض DAS28 أو مكوناتها (P> ٠,٥). كان لإيجابية RF نفس ارتباطات إيجابية أضدادCCP. على الرغم من ارتباط أضدادCCP وRF ارتباطًا وثيقًا، فإن الاختلاف بينهما يكفي للإشارة بضرورة قياس كلاهما في مرضى RA السعوديين. على الرغم من أن أضدادCCP لاعلاقة لها بمستويات فورية من نشاط المرض، يبدو أن المرضى الإيجابيين لأضدادCCP ب حاجة أكبر لتوليف combination أدوية DMARDs.