



The Association of Anti-CCP and Disease Activity in Rheumatoid Arthritis

Romatoid Artritte Hastalık Aktivitesi ile Anti-CCP İlişkisi

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Cukurova Medical Journal 2014;39(4):743-751.

ABSTRACT

Purpose: To determine the value of Anti-CCP as predictor for disease activity in rheumatoid arthritis assessed by DAS-28, and to find the effect of smoking on disease activity in rheumatoid arthritis.

Materials and Methods: One hundred patients with rheumatoid arthritis involved in this study, consisted of 88 female and 12 male who fulfilled the 2010 ACR-EULAR classification criteria for rheumatoid arthritis attending the rheumatology department in general hospital, or attended the center of rheumatology and rehabilitation in sulaimani city, for 6 months (from October, 2012 to March, 2013).

Thorough Demographic information of patients was recorded through history of age, sex, and history of smoking, disease duration, physical evaluation according to DAS-28. and serological test for RF and Anti-CCP.

Results: There was highly significant association between DAS-28 and Anti-CCP value ($p = 0.0001$). there was no significant correlation between DAS-28 and RF ($p = 0.252$), According to smoking there was highly significant association between smoking with Anti-CCP value and DAS-28 ($p = 0.003- 0.0001$) respectively while there was no significant association between smoking and RF ($p = 0.15$).

Conclusion: A highly significant correlation was found between Anti-CCP value and disease activity in rheumatoid arthritis, smoker patients had higher value of Anti-CCP compared to non-smoker patients. Smokers demonstrated a more active and severe disease activity compared to non-smokers.

Key Words: Rheumatoid arthritis, DAS-28, Anti-CCP, RF.

ÖZET

Amaç: DAS-28 ile belirlenen eklem iltihabında hastalığın aktivitesi için belirleyici olan Anti-CCP değerinin saptanması ve eklem iltihabının hastalık aktivitesinde sigara kullanımının etkisini belirlemektir.

Materyal ve Method: 6 ay boyunca (2012 Ekim- 2013 Mart) Süleymaniye kentinde bulunan rehabilitasyon ve romatoloji merkezinde bulunmuş olan veya tam teşekküllü hastanenin romatoloji bölümünde bulunan, 2010 ACR-EULAR eklem iltihabı sınıflandırma kurallarına göre belirlenmiş, 88'i kadın 12'si erkek olmak üzere toplam 100 eklem iltihabı hastası çalışmaya dahil edildi. Hastaların yaş, cinsiyet, sigara kullanımı öyküsü, hastalık süreci, DAS-28'e göre fiziksel değerlendirmesi ve Anti-CCP ve RF için serolojik test sonuçları gibi kapsamlı demografik bilgileri kaydedildi.

Bulgular: DAS-28 ile Anti-CCP değeri arasında oldukça anlamlı bir fark bulundu. (P değeri= 0,0001). DAS-28 ile RF değeri arasında bir fark bulunamadı ($p = 0,252$). Sigara kullanım durumuna göre; sigara içimi ile Anti-CCP değeri ($p = 0,003$) ve DAS-28 ($p = 0,0001$) arasında oldukça anlamlı bir fark bulundu. Ancak; sigara içimi ile RF arasında anlamlı bir fark bulunamadı ($p = 0,15$).

Sonuç: Eklem iltihabında hastalık aktivitesi ile Anti-CCP değeri arasında oldukça önemli bir fark bulundu ayrıca sigara içen hastalar içmeyenlere nazaran daha yüksek Anti-CCP değerine sahiptiler. Sigara içenlerde ise içmeyenlere göre daha şiddetli ve aktif hastalık aktivitesi gözlemlendi.

Anahtar Kelimeler: Anti-CCP, DAS-28, Eklem İltihabı, RF

INTRODUCTION

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. It is the most common inflammatory arthritis, affecting from 0.5 to 1% of the general population worldwide, with a female/male ratio of 2.5:1. The disease may appear at any age, but it is most common among those aged from 40 to 70 years and its incidence increases with age¹. Apart from pain, RA is associated with reduction of functional capacity, and increased comorbidity and mortality^{2,3}.

Genes , environment and a pathogenetic connection

Although the aetiology is unknown, several genetic and environmental factors are obviously important in RA. The HLA-DRB1 product 'shared epitope' (SE) is the best known genetic factor associated with RA, and cigarette smoking is the best described environmental susceptibility factor. A gene–environment interaction has been shown for SE and smoking regarding susceptibility to RF-positive RA^{4,5}, and the presence of Anti-CCP antibodies (CCP+) correlates strongly with the presence of the SE⁶. It has been demonstrated that major histocompatibility complex class II molecules expressing the SE can bind and present citrullinated peptides to T cells⁷, and that a combination of SE-positive (SE+) and CCP+ is highly predictive of future RF-positive RA⁸.

Anti cycliccitrullinated peptide (Anti-CCP):

Are autoantibodies directed against the aminoacids formed by the posttranslational modification of arginine⁹. In recent years, many studies on antibodies against cyclic citrullinated peptide (CCP) have demonstrated that these antibodies are highly specific and predictive for

RA¹⁰ that they can be detected years before onset¹¹, The sensitivity of the Anti-CCP antibody test for RA is similar (70%), but specificity is superior (95%) to RF¹².

Most Anti-CCP are IgG molecules, although IgA, IgM and IgE antibodies have also been described¹³⁻¹⁵.

Anticitrullinated protein antibody (ACPA) level was added to the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) diagnostic criteria for Rheumatoid Arthritis. These criteria, including ACPA levels, identify more patients with Rheumatoid Arthritis than the previous 1987 criteria¹⁶.

Among those already with an established diagnosis of RA, Anti-CCP positivity has been able to predict, in numerous studies, the severity of disease. RA patients with Anti-CCP have more radiographic joint damage as compared to those without these antibodies¹⁷⁻²⁴.

Other studies have revealed that RA patients with Anti-CCP antibodies are more likely to have a higher erythrocyte sedimentation rate, C-reactive protein, and Disease Activity Score 28^{18,25,26}.

MATERIALS And METHODS

A descriptive study conducted on one hundred patients with adult Rheumatoid Arthritis attending Rheumatology department in general hospital or attended the center of Rheumatology and Rehabilitation in Slemani city, for 6 months (from October, 2012 to March, 2013).

A sample of 100 (composed of 88 female and 12 male) patients with Rheumatoid Arthritis as defined by 2010 ACR-EULAR classification criteria for Rheumatoid Arthritis.

The DAS-28 was measured and it is also used to guide treatment decision and describe disease

activity in patients with Rheumatoid Arthritis. Disease activity evaluated according to DAS-28 in which values >5.1 regarded as high disease activity and <3.2 are regarded as low disease activity, and less than 2.6 corresponds for clinical remission in RA.

History included age, sex, history of disease duration and physical evaluation according to Disease Activity Score 28 joint with 3 variables (DAS- 28) including the numbers of tender , swollen 28 joints and visual analog scale with Erythrocyte Sedimentation Rate (ESR)(mm/hr) estimation for each participant. Rheumatoid factor IgM and Anti-ccp was done for each participant by enzyme-linked immunosorbent assay (ELISA-Alegria), and it was considered as positive if the antibody titer was greater than 20U/ml. And negative if antibody titer was less than 20U/ml²⁷.

Regarding smoking history all patients were asked whether they smoked currently or had never smoked. A sample of 100 composed of 22 smokers and 78 nonsmokers.

Statistical Analysis

Statistical method used in our study was conducted according to Microsoft excel program (windows 8.0) and Epi info version 7.0. when applicable data were reported as mean and SD, comparison between variables were assessed with ANOVA and Students t test .A correlation was considered significant with *P* values less than 0.05.

RESULTS

The study consist of 100 cases of adult Rheumatoid Arthritis diagnosed according to the 2010 ACR-EULAR classification criteria for Rheumatoid Arthritis, 12(12%) were male and 88(88%) were female (figure.1) their ages ranged from 21 to 88 years with mean age of 53.74 ± 10.78 (standard deviation) , according to smoking history 22(22%) were smoker and 78(78%) were non smoker.

Table 1: Distribution of the cases in relation to socio-demographic characteristics:

variables		frequency	(%)
gender	Female	88	88%
	Male	12	12%
Age (Years)	21-35	5	5%
	36-50	32	32%
	51-65	50	50%
	66-80	13	13%
Smoking history	Smoker	22	22%
	Non smoker	78	78%
Total		100	100

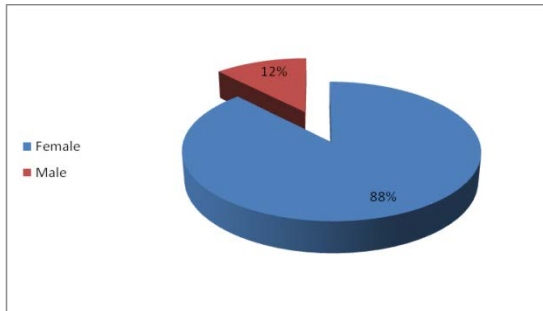


Figure 1.Gender distribution

Among 100 patient 32(32%) were in remission (DAS-28 less than 2.6) had mean titer of Anti-CCP 36.25 U/ml , those with low disease activity (DAS-28 less than 3.2) had mean titer of Anti-CCP 36.95 U/ml, while those with moderate disease activity (DAS-28 range from 3.2-5.1) had mean titer of Anti-CCP 281.51U/ml and those with high active disease (DAS-28 more than 5.1) had mean titer of Anti-CCP 329.65U/ml , the result showing the association of Anti-CCP with activity of disease in RA patients was highly significant(*P* value =0.0001) as shown in table (2).

Table 2: Correlation between Anti-CCP and disease activity score (DAS-28):

DAS28	NO.(%)	Mean titer(SD)of Anti-CCP	P Value
Remission	32(32%)	36.25 (176)	0.0001
Low disease activity	10(10%)	36.95 (57.2)	
Moderate disease activity	22(22%)	281.51 (326.1)	
High disease activity	36(36%)	329.65 (357)	

32 (32%) of patients were in remission their mean titer (SD) of RF was 80.4(275) , 10(10%) of patients were mild disease activity their mean titer (SD) of RF was 91.5 (474) , 22(22%) were in moderate disease activity their mean (SD) titer of

RF was 169.9 (449) , 36(36%) of patients were in high disease activity their mean titer (SD) of RF was 99.9 (239) , so there is no significant correlation between DAS-28 and RF (*P* value 0.252) as shown in table (3).

Table 3: Correlation between DAS-28 and RF:

DAS-28	NO. (%)	Mean titer(SD)of RF	P value
Remission	32(32%)	80.4 (275)	0.252
Low disease activity	10(10%)	91.5 (474)	
Moderate disease activity	22(22%)	169.9 (449)	
High disease activity	36(36%)	99.9 (239)	

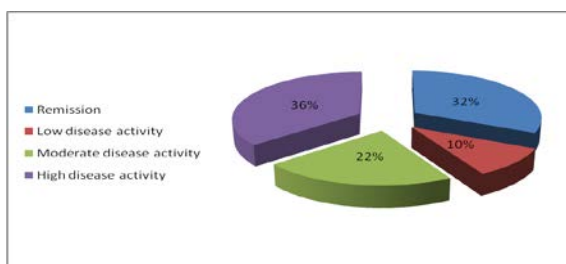


Figure 2. Distribution of disease activity.

Among 100 patients 88 were female 15(15%) of them were smoker and 73(73%)were non smoker while among 12 male patients 7(7%) were smoker and only 5(5%) were non smoker as shown in table(4):

Table 4.Smoking status in relation to gender:

Gender	Smoker	Non smoker	Total
Female	15(15%)	73(73%)	88(88%)
Male	7(7%)	5(5%)	12(12%)

The mean titer and SD of Anti-CCP in smoker RA patients was 368.4(367.6) while in non smoker patients was 147.2(276.3) so there is highly significant correlation between smoking and Anti-CCP (P value= 0.003) , the mean and SD of RF in smoker patients was 153.45(175.97) while in non smoker patients was 95.48(161.56) so there is no

significant association between smoking and RF(P value 0.15) and the mean and SD of DAS-28 in smoker patients was 5.32(1.43) while in non smoker patients was 3.91(1.45) so there is highly significant association between smoking and disease activity in RA patients (P value 0.0001) as shown in (5):

Table:5. Correlation between smoking with Anti-CCP , RF and DAS28:

	Anticcp Mean(SD)	P value	RF Mean (SD)	P value	DAS-28 Mean(SD)	P value
Smoker	368.4 (367.6)	0.003	153.45 (175.97)	0.15	5.32(1.34)	0.0001
Non smoker	147.2 (276.3)		95.48 (161.56)		3.91(1.45)	

DISCUSSION

Today it is generally agreed that RA should be diagnosed as early as possible and that potent anti- rheumatic disease modifying treatment should be started as early as possible^{28,29}.However, ideally the therapeutic strategy should be individually tailored—for example, by distinguishing cases with mild disease and good prognosis from those with severe disease with bad prognosis, in order both to avoid over treatment with potentially toxic anti-rheumatic drugs and to start the most aggressive (and costly) treatments for the patients who would benefit most from this³⁰. To be able to

identify “the right patient for the right treatment strategy”, good predictors are needed^[31,32].

In this study we have found a highly significant association between the presence and the level of Anti-CCP antibody and greater RA activity (P value 0.0001) the result was close to that of N. Del Val Del Amo et al^[33] who found that significant association between Anti-CCP and DAS-28 (P value 0.05) also M. Glasnovic et al^[34] and Omer Kuru et al^[35], support our finding that the presence of Anti-CCP antibody was associated with a higher probability of erosive disease,Kastbom et al.^[36] showed that Anti- CCP is

good predictor of disease activity even better than RF in predicting disease activity, Önder B et al³⁷ found that Anti-CCP was associated with higher scores of DAS-28, longer duration of morning stiffness.

While MünevverSerdaroflu et al³⁸ was found that there is no significant association between Anti-CCP and DAS-28 (P value 0.63) this is due that only (14.3%) patients with RA were positive for Anti-CCP antibodies and (85.7%) patients with RA were negative while in our study only (21%) patients with RA were negative for Anti-CCP while (79%) patients were positive for Anti-CCP.

In contrast to our study MünevverSerdaroflu et al^[38] found a significant association between RF and disease activity in RA (P value = 0.03) while in our study we found no significant association between RF and disease activity (P value =0.252) this is due to that 49% of our patients were negative for RF.

According to the smoking we found a significant association between smoking and Anti-CCP value (P value=0.003), while there is no significant interaction was found between tobacco exposure in relation to the presence of RF (P value=0.15) this result close to Linn-Rasker S P et al³⁹ who found No effect of tobacco exposure on RF status (P value=0.37) while there was association between smoking and Anti-CCP value (P value =0.01), Lee DM et al⁴⁰ found that RA patients with a history of tobacco use demonstrate a mean Anti-CCP value twice that seen in nonsmoking RA subjects. By contrast, no elevation in RF was noted in patients with a history of smoking that support our study.

In contrast to our result Ted R. Mikulset al⁴¹ found no significant association of smoking status or cumulative tobacco exposure with Anti-CCP antibody (P value =0.95) this due to genetic difference between African Americans and Asian people. Frederick Wolfe et al⁴² found there is a significant association between smoking and seropositive RA this due to small number of

smoker patients in addition to high number of seronegative patients in our study.

About the relation between smoking and disease activity in RA, N.G. Papadopoulos et al⁴³ who found a significant association between smoking and DAS-28 (P value=0.001) which is close to our study (P value=0.0001), V. F. Manfredsdottir et al⁴⁴ found gradient of increase in disease activity was observed from never smokers to former smokers to current smokers defined by number of swollen joints (SJC), tender joints (TJC) and visual analogue scale for pain, while Vesperini V et al⁴⁵ found smoking status had no significant effect on disease activity and disability but did reduce 1-year radiographic disease progression, this due to difference in number of smoker and non smoker in that study the number of smoker was 138 and 335 was non smoker while in our study the number of smoker was 22 while non smoker was 78.

Recommendations:

1. Anti-CCP is recommended for Rheumatoid Arthritis patient when follow up is needed for disease activity.
2. Depending on Anti-CCP value as guide treatment decision and describe disease activity in patients with Rheumatoid Arthritis particularly when a decision is taken to start biologic agents.
3. Education of the RA patients about the effect of smoking on disease activity and encourage the smoker patients to stop smoking.

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Geliştarihi/Received on : 02.04.2014

Kabul tarihi/Accepted on: 09.04.2014