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Original Article

Role of Antibodies Against Carbamylated Proteins in Early Detection of Psoriatic Arthritis Patients

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Abstract:

Background: The most prevalent symptoms of psoriatic arthritis (PsA), a chronic musculoskeletal illness linked with psoriasis (PSO), include spondylitis, dactylitis, enthesitis, and peripheral arthritis. Even in the absence of anti-cyclic citrullinated peptide (anti-CCP) antibodies, anti-carbamylated protein (anti-CarP) was linked to joint damage in RA. This finding raised awareness of carbamylation's role in autoimmune and chronic inflammatory disorders.

Aim: To assess the role of antibodies in the early detection of PsA. Its relation to disorder activity, severity and ultrasonographic (US) findings.

Patients and Methods: Observational, comparative study on patients followed up in the Rheumatology and Rehabilitation outpatient clinic and Dermatology departments in Sohag University Hospitals, Faculty of Medicine. Thirty PsA subjects diagnosed based on the Classification Criteria of PsA study; thirty PSO patients diagnosed based on clinical examination by a dermatologist and thirty healthy subjects matching in age and sex considered as controls were included.

Results: There's a highly considerable difference between our studied groups concerning anti-CarP abs. There is a highly significant strong positive correlation between anti-CarP abs concerning DAPSA and DAS 28. There's a highly significant difference in anti-CarP abs regarding US findings.

Conclusion: Since anti-CarP may contribute to the pathogenesis of PsA and is a useful indicator of disease progression, it may be a promising indicator of joint dmage and disease activity in PsA patients and is associated with disease activitv.

Keywords: Psoriatic Arthritis, Anti-Carbamylated proteins, Psoriasis

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Introduction:

The most prevalent symptoms of PsA, a persistent inflammatory musculoskeletal illness linked with PSO, include spondylitis, enthesitis, dactylitis, and peripheral arthritis. PsA has an annual incidence of 6 per 100,000 people and a prevalence of 1-2 per 1,000 people in the general population. [1]

In subjects with PSO, PsA prevalence has been found to be 6%-41% [1], with an annual incidence of 2.7% [2]

Skin and joint symptoms can appear simultaneously in some people, and in 10–15% of cases, the arthritis appears first. In most patients, the skin signs appear first, then the arthritis. [2]

PsA is linked to a negative effect on health related quality of life. [3,4] Higher mortality and increasing joint damage are linked to increased disease activity. [5,6] Early PsA diagnosis and therapy initiation are critical to better long-term results.[7, 8]

The majority of patients have negative results from serological tests for PsA. Although cytokines such as tumor necrosis factor-α (TNF-α). [11] and interleukins (ILs). [12, 13] have been implicated in PsA cases, there are unfortunately no specific indicators for the disorder. [9, 10] Additionally, conventional radiography is not very useful for early detection. [14] Thus, the need for new biomarkers that may be helpful in the diagnosis, prediction, or follow-up of PsA cases remains constant. [15]

Antibodies (Abs) against citrullinated proteins (ACPAs) are essential for patient classification and have emerged as a particular early serological indicator of the disease. Apart from citrulline, carbamyl adducts have also been demonstrated to function as neoepitopes in juvenile idiopathic arthritis [17] and rheumatoid arthritis (RA) [16], resulting in Abs progression that selectively target carbamylated residues (anti-CarP).

RA development was found to be predicted by the existence of anti-CarP linked with joint destruction, regardless of anti-CCP Abs existence .[18]

Protein carbamylation is the non-enzymatic, cyanate-dependent transformation of N-terminal amino groups and lysine residues into α-carbamyl amino acids and ε-carbamyl-lysine (homo-citrulline), respectively. Recent research revealed a new pathway that links inflammation to carbamylation through myeloperoxidase (MPO) activation. Activated neutrophils release MPO, a haem peroxidase. When hydrogen peroxide is present, it catalyzes the conversion of thiocyanate to cyanate, which results in the formation of homo-citrulline. [19] This finding raised awareness of carbamylation's role in autoimmune and chronic inflammatory disorders.

Objective:

To identify the role of anti-CarP Abs in the early detection of PsA. Its relation to disease activity, severity and US findings.

Subjects and Methods:

Design:

This research was carried out as an observational, single-center, comparative study on patients followed up in the Rheumatology and Rehabilitation outpatient clinic and Dermatology departents in Sohag University Hospitals, Faculty of Medicine.

Subjects:

- Thirty PsA cases were diagnosed based on "the Classification Criteria of PsA (CASPAR) study". [20]
- Thirty PSO cases were diagnosed based on clinical examination by a dermatologist.
- Thirty healthy participants matching in age and gender considered as a controls.

Patients' criteria:

Inclusion:

1. >18 years old
2. PsA patients met the diagnostic standards defined by the CASPAR study and with confirmation diagnosis by a Rheumatologist.
3. PSO patients who were diagnosed based on clinical examination by a dermatologist.

Exclusion:

1. Patients <18 years old.
2. Other autoimmune diseases.
3. Malignancy, Hepatitis and active infectious disorders.

Methods:

Clinical evaluation:

- All patients underwent a complete history taking and physical examination with a focus on:
  - Demographic features such as age, gender, residence, education, and occupation.
  - Clinical data as disease onset, duration, and activity, severity parameters, affected joints,

extra-articular characteristics, family history and association with other conditions such as diabetes and hypertension.

- Other system affection as:

1. Ocular as: sicca symptoms (dry eye) \conjunctivitis \ uveitis\ iritis
2. Pulmonary, Neurological, Cardiac, Hematologic, GIT, Renal and Hepatic.

- Treatment: Duration of each drug, single or combined treatment.

Laboratory assessment including:

- Hemoglobin Test (Hb) g\dl
- C- Reactive Protein (CRP) mg\L is a protein in the acute stage that is most commonly estimated. It can be estimated quantitatively using simple and rapid immunoassays.
- Erythrocyte Sedimentation Rate (ESR) mm/hour is a commonly estimated laboratory parameter of disorder activity. It indirectly refers to the considerably elevated levels of serum proteins.
- Rheumatoid factor (RF) IU\ML.
- Venous blood was withdraw using a clean venipuncture and Serum anti-CarP Ab level was estimated by enzyme-linked immunosorbent assay (ELISA) Kit (SinoGenecion, China).

Assessment of disease activity by:

- Disease Activity Score of 28 joints (DAS28).
- The Disease Activity Index for PsA (DAPSA).

Radiographic findings:

- Bilateral US examinations of the proximal interphalangeal (PIP), distal interphalangeal (DIP), and metacarpophalangeal (MCP) joints were performed on all patients.
- Greyscale and Power Doppler studies were done on 28 hand (10 MCP, 8 PIP, and 10 DIP) in both transverse and longitudinal planes. Synovial thickening presence, tendinitis, periosteal reaction, joint synovitis, erosions, and PD abnormality were examined for each patient.
- The severity grade of GS score was defined based on the following grading of synovial thickness [21, 22]: Grade (G) 0: no/minimal thickening (normal); G 1: thickening that protrudes over the line connecting the tops of the bones to form the joint without extending along the diaphyses of the bones; G 2: thickening involves one of the metadiaphyses and G 3: extension involves both metadiaphyses. These scores were applied to derive the US joint count (JC) and joint score (JS) where the GSJC represent the frequency of joints scoring either 1, 2, or 3, out of 28 while the GSJS from the sum of the scores in all 28 joints, out of a total of 84. Accordingly, the GSJC represented the frequency of normal or abnormal joints, similar to the TJC and SJC system employed in the DAS28, whereas the GSJS suggested an assessment of severity. [23]

Ethical Considerations:

- The Scientific Ethical Committee of Sohag University Hospital revised this work.
- All participants provided written consent.
- A brief resume was described to the study participant before inclusion in the study about the aim advantages and any hazards of the research.

Statistical Analysis:

- Data was processed using Statistical Software version 27 (IBM SPSS, Chicago, IL, USA). Description of qualitative data was done as frequencies (%), whereas quantitative ones were represented as mean (±SD), median and range. The normality of the data was tested by the Kolmogorov-Smirnov test. Nonparametric parameters were compared by using the Mann-Whitney Test for the two tested groups and Kruskal-Wallis Test for the 3 or more tested groups Qualitative parameters were compared using the Fisher exact and Chi-square tests. The Spearman rank correlation was done to determine the relationships.
- Sensitivity, specificity, negative and positive predictive values and accuracy tests were determined by using contingency tables. Scatter plots and ROC curve graphs were used. p-value was considered significant if it was less than 0.05

Results:

In our study, most of the studied population were males (60%). The mean age of the studied population was 43±13 SD; the minimum age included was 20 years and the maximum age was 69 years old.

There's a highly significant difference between our studied groups (PsA, PSO and Controls) concerning anti-CarP abs as p-value <0.0001 by

post hoc pairwise tests reveal that there is a significant difference between (PsA and PSO) and (PsA vs Controls) as p <0.0001 (table 1).

There is a highly considerable variation in anti-CarP abs concerning onset as it is higher in acute onset than gradual and there is a highly significant association between anti-CarP abs and duration of PsA as it increases by increasing duration of PsA as p <0.0001. However, there is no marked variance in anti-CarP abs regarding gender, course and PSO duration (table 2).

There's a potential variance in anti-CarP abs in the presence of family history as the p (0.03), more with a family history of PsA (table 3).

There's a highly considerable variation in anti-CarP abs concerning CRP and ESR, but not HB level (table 4 and Figure 1).

There is a highly considerable strong positive relation between anti-CarP abs concerning DAPSA and DAS 28 as correlation coefficient (r)= 0.75, 0.88 with p <0.0001, (table 5 and figures 2 and 3).

There's a highly significant difference in anti-CarP abs regarding normal US as p-value <0.0001 as anti-CarP abs are higher with US findings than normal US. There is also a potential moderate positive relationship between anti-CarP abs regard to GSJC as coefficient (r)= 0.41, with p= 0.025, and a considerable weak positive relationship between anti-CarP abs regard to GSJS as coefficient (r)= 0.39, with p-value 0.035. There's a highly significant difference in anti-CarP abs in PD activity, affection of Right wrist and affection of left wrist as p (<0.0001). However, there's no considerable variation in enzyme regard to erosions as p-value 0.3 (table 6).

ROC curve analysis of anti-CarP abs as a predictor of diagnosis of PsA was shown in table (7) and figure (4); the best cut-off point was chosen for the higher specificity; the most upper left point where the anti-CarP abs were > 2.4. The curve was drawn with the y-axis for sensitivity and the x-axis for (1- specificity). The area under the curve (AUC) was 0. 95 at a confidence level of 95% and confidence limits (0.91 – 0.99) within which the AUC lies. Anti-CarP abs detection as a predictor of PsA was found to be highly specific possessing a high negative predictive value (98.2 %) and highly sensitive with a high positive predictive value (80.5 %). These results were found to be very highly significant (P < 0.0003).

Table 1. Comparison between studied groups as regards anti-CarP abs:

anti-CarP abs	No of cases	Groups			p
		PsA	PSO	Control	
Negative	54	1	25	28	**<0.0001***
Positives	36	29	5	2	
	Mean±SD	4.6±2.7	2±0.8	1.8±0.5	
		P1: <0.001	**P2: <0.001**	**P3: 0.42**	

P1= PsA vs PSO P2= PsA vs Controls P3= PSO vs Controls

Table (2). Comparison between anti-CarP abs concerning gender in our studied groups:

Parameters		No of cases	anti-CarP abs (ng/ml)		p
			Mean± SD	Median (min-max)	
Sex	Male	54	3±2.4	2(1-13.8)	0.34
	Female	36	2.5±1.5	1.8(1-8.2)	
Onset	Acute	22	4.9±3.2	3.7(1.4-13.8)	**<0.0001**
	Gradual	38	2.4±0.9	2.1(1.4-5)	
Course	Progressive	35	3.4±2.6	2.8(1.4-13.8)	0.18
	Regressive	4	3.7±1	3.4(3-5.2)	
	Intermittent	20	3.2±2.2	2.3(1.4-8.5)	
	Stationary	1	1.42	1.42	

anti-CarP abs versus	Duration psoriasis (Years)	Duration PsA (month)
Spearman's Correlation (r)	-0.11	0.72
p	0.39	**<0.0001**

Table (3). Family history among PsA and PSO groups, n=60

Family History	No of cases	Groups			P value
		PsA	PSO		
No family history of autoimmune disease (Non)	35	15(50%)	20(66.7%)		**0.002**
Family history of psoriasis (FS of PSO)	14	8(26.7%)	6(20%)		
Family history of PsA (FH of PsA)	11	7(23.3%)	4(13.3%)		
		Non	**FH of PSO**	**FS of PsA**	**P value**
anti CarP abs (ng/ml)	Mean±SD	3±2.4	2.8±0.9	4.5±3.2	**0.03**
	Post hoc test	**P1:** 0.42	**P2: 0.009**	**P3:** 0.11	

P1= Non vs FH of PSO P2= Non vs FS of PsA P3= FH of PSO vs FH of PsA

Table (4).Comparison between anti-CarP abs concerning different laboratory investigations in our studied groups:

Parameters		No of cases	anti-CarP abs (ng/ml)		p-value
			Mean±SD	Median(range)	
HB	Normal	80	2.8±2	2 (1-13.8)	0.42
	Anemia	10	2.7±1.7	1.7 (1-5.8)	
CRP	Negative (<6) (P1)	49	1.9±0.5	1.7 (1-3.6)	**<0.0001**
	Positive (>6) (P2)		3±1.2	2.9 (1-5.8)	
	Highly positive (>12) (P3)		9.3±2.2	8.5 (8.2-13.8)	
	Post Hoc test		**P1 vs P2**	**P1 vs P3**	**P2 vs P3**
			<0.001	**<0.001**	**0.007**
anti-CarP abs versus ESR					
Spearman's Correlation (r)			0.58		
p-value			**<0.001**		

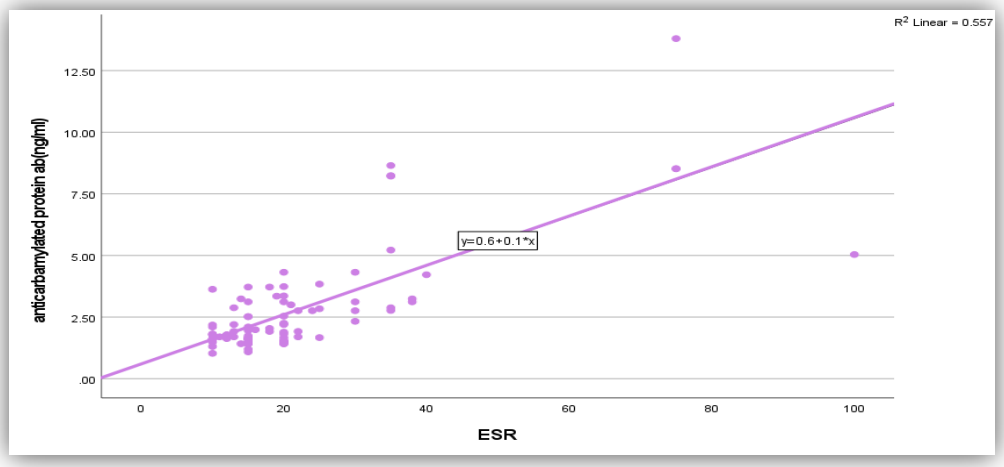

Figure (1). Relationship between anti-CarP abs and ESR

Table (5). Relationship between anti-CarP abs and activity markers in PsA cases, n=30

anti-CarP abs versus	DAS 28	DAPSA
Spearman's Correlation (r)	0.88	0.75
P	**<0.0001**	**<0.0001**

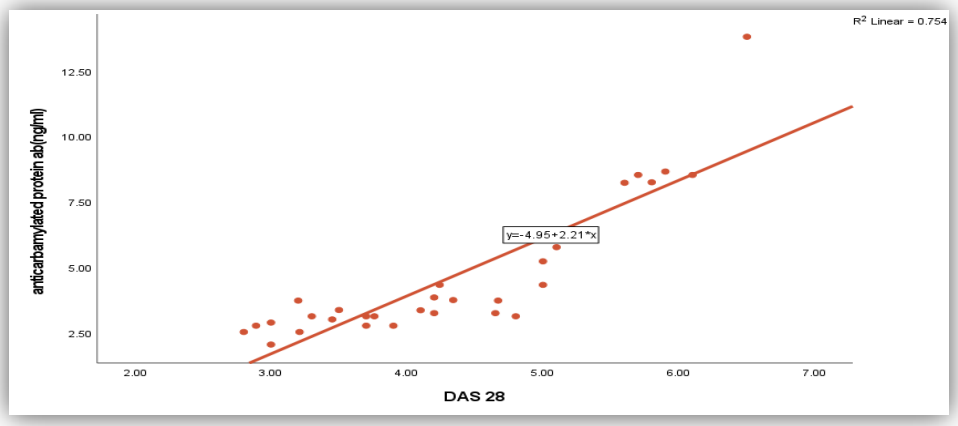

Figure (2). The relationship between anti-CarP abs and DAS 28

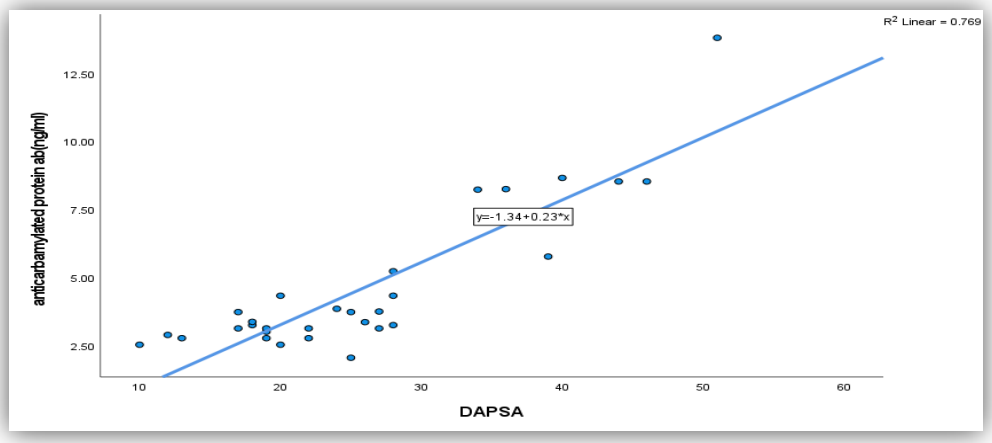

Figure (3). The relation between anti-CarP abs and DAPSA

Table (6). Relationship between anti-CarP abs and GSJC and GSJS in our PsA and PSO groups

Parameters		**No of cases**	**anti-CarP abs (ng/ml)**		**p**
			Mean±SD	**Median(range)**	
Erosions	No	56	3.3±2.4	2.6(1.4-13.8)	0.3
	One joint	2	3.7±0	3.7(3.7-3.7)	
	Two joints	2	3.2±0.16	3.2(3.1-3.4)	
PD activity	No	49	2.5±1	2.2(1.4-5.2)	**<0.001**
	Yes	11	6.8±3.4	8.2(2.8-13.8)	
Right wrist	No (P1)	42	2.7±2	1.96(1.4-13.8)	**<0.001**
	Grade 1 (P2)	7	3.2±0.7	3(2-4.3)	
	Grade 2 (P3)	11	5.7±2.7	5.8(2.8-8.7)	
	Post Hoc test		**P1 vs P2**	**P1 vs P3**	**P2 vs P3**
			0.04	**<0.001**	0.36
Left wrist	No (P1)	40	2.3±1	1.9(1.4-5.2)	**<0.001**
	Grade 1 (P2)	7	3.3±0.66	3.2(2.5-4.3)	
	Grade 2 (P3)	13	6.3±3.4	5.8(2.8-8.7)	
	Post Hoc test		**P1 vs P2**	**P1 vs P3**	**P2 vs P3**
			0.02	**<0.001**	0.23

anti-CarP abs versus GSJC and GSJS	**GSJC**	**GSJS**
Spearman's Correlation (r)	0.41	0.39
p-value	**0.025**	**0.035**

Table (7): shows the ROC curve analysis of anti-CarP abs as a predictor of diagnosis of PsA

Best cut off point	2.425
Sensitivity (%)	96.7%
Specificity (%)	88.3%
PPV (%)	80.5%
NPP (%)	98.2%
Area under curve	0.952, 95.2%
Confidence interval (CI)	(0.91:0.99)
p-value	<0.0001

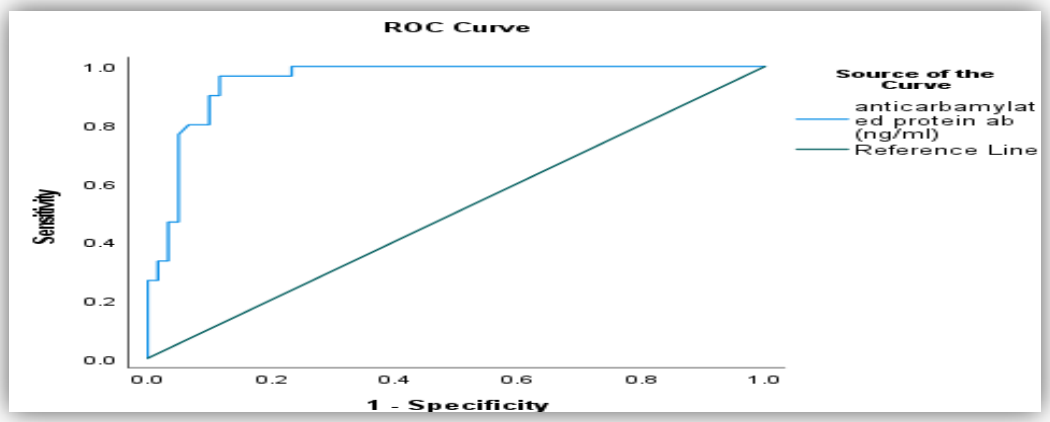

Figure (4). shows ROC curve analysis of anti-CarP abs as a predictor of diagnosis of PsA

Discussion:

PsA is a persistent inflammatory arthropathy identified by enthesitis and synovitis linked with PSO, which lead to cumulative articular cartilage and bone destruction.[24] The implementation of reliable parameters helps in early disease diagnosis and understanding of the pathogenesis. Delay in diagnosis and treatment in subjects with arthritis results in progressive articular damage. [25]

The present work aimed to assess the role of anti-CarP abs in the early detection of PsA, and its relation to the disorder activity, severity and US findings.

Regarding the demographic characteristics of the studied cases, this work revealed no marked variations between the categories as regards age and gender, the mean age of the studied subjects was 43±13 years old and 60% of them were males. Such findings are in agreement with Ibrahim et al. [26] who enrolled 45 PsA patients and 45 matched controls and demonstrated that the mean age of the studied subjectswas 44.58±6.76 years, however, the majority of their cases were females. In accordance, Aboeldahab et al. [27] reported that of the 200 Egyptian PSO cases with a mean age of 42.83±17.3 years; 60% were males. Additionally, Groen et al. [28] included 30 PsA patients and indicated that the mean age was 45.9 years old. Furthermore, Li et al. [15] enrolled 71 patients with PsA and indicated that their average age was 50.2 ±14.3 years old and the male gender represented 61.9%.

There's a highly significant difference between our studied groups (PsA, PSO and Controls) concerning anti-CarP antibodies. Such findings were in agreement with Chimenti et al. [29] who analyzed the anti-CarP ab in sera of 30 patients with active PsA who were negative for ACPA and found significantly increased levels compared to controls (74.6 ±41.3 vs. 13.6 ±9.3 AU/ml, respectively). Similarly, Ibrahim et al. [26] reported that anti-CarP ab serum concentrations were elevated in PsA cases (33.48 ± 14.05 ng/ml) compared to controls (12.21 ± 4.71 ng/ml). Additionally, a previous study by Regueiro et al. [30] assessed the anti-CarP ab as short-term prognostic biomarkers on 978 early arthritis subjects who were followed for two years and found an association of anti-CarP ab with elevated concentrations of all the disease activity variables after arthritis onset. Similarly, Frasca et al. [31] who included 32 adult

PsA cases relying on the CASPAR classification criteria for PsA reported that anti-CarP Abs are present in PsA Synovial Fluid/plasma and, at lower extent, in PSO plasma, but not in controls.

Regarding the clinical characteristics of PsA and PSO groups, the present study indicated that there was a marked elevation in the proportion of subjects who developed acute onset PsA and a considerable elevation in the proportion of individuals who developed gradual onset PSO (P value <0.003). In accordance, El-Komy et al. [32] study included 2534 PSO patients and reported that the majority of cases (85%) had gradual onset disease. A previous study by Zabotti et al. [33] reported that after stimulating infections or following an acute musculoskeletal harm, PsA can be an acute onset of mono-oligoarthritis or oligoarthritis. There was a highly considerable association between Anti-CarP ab and the duration of PsA by month as it increased by increasing the duration of PsA.

The present study indicated that the mean ESR and CRP were markedly higher among PsA cases compared with patients with PSO and controls (P value<0.001). Such findings are in agreement with Ibrahim et al. [26] who reported that a significant correlation was found between the levels of anti-CarP ab among PsA patients and ESR, CRP, and disease activity. Such findings are in agreement with Loo et al. [34] who enrolled 360 cases with PSO, of whom 107 (29.7%) had PsA and demonstrated that PsA was potentially linked with an increased ESR and CRP. Additionally, a previous work by Haroon et al. [35] revealed that high CRP is linked with radiographic damage, the disease being more reluctant to therapy and also has a greater frequency of potential comorbidities.

The current research indicated that a highly considerable strong positive relation between anti-CarP ab and DAPSA (r=0.75) and DAS 28 (r=0.88). Such findings are in line with Ibrahim et al. [26] who reported that a considerable relation between anti-CarP ab and DAS28. Additionally, Chimenti et al. [29] discovered a marked linkage between anti-CarP ab and illness activity in PsA cases. In accordance, Truchetet et al. [36] revealed that anti-CarP–positive subjects had a considerably greater DAS 28 using the ESR at month 36 than anti-CarP–negative individuals (3.1 ± 0.11 versus 2.8 ± 0.06). Anti-CarP–positive early arthritis was linked with a greater risk of experiencing erosions following 96 months of follow-up.

The present study indicated that abnormal ultrasound was found in all patients with PsA (P value<0.001). The current study revealed a marked moderate positive correlation between anti-CarP abs regard to GSJC (r= 0.41, p=0.025), and a considerable weak positive relation between anti-CarP abs regard to GSJS as correlation coefficient (r)= 0.39, with p-value 0.035. There's a highly significant difference in anti-CarP abs in PD activity, affection of Right wrist and affection of left wrist as p-value (<0.0001, <0.0001 and <0.0001 respectively). However, there's no significant difference in enzyme regard to erosions as p-value 0.3. Such findings are in agreement with Ibrahim et al. [26] who evaluated PsA patients and reported a considerable relationship between anti-CarP ab and the musculoskeletal US of the small hand joints using grey scale (GS) and power Doppler (PD) joint counts (r = 0.96, r = 0.9, respectively) as well as with the US joint scores; GS joint score and PD joint score (r = 0.98, r = 0.97 respectively) denoting severity.

The present results indicated that the best cut-off point for anti-CarP ab to diagnose PsA was 2.425, with sensitivity, specificity and AUC 96.7%, 88.3% and 0.952, respectively. Similarly, Chimenti et al. [29] measured the anti-CarP Abs in sera of 30 cases with active PsA who were negative for anti-citrullinated protein Ab and found that the ROC and the AUC using anti-CarP Ab levels registered in the PsA subjects revealed a good accuracy to discriminate PsA cases from the controls. The cutoff value obtained was 32.2 AU/ml, with 100% specificity and 92.3% sensitivity.

Our findings revealed that: Anti-CarP Abs are detectable early with great specificity and sensitivity in PsA cases suggesting an autoimmune background of PsA. There is a correlation between anti-CarP levels and disorder activity. So anti-CarP may be acted as the first evidence of the autoantibodies presence in PsA, represent a promising parameter to predict joint injury and disorder activity in PsA cases and can be useful in improving PsA diagnosis and are related with disease activity.

Conclusion:

The study concluded that:

Anti-CarP Abs are detectable early with great sensitivity, specificity and AUC 96.7%, 88.3% and 0.952, respectively in PsA subjects proposing an autoimmune background.

1. There is a relation between anti-CarP levels and the illness activity
2. Anti-CarP may play a role in the pathogenesis of PsA making it a valuable marker for disease progression, hence anti-CarP may represent a promising marker to predict joint injury and disorder activity in PsA and are correlated with disease activity.
3. The best cut-off point for anti-CarP ab to diagnose PsA was 2.425

Recommendation:

1. Larger scale studies with longer follow-ups are recommended.
2. Future studies are recommended to compare the concentration of anti-CarP Abs in PsA and rheumatoid arthritis cases.
3. Further research is recommended to investigate the predictive role of anti-CarP Abs in response to PsA treatment.

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