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Is there an association between Anti-Citrullinated Peptide Antibodies and the Severity of Rheumatoid Arthritis Parameters in Algerian Patients?

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ABSTRACT

Objectives: The aim of this study was to demonstrate the relationships between anti-citrullinated peptide/protein antibodies status and clinical characteristics, disease severity, radiological damages and laboratory assessment in Algerian patients with Rheumatoid arthritis, as well as their importance like a predictive factor for the diagnosis of Rheumatoid arthritis (RA).

Methods: 281 patients diagnosed with RA according to ACR 1987 criteria in the internal medicine and Functional Rehabilitation departments (the University Hospital of Sidi Bel Abbes) were enrolled in the study based on medical records including age, gender, disease duration, disease activity score (DAS28), joint damages, laboratory tests and treatment. All data were processed and analyzed via SPSS 22.0.

Results: 86.5% of patients were females with a mean age and disease duration of respectively 52.665±12.3477, 4.19±4.050. Patients with Anti-CCP positive (79.7%) presented a high disease activity (**p<0.0001**), a long disease duration (**p=0.016**) and a erosion damages (**p<0.0001**). we did not found any significant relation between gender, hands damages and CRP..A logistic regression showed that the presence of Anti-CCP was associated with Erosion, disease activity, age and RF presence.

Conclusion: There was a strong relation between Anti-CCP antibodies status and the development of RA in Algerian patients. It could be considered as a useful predictor of disease severity.

Keywords: Rheumatoid Arthritis, Algerian Patients, Anti-Citrullinated Peptide/Protein Antibodies, Disease activity, Erosion, Severity.

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INTRODUCTION:

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease and sometimes extra-articular, characterized by irreversible destruction of joints and bones, disability and los of function [1-2-3]. With a prevalence of 0.5% among adults in Western countries, and 0.13% in north Africa (Algeria in particular)[4-5], reliable clinical research with the use of specific tests would be very useful for the early diagnosis of rheumatoid arthritis and therapeutic protocol[6].

Several studies prove that anti-CCP (anti-citrullinated peptide/protein antibodies) and Rheumatoid Factors (RF), have been regarded as major factors in joint destruction[7]. Anti-CCP is a more specific marker compared to RF, due to their high specificity to RA [8].

Recently, the Anti-CCP became a major test of disease course, joints erosion, severity and early diagnosis[9-10-11]. It may be detectable before the onset of RA symptoms[12], which proves their importance in the pathophysiology of RA[13].Furthermore, Anti-CCP antibodies has been involved in criteria for ACR/EURL 2010 classification (the American College of Rheumatology/European League Against Rheumatism)[14]

The aim of this study was to investigate Anti-CCP status in western Algeria population and their association with clinical feature and medical managements (Disease activity, radiographic damages, erosion …) of Algerian patients with RA.as well as their importance in the diagnosis of RA.

PATIENTS AND METHODS:

The population:

We carried out a cross study based on medical records over 281 patients with RA aged of 14 years or over; diagnosed between 2016 and 2019 at the level of Internal Medicine in partnership with Functional Rehabilitation Departments of the University Hospital of Sidi Bel Abbes.

Patients were diagnosed according to ACR 1987 criteria [15]. The local Ethics Committee of University Hospital has approved our study.

We recorded the demographic characteristic such as: sex, age; and clinical and managements like: Disease duration, Disease activity score (DAS28) (running from 0 to 10), Erosion, Radiologic Joint damage, Laboratory assessment and Medication.

Concerning DAS28, the threshold values are over 5.1 for high activity, from 5.1 to 3.2 for moderate activity, between 3.2 and 2.6 for low activity and less than 2.6 for remission [16].

Statistical Analysis:

Patients' characteristics were presented as means and standard deviation for continuous variables and as frequencies and percentages for categorical variables.

For descriptive analysis we present the results as Mean±standard deviation and frequency (%). For the cross study, the categorical variables were tested using Pearson's Khi² test (χ^2) and T test for continuous variables. Logistic regression was used to estimate the independent effects of some RA characteristics on the presence of anti-CCP.

All data were processed and analyzed via SPSS 22.0 **(Statistical Package for the Social Sciences, IBM Corporation; Chicago, IL. August 2013).**The level of significance was <5%

RESULTS:

A total of 281 patients with rheumatoid arthritis were included in our cross study (86.5% were women ; females/males ratio 7.3947), the mean age was of 52.665±12.3477 (range 14-80); The most affected age group was ≥46 years with a rate of 74.4%, 8.2% of males were smokers, More than half of our patients were affected in hands joints (68.3%) followed by wrists (60.1%).The mean disease duration and DAS28 of the enrolled participants were 4.19±4.050 and 4.5128±1.23452 respectively. Concerning the disease activity, 1.1% of patients in the remission status, 13.5% with a low activity, 54.4% with a moderate activity and 31% with a high activity. Positive anti-ccp and RF were noted in 79.7% and 80.4% of patients respectively (Table 1).

Table 2 demonstrate a comparison of various factors such as gender; age; disease duration; erosion; tobacco status; joint damage; ESR; CRP and medication in two rheumatoid arthritis groups (positive and negative Anti-CCP groups).We noted a high signification between the erosion; DAS 28,high activity ; shoulders joints and the positive Anti-CCP group (p=<0.0001). We reported also a signification between Anti-CCp status and tobacco (p=0.047), ESR (p=0.001), Methotrexate use (p=0.003).

Table 03 indicates an analysis of the characteristics of RA such as age; DAS28, joint damage, erosion, ESR in accordance with RF and Anti-CCP status.

We noticed a mutual association of Anti-CCP rate with DAS28 (Figure 1) and Disease duration (Figure 2)

The Binary logistic regression illustrated that the Anti-CCP status was significantly associated with age; disease duration; DAS28; ESR and RF (Table 4).

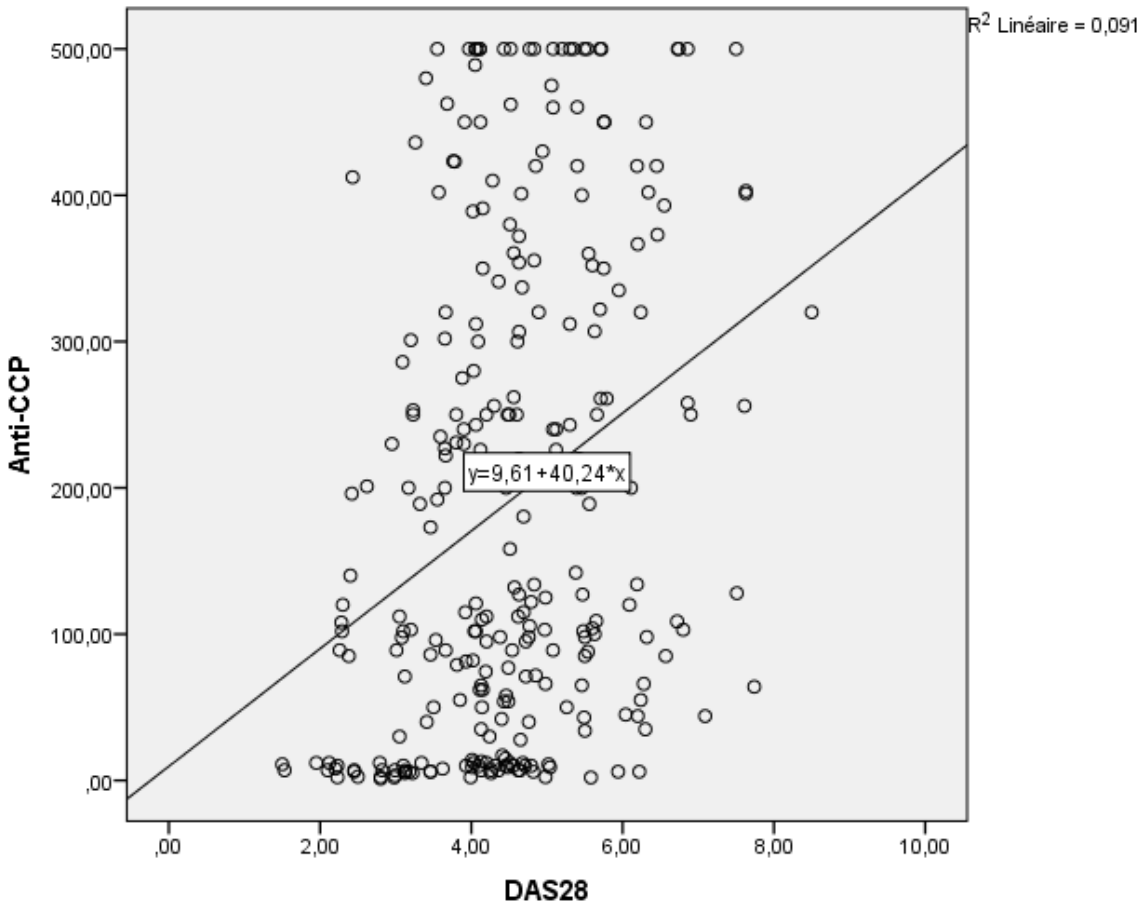

Figure 1: linear correlation between Anti-CCP titer and disease activity score (DAS28)

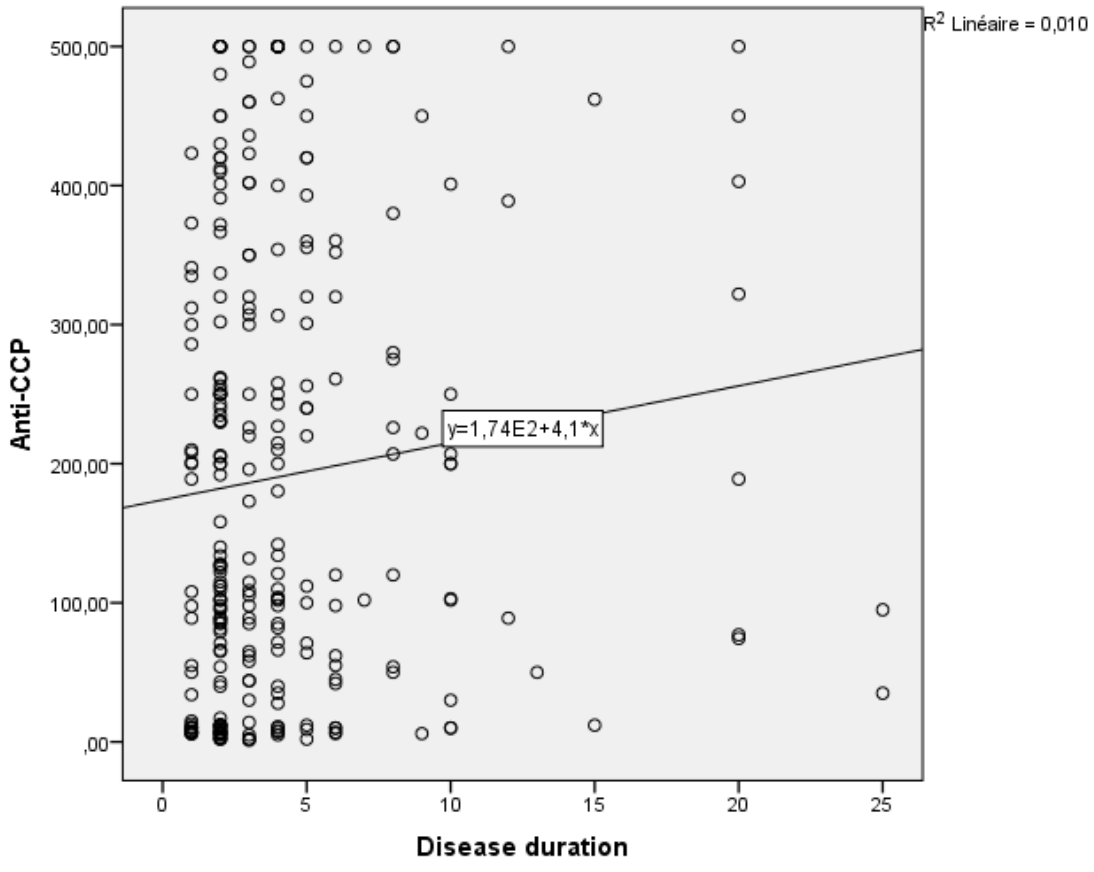

Figure 2: linear correlation between Anti-CCP titer and Disease duration

Table 1 : Charactéristics of RA patients

Characteristics (Mean±SD) or n(%)	**Rheumatoid arthritis n=281**
Female gender	243(86.5%)
Age (years)	52.665±12.3477
≤ 45	72(25.6%)
≥46	209(74.4%)
Disease duration (years)	4.19±4.050
Comorbidity	
Type 2 diabetes	40(14.2%)
Hypertension	114(40.6%)
active tobacco (males)	23(8.2%)
Radiologic Joint damage	
Hands	192(68.3%)
Wrists	169(60.1%)
Knees	158(56.2%)
Elbows	109(38.8%)
Shoulders	100(35.6%)
Feet	86(30.6%)
Ankle	44(15.7%)
Erosion	67(23.8%)
DAS28	4.5128±1.23452
Disease activity	
Remission	3(1.1%)
Low	38(13.5%)
Moderate	153(54.4%)
High	87(31%)
Anti-CCP titer (Ul/ml)	191.1977±164.87025
Positive Anti-CCP	224(79.7%)
RF titer (Ul/ml)	68.5438±76.30074
Positive RF	226(80.4%)
ESR titer (mm/h)	43.434±24.8095
Accelerated ESR	230(81.9%)
CRP titer	17.9390±28.69422
Positive CRP	184(65.5%)
Medication	
Methotrexate	226(80.4%)
leflunomide	45(16%)
Hydroxychloroquine	4(1.4%)
Glucocorticoid	159(56.6%)

Table 2: Data based on Anti-CCP status in RA patients

Characteristics n(%)	**RA patients n=281**		**P value**
	Positive Anti-CCP n=224	**Negative Anti-CCP n=57**	
Female gender	32(11.39%)	6(2.14%)	0.459
Age (years)	51.192±12.940	58.456±11.2870	**<0.0001**
Disease duration (years)	4.48±4.280	3.04±2.712	**0.016**
Erosion	64(22.78%)	3(1.07%)	**<0.0001**
Active tobacco (males)	22(7.83%)	1(0.36%)	**0.047**
Disease activity			
Remission	1(0.36%)	2(0.71%)	**0.045**
Low	18(6.41%)	20(7.12%)	**<0.0001**
Moderate	123(43.77%)	30(10.68%)	0.758
High	82(29.18%)	5(1.78%)	**<0.0001**
DAS28	4.7166±1.19056	3.7119±1.07554	**<0.0001**
Joint damage			
Hands	158(56.23%)	34(12.10%)	0.115
Wrists	144(51.25%)	25(8.90%)	**0.005**
Knees	126(44.84%)	32(11.39%)	0.988
Elbows	94(33.45%)	15(5.34%)	**0.030**
Shoulders	93(33.10%)	7(2.49%)	**<0.0001**
Feet	71(25.27%)	15(5.34%)	0.431
Ankle	39(13.88%)	5(1.78%)	0.109
Laboratory assessment			
ESR(mm/h)	45.875±25.0779	33.842±21.3473	**0.001**
CRP (Ul/ml)	19.0826±31.27544	13.4451±13.99490	0.186
Drugs use			
Methotrexate	188(66.90%)	38(13.52%)	**0.003**
leflunomide	35(12.46%)	10(3.56%)	0.724
Hydroxychloroquine	3(1.07%)	1(0.36%)	0.813
Glucocorticoid	132(46.98%)	27(9.61%)	0.116

Table 3: Charactiristics of RA patients according to Anti-CCP and RF status.

Characteristics n(%)/(Mean±SD)	RA patients n=281			P value
	Anti-CCP- FR- N=55	Anti-CCP- FR+ N=2	Anti-CCP+ RF+ N=224	
Female gender	50(17.79%)	1(0.36%)	192(68.33%)	0.191
Age (years)				
≤ 45	6(2.14%)	00	66(23.49%)	**0.013**
≥46	49(17.44%)	2(0.71%)	158(56.23%)	
Disease duration (years)				
<4	41(14.59%)	1(0.36%)	124(44.13%)	**0.033**
5-11	13(4.63%)	1(0.36%)	86(30.60%)	0.112
12-18	1(0.36)	00	5(1.78%)	0.961
>18	00	00	9(3.20%)	0.306
Erosion	2(0.71%)	1(0.36%)	64(22.78%)	**<0.0001**
Active tobacco(males)	00	1(0.36%)	22(7.83)	**0.006**
Disease activity				
Remission	2(0.71%)	00	1(0.36%)	0.118
Low	20(7.12%)	00	18(6.41%)	**<0.0001**
Moderate	28(9.96%)	2(0.71%)	123	0.373
High	5(1.78%)	00	82(29.18%)	**<0.0001**
Joint damage				
Hands	33(11.74%)	1(0.36%)	158(56.23%)	0.276
Wrists	23(8.19%)	2(0.71%)	144(51.25%)	**0.005**
Knees	31(11.03%)	1(0.36%)	126(44.84%)	0.948
Elbows	14(4.98%)	1(0.36%)	94(33.45%)	0.075
Shoulders	6(2.14%)	1(0.36%)	93(33.10%)	**<0.0001**
Feet	14(4.98%)	1(0.36%)	71(25.27%)	0.558
Ankle	4(1.42%)	1(0.36%)	39(13.88%)	0.073
Accelerated ESR	39(13.88%)	2(0.71%)	189(6.26%)	0.054
Positive CRP	32(11.39%)	1(0.36%)	151(53.74%)	0.391
Methotrexate intake	36(12.81%)	2(0.71%)	188(66.90%)	**0.007**

Table 4: Binary regression for the presence of Anti-CCP

Factors	RA Patients n= 281		
	OR	95% IC	P value
Age (years)	0.945	0,919-0.973	**<0.0001**
Disease duration (years)	1.159	1.023-1.313	**0.021**
DAS28	2.230	1.648-3.017	**<0.0001**
ESR(mm/h)	1.024	1.009-1.039	**0.001**
CRP (Ul/ml)	1.014	0.995-1.034	0.146
RF (Ul/ml)	1.158	1.112-1.206	**<0.0001**

DISCUSSION:

Positive anti-CCP status is primarily associated with bone loss, disability, disease duration and disease activity in RA patients [17]. Our cross study showed this relationship between clinical characteristics, disease activity, joints damages and Anti-CCP status in Algerian RA patient from western Algeria (Sidi Bel Abbes region in particular).

BARRA.L et al illustrated that positive Anti-CCP group were younger (p<0.0001) with a longer disease duration [18]. Moreover, ARNAB.B et al, reported a similar results regarding the duration of the disease and Anti-CCP (p=0.003) [19]. Orsolini. G et al [20] reported as well a correlation between disease duration and Anti-CCP status (p=0.014). Anti-CCP negative patients were older with less disease activity [21].

There is a strong association between anti-CCPs and radiological joints damages [22]. Ghozlani et al [23] confirm the influence of anti-CCPs status on radiological erosion (p=0.001). Furthermore. Yang et al[24] noted a high correlation between Anti-CCP positive and sever joint damage(<0.005).Another study by Im et al[13] showed a significant association between erosion and Anti-CCP positive (p=0.0024). Barra et al [18] conclude the same result in 160 patients (p=0.0058). However, the results of Slimani et al [21] disagreed with previous investigations, they did not find any relation between erosion and Anti-CCP status.

In RA there is a significant association between RF, anti-ccp and disease severity [23-25]. However, patients positive for anti-CCPand RF both had a high risk of disease progression [26]. In addition, Forslind et al.[22] show that anti-CCP appeared to be an important predictor in early RA. Nonetheless, Barra et al [18] did not find any significant association between RF positivity and erosive disease.

A significant relation between radiologic assessment of wrist, hands and positive Anti-CCP was observed in the Serdaroğlu et al data[27]. In our investigation we found a significant correlation between wrist radiologic damages and positive Anti-CCP patients (p=0.005)

According to another investigation [28-29-30-31]. Our study demonstrate a high association between Anti-CCP status and DAS28 (p**<0.0001).** These results were in contradiction with some studies from Tunisia, Thailand, Egypt and Italy [25-30-32-20].

There was no significant correlation between the analyses of laboratory assessment and positive Anti-CCP[23-33-18-27], many studies disagreed with this investigation[19-21-22-34-35], they found a high significant relation between ESR and Anti-CCP status similar to our results (p=0.001).

Smoking increases the high secretion of anti-CCP antibodies in RA patients with shared epitope[36-37]. Forslind et al [22], García de Veas Silva et al [38] reported a high significant association between Anti-CCP status and smoking. Our data demonstrate a significant association (p=0.047). Other studies [18-20] were paradoxical with previous results that showed no significant difference between tobacco status and positive Anti-CCP.

Likewise, The most common received drug in our data was Methotrexate with a significant different with Positive Anti-CCP patients (p=0.003).Nevertheless, some studies did not find any correlation between Methorexate use and Anti-CCP positive [18-21]

CONCLUSION:

Our data showed that Algerian RA patients with positive Anti-CCP antibodies have an active high disease activity and long disease duration. Anti-CCP was considered as a predicator factor for, radiologic erosion joint progression and as prognostic factor of RA to predict the course of disease activity and the effectiveness of the treatment. Further studies on larger numbers of patients are needed to confirm our findings.

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Conflict of interest:

The authors declare no conflicts of interest

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