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Article

Serum level of Anti-Carp, IL-21 and IL-22 in patients with Rheumatoid Arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is a common autoimmune disease characterized by chronic inflammation of synovial joints. Throughout the last decades, several autoantibody systems have been discovered that are associated with RA: anti-CCP test (which measures antibodies directed to cyclic citrullinated peptides), anti-carp test(to determine the levels of anti-CarP antibodies in RA patients), IL-21 and IL-22 levels. The studied group included 60 patients with RA (19 males and 41 females), diagnosed according to the revised diagnostic criteria established by the American College of Rheumatology (ACR) in 2010. The results of the investigations were compared with 30 healthy, apparently controlled individuals. Enzyme-linked immunosorbent assay (ELISA) has been used to estimate the levels of IL-22, IL-21, Anti-CARP, and ACPA in the serum of the studied group**;** the results were then analyzed using IBM SPSS version 28.0.

Keywords: Anti-Carp, IL-21, IL-22, Rheumatoid Arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease that causes progressive articular damage, functional loss, and comorbidity [1]. RA is a systemic disease that affects various body organs such as the lungs, heart, eyes, hands, and red blood cells [2]. RA results from an immune response in which the body's immune system attacks its healthy cells, especially the lining of the joints, known as the synovial membrane, or synovium, causing an inflammatory response (Centers for Disease Control and Prevention, 2020). Meanwhile, RA involves diverse pathogenetic factors, including genetic, environmental, and immunological factors. Recently, it has been reported that a complex regulatory network, including various proinflammatory cytokines and chemokines, may be directly implicated in the specific immunological processes of RA, boosting chronic inflammation and joint destruction [3].

Several autoantibody systems associated with RA have been discovered throughout the last decades. Determination of the presence of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs) is commonly used to diagnose RA [4]. RF positivity has been associated with aggressive and poorer outcomes [5]. Likewise, ACPAs have been associated with disease severity, disability and radiological progression of the disease [6]. ACCP antibodies are principally autoantibodies directed against citrullinated proteins in the synovium of RA patients [7].

Anti-carbamylated protein (anti-CarP) antibodies have been extensively described in RA patients [8], and their presence is associated with radiological damage [9]. Antibodies to carbamylated proteins (anti-CarP antibodies) have been detected in the serum of 36-45% of RA patients [10]. However, risk factors proposed to influence the production of anti-CarP antibodies remain unsubstantiated [11]. Carbamylation is a post-translational modification due to the conversion of amino acid lysine into homocitrulline, in which cyanate is required [12].

Recent findings suggest that Several cytokines may play an essential role in the pathogenesis of various autoimmune diseases, including RA. Accordingly, the search for new cytokines and other modalities of therapy for RA continues. Recently, numerous have shown that cytokine IL-22 is important in RA pathogenesis [13]. In RA, IL-22 possibly induces the proliferation of synovial fibroblasts and the production of chemokines, suggesting its contribution to synovium hyperplasia during RA progression [14]. Higher proportions of IL-22-expressing T cells were found in RA patients' circulation and inflamed synovium [15]. Recently, a few studies suggest the pro-inflammatory/pathogenic role of IL-22 in the onset and development of RA, and IL-22 levels have been associated with radiographic progression in RA [16].

The role of IL-21 in the pathogenesis of RA is poorly understood. Elevated levels of IL-21 have been demonstrated in the synovial tissue of RA patients [17], and Increased IL-21 plasma levels are associated with enhanced disease activity and radiographic status in RA patients [18].

MATERIAL AND METHOD

Subjects:

A group of patients representing a homogeneous sample of rheumatoid arthritis who were referred to the rheumatology unit in Baghdad Teaching Hospital was studied.

60 RA patients (19 males and 41 females) were ascertained and enrolled in the study, and their ages ranged from 25-65 years. The diagnosis was made by the consultant medical staff at the Rheumatology Unit. It was based on clinical examination, X-ray findings and laboratory tests. The diagnosis was according to the Revised diagnostic criteria established by the American College of Rheumatology (ACR), 2010, which included tender and swollen joint counts, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and rheumatoid factors (RF).

The control group was selected from the Iraqi population, which had no history or clinical evidence of RA or any chronic disease and consisted of 30 healthy individuals (11 male, 19 female). Serum samples were tested for (anti-carp, anti-CCP, IL-21, IL-22) by using kits based on sandwich enzyme-linked immune-sorbent assay technology (ELISA).

RESULT

Clinical and demographical picture of the studied Groups

The demographical picture of the studied group in Table 1 reveals that most RA patients are females (41 females out of 68.3%). Moreover, the mean age for RA was (49.45 ± 1.38 years). Additionally, the smokers patients more than non-smokers [(36 (60.0%), 24 (40.0%)] respectively.

Parameter	RA	Control
No.	60	**30**
Gender (F/M)	41 (68.3%) / 19(31.7%)	**19 (63.3%) / 11 (36.7%)**
Age [years] Mean ± SD	49.45 ± 1.38	**49.27 ± 1.94**
Smoking (S/NS)	36 (60.0%) / 24 (40.0%)	**10 (33.3%) / 20 (66.7%)**
No – number of patients, F – number of females, M – number of males, S – number of smokers, NS – number of non-smokers.		

Table 1. Clinical and demographic parameters of patients with rheumatoid arthritis (RA) and control group

Level of Anti-Carp Antibodies in the sera of the studied group

The new diagnostic marker for RA anti-carp was detected in the sera of the RA patients' group. High anti-Carp level means among the RA patients sera (3896.89 ± 343.90) rather than the control group (39.37 ± 5.59). To observe the relation between studied anti-carp antibodies and gender in RA patients and controls, we compared the distribution of Anti-carp antibodies between male and female patients and controls. Male RA patients were observed to have an anti-carp antibody level mean (3979.86 ± 643.08), which was more than that of female patients (3858.44 ± 411.01), but such difference was not significant($P > 0.05$) Table 2.

Gender	Anti-carp antibody level mean ± SE (Unit)		Probability
	Patients group	Control group	
Males	3979.86 ± 643.08	49.10 ± 14.78	$P < 0.001$
Females	3858.44 ± 411.01	33.75 ± 2.11	$P < 0.001$
Total	3896.89 ± 343.90	39.37 ± 5.59	$P < 0.001$
Probability	$P > 0.05$	$P > 0.05$	

Table 2. Distributions of Males and Females according to anti-carbamylated protein (Anti-carp) Antibodies.

Additionally, the associations between the studied Anti-carp antibodies and clinical parameters (smoking) of RA and control were examined. Smoker RA patients were observed to have an Anti-carp level mean (3790.99 ± 438.91),

which was less than that of non-smoker patients (4055.73 ± 562.95), but such difference was not significant. Table 3.

Smoking status	Anti-carp antibody level mean ± SE (Unit)		Probability
	Patients group	Control group	
Smokers	3790.99 ± 438.91	52.12 ± 16.16	P < 0.001
Non-smokers	4055.73 ± 562.95	33.0 ± 1.81	P < 0.001
Total	3896.89 ± 343.90	39.37 ± 5.59	P < 0.001
Probability	P > 0.05	P < 0.05	

Table 3. Distributions of Smokers and Non-smokers according to anti-carbamylated protein (Anti-carp) Antibodies.

Level of Anti-CCP Antibodies in the sera of the studied group

The diagnostic marker for RA is Anti-CCP Antibody, which was detected in the sera of the studied group. The results of its frequency among RA and Control groups are listed in Table 4. The ACCP Antibodies and their relationship to gender were also examined by comparing the distribution of anti-CCP antibodies between male and female patients and controls. Male RA patients were observed to have ACCP level mean (314.65 ± 50.74), which was more than that of female patients (305.07 ± 32.43), but such difference was not significant. (P > 0.05).

Gender	Anti-CCP antibody level mean ± SE (Unit)		Probability
	Patients group	Control group	
Males	314.65 ± 50.74	4.52 ± 1.17	P < 0.001
Females	305.07 ± 32.43	3.31 ± 0.17	P < 0.001
Total	308.11 ± 27.13	3.75 ± 0.44	P < 0.001
Probability	P > 0.05	P > 0.05	

Table 4. Distributions of Males and Females according to anti-cyclic Citrullinated Peptide (ACCP) Antibodies.

Moreover, the associations between the studied anti-CCP antibodies and clinical parameters (smoking) of RA and control were studied. There is a significantly increased anti-CCP antibody level mean of smoker patients compared to smoker controls and non-smoker patients compared to non-smoker controls Table 5.

Smoking status	Anti-CCP antibody level mean ± SE (Unit)		Probability
	Patients group	Control group	
Smokers	299.75 ± 34.63	4.75 ± 1.28	P < 0.001
Non-smokers	320.64 ± 44.42	3.25 ± 0.14	P < 0.001
Total	308.11 ± 27.14	3.75 ± 0.44	P < 0.001
Probability	P > 0.05	P < 0.05	

Table 5. Distributions of Smokers and Non-smokers according to anti-cyclic Citrullinated Peptide (ACCP) Antibodies.

Level of IL-22 Antibodies in the sera of studied Groups

IL-22 level was detected in the sera of RA patients, with a high level of IL-22 among RA patients (148.70 ± 6.07) rather than the control group (55.86 ± 4.73). IL-22 level in male patients (157.88 ± 16.75) was higher than in females (144.44 ± 4.43), but such an increase was not significant (P > 0.05) Table 6.

Gender	IL-22 level mean ± SE (Unit)		Probability
	Patients group	Control group	
Males	157.88 ± 16.75	60.14 ± 7.94	P < 0.001
Females	144.44 ± 4.43	53.38 ± 5.98	P < 0.001
Total	148.70 ± 6.07	55.86 ± 4.73	P < 0.001
Probability	P > 0.05	P > 0.05	

Table 6. Distributions of Males and Females according to Interleukin 22 (IL-22).

The correlation between IL-22 and smoking was also studied, revealing that the IL-22 levels were increased in non-smokers of RA patients compared to smokers, but such an increase was not significant. Table 7.

Smoking status	IL-22 level mean ± SE (Unit)		Probability
	Patients group	Control group	
Smokers	146.24 ± 8.69	61.03 ± 10.60	P < 0.001
Non-smokers	152.38 ± 7.94	53.27 ± 4.86	P < 0.001
Total	148.70 ± 6.07	55.86 ± 4.73	P < 0.001
Probability	P > 0.05	P > 0.05	

Table 7. Distributions of Smokers and Non-smokers according to Interleukin 22 (IL-22).

Level of IL-21 Antibodies in the sera of the studied group

The studies found that IL-21 level was detected in the sera of RA patients, IL-21 level was elevated among RA patients (118.69 ± 13.09) compared to a control group (27.89 ± 3.77), and the level of IL-21 in male patients (143.53 ± 36.14) was higher than female(107.18 ± 5.58), but such increased was not significant (P > 0.05) Table 8.

Gender	IL-21 level mean ± SE (Unit)		Probability
	Patients group	Control group	
Males	143.53 ± 36.14	32.04 ± 7.52	P < 0.05
Females	107.18 ± 5.58	25.45 ± 4.14	P < 0.001
Total	118.69 ± 13.09	27.89 ± 3.77	P < 0.001
Probability	P > 0.05	P > 0.05	

Table 8. Distributions of Males and Females according to Interleukin 21 (IL-21).

And also studied the relationship between IL-21 and smoking. There is no significant increased IL-21 level mean of non-smoker patients(133.31 ± 24.23) compared to smokers (108.94 ± 12.03) Table 9.

Smoking status	IL-21 level mean ± SE (Unit)		Probability
	Patients group	Control group	
Smokers	108.94 ± 12.03	33.29 ± 7.65	P < 0.05
Non-smokers	133.31 ± 24.23	25.16 ± 4.19	P < 0.001
Total	118.69 ± 12.06	27.87 ± 3.77	P < 0.001
Probability	P > 0.05	P > 0.05	

Table 9. Distributions of Smokers and Non-smokers according to Interleukin 21 (IL-21).

Correlation between serological parameters

Table 10 shows the relation between parameters (Age, IL-22, IL-21, Anti-CARP, and Anti-CCP). Found there was a weak positive correlation between age and IL-21 (0.027), which means the level of IL-22 increased with age. Also, there was a strong positive correlation between Anti-CARP and Anti-CCP (1.000**); this supports the findings of the study by [19]. furthermore, there was a strong correlation between IL-22 and IL-21 (0.745**); this supports the findings of the study by [20], which found that IL-21 induces the differentiation of CD4+ T cells that produce IL-22 by a mechanism that involves the transcription factors STAT3 and aryl hydrocarbon receptor (AhR). This may explain the correlation that was found between IL21 and IL-22.

		Age	Anti-carp antibody level	Anti-CCP antibody level	IL-22 level	IL-21 level
Age	Pearson Correlation		0.072	0.072	0.171	**0.232***
	Sig. (2-tailed)		0.498	0.498	0.107	0.027
Anti-carp antibody level	Pearson Correlation			**1.000****	**0.465****	**0.291****
	Sig. (2-tailed)			<0.001	<0.001	0.005
Anti-CCP antibody level	Pearson Correlation				**0.465****	**0.291****
	Sig. (2-tailed)				<0.001	0.005
IL-22 level	Pearson Correlation					**0.745****
	Sig. (2-tailed)					<0.001
IL-21 level	Pearson Correlation					
	Sig. (2-tailed)					
***. Correlation is significant at the 0.05 level (2-tailed).**						
****. Correlation is significant at the 0.01 level (2-tailed).**						

Table 10. Correlations between the studied parameter

DISCUSSION

Though the disease usually begins after 65 years [21], the majority of our patients were 49.45 ± 1.38yrs. This was comparable to the study done by [30]. the mean age was 41.6 ± 11.7 years. As RA is an autoimmune disease, the sex ratio in our study was more in favor of females, supported by the findings [28].

Through our study, it was found that the disease affects smokers more than non-smokers. This was comparable to the study done by [31]. conducted the first meta-analysis investigating the significance of smoking as a risk for developing RA, which suggested that smoking is indeed a risk factor for RA in RF-positive men and heavy smokers. The risk of developing RA was approximately twice as high for smokers than for non-smokers.

Smoking was found to be associated with multiple autoantibody positivity (RF, anti-CCP2, and anti-CarP antibodies) in a previous multicentre cohort study (Netherlands, n=678; United Kingdom, n=761 and Sweden, n=795) [22] But, in our study, it was found that smoking is not associated with risk of autoantibodies.

Increased levels of anti-CarP antibodies were demonstrated in RA patients compared with our study's healthy controls (Table 2). This finding is similar to that in the study performed by [23] in which significantly varied anti-CarP levels were observed in a Japanese RA cohort (p<0.001).

A high level of ACCP was detected in RA patients when compared with the healthy controls in our study (Table 4). This result is similar to that in the study performed by [24], which indicates that the serum anti-CCP antibody level is a valuable potential diagnostic indicator of RA.

A significant correlation was found between ACPA, and anti-CarP antibodies were present (p<0.001), as shown in (Table 10). This supports the findings of the study by [19]. A significant correlation was found when the positivity of ACPA1 and anti-CarP antibodies was present (p=0.026).

The level of IL21 in rheumatoid patients was high compared to control, as shown in Table 8. This agrees with the [25] in which RA patients (19.6 ± 0.79 ng/mL) displayed significantly higher levels of plasma IL-21 compared to healthy controls (2.12 ± 0.08 ng/mL) ($p < 0.0001$). Additionally, the level of IL22 in RA patients was significantly increased compared to control (mean 148.70 ± 6.07pg/ml and 55.86 ± 4.73pg/ml, respectively; p < 0.001) as shown in Table 6. This finding is similar to that in the study performed by [27], in which IL-22 levels were increased in patients with RA compared with controls (mean 432.37 pg/ml and 67.45 pg/ml, respectively; p < 0.001)[34,35].

CONCLUSIONS

The present results revealed that a higher positivity of patients sera for ACPA, Anti-CARP, IL-21 and IL-22 (308.11 ± 27.13, 3896.89 ± 343.90, 118.69 ± 13.09 and 148.70 ± 6.07) respectively in comparison with control groups (3.75 ± 0.44, 39.37 ± 5.59, 27.89 ± 3.77 and 55.86 ± 4.73) correspondingly with highly significant differences (P < 0.001). On the other hand, a significant correlation was found between serum levels of ACPA and anti-CarP antibodies were present (p<0.001), as well as between IL-21 and IL-22 (P < 0.001).

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