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ORIGINAL ARTICLE

Serum Peptidyl Argenine Deiminase - 4 (PADI4) Antibodies in Rheumatoid Arthritis and their Correlation with Disease Activity

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ABSTRACT

Background: Autoantibodies are the hallmark of autoimmune diseases. For Rheumatoid arthritis (RA), they represent equipment for prognosis, detection and analysis of the disease. Several serological markers have recently emerged. For instance, serum Anti-PADI4 that is the enzyme that causes citrullination of proteins leading to autoantibodies production. The goal of this work was to assess the role of peptidyl arginine deiminase type 4 (PADI4) in diagnosis of rheumatoid arthritis and association of its serum level with disease activity.

Methods: A case-control study involving 58 subjects, 29 patients with RA and 29 healthy controls matched in age and sex, was carried out at Department of Rheumatology and Rehabilitation, Zagazig University Hospitals. Detailed history taking, clinical examination and assessment of disease activity using: - DAS-28, modified HAQ, CRP, ESR and PGA. Serum Anti-PADI4 was measured in RA patients and healthy controls using quantitative ELISA technique.

Results: Statistical analysis of the obtained clinical and laboratory data showed a significant elevation of serum Anti-PADI4 in RA patients 15.39±8.89 ng/ml when compared to controls 6.32±10.3* ng/ml (P<0.001). In our study there were no correlations between serum Anti-PADI4, NTJ, NSJ, MHAQ score, ESR, CRP or DAS28. Our study highlighted that Anti-PADI4 sensitivity was 89.5% and specificity was 78.3%.

Conclusions: Serum Anti-PADI4 Abs had a diagnostic value, with no correlation with disease activity.

Keywords: Peptidyl Argenine Deiminase- 4, Rheumatoid arthritis, DAS28 or disease activity, diagnostic, MHAQ

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease of unknown etiology characterized by irreversible joint damage that begins from the first stages of the disease and can lead to deformities, disabilities and deterioration in the patient' s quality of life. Early intervention is critical in preventing irreversible joint damage, so diagnosis as early as possible in first stages is essential [1]. In addition to rheumatoid factor (RF), anti-citrullinated protein/peptide autoantibodies (ACCP) were found to be specific for early stage of RA and have a prognostic value alone or with RF [2]. In addition to the broadly used RF and ACCP autoantibody, several investigations have come into sight for early detection of RA such as serum anti PADI4, Anti-carbamylated protein antibodies, serum anti PADI4 is the ezyme that causing proteins citrullination with autoantibodies production. The autoantibody against Peptidyl Arginine Deaminase (anti PADI4) has been suggested to be a promising serological marker of RA. However, it has not yet been introduced as a routine diagnostic marker [3, 4, 5].There are five PAD enzymes isoforms (PADs 1 to 4 and PAD6), that have been found in humans, with different tissue and cellular distribution. They are chargeable for a process known as citrullination which is post-translational modification of the amino acid arginine to citrulline [6].

The process of citrullination is possibly to be of importance in patients with RA as Anti-PAIDs are expressed in synovial tissues; additionally neutrophils express high levels of anti-PAID and accumulate in the synovial fluid (SF) during disease activity. Of these families, anti-PADI4

found extensively expressed in T cells, B cells, other immune cells such as macrophages, neutrophils, fibroblast-like cells and endothelial cells within the lining and sublining areas of the RA synovium. The immune reactivity induced by PADI4 enzyme activity is a possible antigen of RA autoimmunity [7]. Yang et al [8] showed that PADI4 as an antigen generates antibody responses in patients with RA and these Anti PADI4 antibodies can be used as an additional serological marker with anti CCP and RF. Samara et al [9] and Umeda et al [5] had assessed the value of serum anti-PADI4 as a serological marker of RA and concluded that PADI4 is a possible prognostic tool, either individually or in combination with RF.

Given the above, we decided to evaluate the value and diagnostic significance of anti-PADI4 in RA patients and association of its serum level with disease activity.

METHODS

Study design: A case-control study included fifty-eight subjects: 29 patients with Rheumatoid arthritis and 29 healthy individuals as a control group- was carried out at Zagazig University Hospitals Department of Rheumatology and Rehabilitation Outpatien, betw een April 2019 to November 2019. **Inclusion criteria were:** Age > 16 years old, Patients who fulfilled the 2010 American College of Rheumatology/ European League Against Rheumatism classification criteria for RA **(Aletaha et al., 2010).** Patients with concomitant autoimmune disease, associated with malignancy or infections e.g HCV were excluded. Written Informed consent was obtained from each subject before participation. The approval for the study was obtained from Faculty of Medicine, Zagazig University Hospitals after the approval of the Institutional Review Board (IRB)(IRB#:5311-14-3-2019) in accordance with the Decleration of Helsinki.

Clinical assessment: All patients and controls were subjected to full medical history taking as well as clinical examination. The RA disease activity was assessed using the disease activity score (DAS28) [10] which ranged from <2.6 = remission, < 3.2 = low activity of disease, >3.2 to 5.1 = moderate activity of disease and >5.1 = high activity of disease. Regarding disease activity measured by DAS28, patients were divided in 2 groups (active and inactive).

In addition, Patient's Global Assessment (PGA) of RA disease activity was performed on visual analogue scale (VAS) [11]. Disease-related disability was assessed with the Modified Health Assessment Questionnaire disability index (MHAQ) [12].

Laboratory investigations as erythrocyte sedimentation rate (ESR) using Westergren technique (mm/hr) [13], complete blood count (CBC) was performed through Cell Dyn- Ruby apparatus, liver and kidney functions, C-reactive protein (CRP) through BN prospec nephlometer Semines with normal range (1-6 mg/dl) [14], serum rheumatoid factor using latex agglutination method for RA patients [15].

Using quantitative enzyme linked immune sorbent assay (ELISA) technique, serum Anti-PADI4 was measured in RA patients and healthy controls.

STATISTICAL ANALYSIS

Data were analyzed statistically using IBM SPSS statistics (Statistical Package for Social Sciences) software version 22.0, IBM Corp., Chicago, USA, 2013. According to the type of data qualitative represent as number and percentage, quantitative continues group represent by mean ± SD, the following tests were used to test differences for significance; difference and association of qualitative variable by Chi square test (X2). Differences between quantitative independent groups by t test or Mann Whitney, correlation by Pearson's correlation or Spearman's. Receiver operating characteristic (ROC) curve was used to evaluate the diagnostic performance of markers and find out best cutoff points. P value was set at <0.05 for significant results & <0.001 for high significant result.

RESULTS

Regarding demographic characteristics, RA patients were (25) females (86.2%) and (4) males (13.8 %), their ages were ranging from 22 to 60 years with a mean of (39.62±10.02), while control group were (22) females (75.9 %) and (7) males (24.1 %), their ages ranged from 24 to 55 years with a mean of (37.75±8.63) with no statistically significant difference between both groups. According to disease activity, RA patients are sub grouped into (active and inactive group). This included 24 (82.8%) patients with active RA (22) females (91.7%) and (2) males (8.3%), their ages ranged from 22 to 55 years with a mean of 38.62±9.71 with disease duration ranged from 1 to 15 years, in addition to 5 (17.2%) patients with inactive RA 3 females (60 %) and 2 males (40%), their ages ranged from 30 to 60 years with a mean of 44.4±11.26 (Table 1). As regards disease assessment we noticed that the mean of patient global assessment (PGA) was (4.68±1.25), while that of the functional disease scoring MHAQ was (0.85±0.75) and the mean of disease activity score (DAS28) was (4.35 ±1.17) with (24.1%) had severe disease activity, (44.8%) had moderate disease activity, (13.8 %) had mild disease activity while (17.2%) had disease remission (table 2). The ROC curve of Anti-PADI4 showed that PADI4 has a good sensitivity (89.5%), specificity (78.3%) and accuracy (83.3%) as a diagnostic marker for RA patients with Significant area under curve with

cutoff >10.25 (Figure 1) and (Table 3 and 4). In RA patients Anti PADI4 serum level was ranging from 3.5-41.9 ng/ml with a mean of (15.39±8.89) while in control group its level ranged from 1.3 to 28ng/ml with a mean of (6.32±10.3). This highlighted those controls significantly lowers than cases as regard serum Anti-PADI4, indicating that Anti-PADI4 provides diagnostic value for RA. The range of Anti-PADI4 serum level was from 5.5 to 41.9 ng/ml with a mean of (5.4±8.22) in RA active group, while in inactive group its level was ranging from 3.5 to 39.6 ng/ ml with a mean of (7.11±11.3) with no significance difference (table 5).

There was significant positive correlation between Anti-PADI4 positivity and positive RF status (Table 7). However, no significance association were found between Anti-PAID4 and morning stiffness, tender joints, swollen joints, MHAQ, PGA, DAS28 and ESR. This highlighted that serum PADI4 isn't associated with disease activity (Table 6).

(Table 1) Demographic characteristics of RA patients and RA subgroups (active group and inactive group).

			Control N =29	RA patients N=29	P. value	RA patients N=29		P. value
						Active RA patients N=24	Inactive RA patients N=5	
Demographic data	Age	Mean±SD	37.75±8.63	39.62±10.02	0.45	38.62±9.71	44.4±11.26	0.24
		(Range)	(24-55)	(22-60)		(22-55)	(30-60)	
	Sex	Female	22 (75.9%)	25 (86.2%)	0.31	22(91.7%)	3(60%)	0.062
		Male	7 (24.1%)	4 (13.8%)		2(8.3%)	2(40%)	
	Smoking	Number (%)	5 (17.2%)	3 (10.3%)	0.44	1 20.0%	2 8.3%	0.41
	BMI	Mean±SD	31.62±2.79	30.13±2.87	0.054			
		(Range)	(25-35)	(25-36)				
	Duration s/years	Mean±SD				4.53±3.98	4.0±3.84	0.8
		(Range)				(1-15)	(2-11)	

MW= Mann-Whitnney test of sig, t =t test of significant, SD= Standard Deviation, BMI=body mass index. Age, BMI and disease duration represented as Mean ± SD; the data were analyzed by student t test. While Sex, smoking, are represented as F (%) frequency and percent; the data were analyzed by X2 test. * p. .value <0.05 is significant, ** p. value <0.01 is highly significant

Table (2): PGA, MHAQ and DAS28 among group (1) cases:

		Mean±SD	Range
PGA		4.68±1.25	3-8
MHAQ		0.85±0.75	0-2.7
DAS28		4.35±1.17	1.55-6.77
DAS28 among RA patients		**Number**	**%**
Disease activity	**Mild >2.6 - 3.2**	4	13.8 **%**
	Moderate >3.2 -5.1	13	44.8 **%**
	Severe >5.1	7	24.1 **%**
	Remission ⩽2.6	5	17.2 **%**

PGA (patient global assessment), MHAQ (Modified Health Assessment Questionnaire disability index) and DAS28 (disease assessment score) are represented as Mean ± SD; the data were analyzed by student t test. While Disease activity is represented as F (%) frequency and percent; the data were analyzed by X2 test.

Table (3): showing the ROC curve data for PADI4 cutoff as regard cases

Area Under the Curve (AUC)				
Test Result Variable(s): PAD4				
Area	Cutoff	P	95% Confidence Interval	
			Lower Bound	Upper Bound
0.875	>10.2	0.00**	0.773	0.976
Significant area under curve with cutoff >10.2				

Table (4): Diagnostic characteristics of Anti PADI4

Characters	Value	95% CI
Sensitivity	89.5%	0.41-0.85
Specificity	78.3%	1.0-1.0
Diagnostic accuracy (DA)	83.3%	0.49-0.95
Positive Predictive value (PPV)	79.0%	1.0-1.0
Negative Predictive value (NPV)	88.5%	0.58-0.86

Table (5): serum anti-PADI4 among case, control group and RA subgroups

		Mean±SD	Range	Mann Whitnet	P. value
serum anti-PADI4 among case and control group	Control (N=29)	6.32±10.3*	1.3-28	3.55	0.003*
	RA patients (N=29)	15.39±8.89	3.5-41.9		
Serum anti-PADI4 among RA subgroups	Active RA (N=24)	16.4±8.22	5.5-41.9	1.65	0.087
	Inactive RA (N=5)	14.11±11.3	3.5-39.6		

SD= Standard Deviation. The data were analyzed by Mann-whitney U test.
* P. value <0.05 is significant, ** p. value <0.01 is highly significant.

Table (6): The clinical data of RA positive and negative for Anti-PAD4

	Anti-PAD4 negative	Anti-PAD4 positive	P
Age	38.16±8.76	41.55±12.14	0.32
Sex (M/F)	39/10	8/1	0.51
BMI(kg/CM$^{2)}$	30.67±3.06	32.0±1.5	0.21
Smoking	7/42	1/8	0.81
Disease duration (months)	4.59±2.43	3.97±1.38	0.084
Morning stiffness (minutes)	22.68±11.85	25.42±9.85	0.079
Number of tender joint	9.09±3.98	8.42±2.11	0.214
Number of swollen joint	2.45±0.95	2.57±0.98	0.74
DAS28	4.48±1.21	3.92±0.99	0.098
MHAQ	0.96±0.39	0.91±0.27	0.485
Rheumatoid factor (U/ml)	133.44±51.5	168.71±54.6	0.025*
ESR(mm/hour)	25.18±9.85	21.0±7.11	0.358
CRP	13.28±4.52	15.0±1.88	0.285

BMI (body mass index), DAS28 (disease assessment score), ESR (erythrocyte sedimentation rate), RF (rheumatoid factor), MHAQ (Modified Health Assessment Questionnaire disability index) and CRP (c-reactive protein).
Age, BMI, disease duration, DAS28, CRP, RF, ESR, Morning stiffness, Number of Tender joints, Number of Swollen joints, MHAQ, are represented as Mean ± SD; the data were analyzed by student t test. While Sex and Smoking represented as F (%) frequency and percent; the data were analyzed by X2 test. * p. value <0.05 is significant, ** p. value <0.01 is highly significant.

Table (7): Correlation between PADI4 and clinical, laboratory parameters among group 1 (N=29)

Patient parameters	Anti-PADI4	
	R	P
Age	0.019	0.92
BMI	0.014	0.945
Disease duration	-0.11	0.48
Morning stiffness	0.195	0.313
Number of Tender joints	0.198	0.311
Number of Swollen joints	-0.01	0.92
DAS28	-0.248	0.204
MHAQ	-0.24	0.205
ESR	0.07	0.71
CRP	-0.178	0.285
RF	39.5	0.02*

BMI (body mass index),DAS28(disease assessment score), ESR(erythrocyte sedimentation rate), RF(rheumatoid factor), MHAQ(Modified Health Assessment Questionnaire disability index) and CRP(c-reactive protein). *Correlation is significant at the 0.05 level. ** Correlation is significant at the 0.01 level.

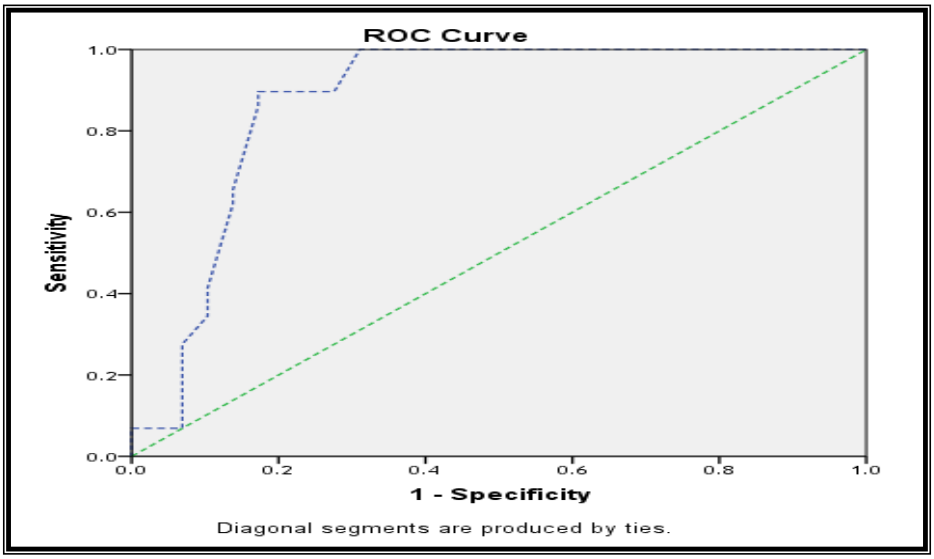

Figure (1): The ROC curve for PAD4 cutoff as regard cases

DISCUSSION

In our study it was found that, the serum level of anti- PADI4 antibodies was significantly higher in RA patients than in healthy control group, the Mean ± SD of its serum level was 15.39±8.89 ng/mL versus healthy controls 6.32±10.3 ng/mL (P<0.001). The cut-off value of PADI4 was (0.2-60) ng/mL, 29 of our patients were above this cut-off value. Significant area under curve with cutoff >10.25. This finding was in agreement with Basu et al. [16] who measured PADI4 antibodies in RA patients in comparison to controls and found a marked increase in PADI4 antibodies in RA patients (P < 0.001). The same results were reported by Ishigami et al. [17] who collected plasma samples from 32 patients with RA, and 20 healthy controls and found that PADI4 levels were 0.89 ± 1.12 ng/ml in RA patients and 0.33 ± 0.12 ng/mL in healthy controls. Significant differences were observed between the RA and the healthy controls (p < 0.01). In addition, Umeda and his colleagues in [5] measured plasma level of PADI4 antibodies in RA patients, SLE patients, and healthy controls and found that the mean PADI4 antibodies levels were 111.9 U/ml in the RA patients, 30.4 U/ml in the SLE patients, and 46.6 U/ml in the healthy controls. The PADI4 antibodies levels were significantly higher in the RA patients than in the SLE patients and the healthy controls (P<0.01, respectively), with cutoff value of 104.7 U/ml.

In our study Anti-PADI4 sensitivity was 89.5% (CI =41%–85%) Specificity was 78.3%% (CI=100.0%). El-Hallous et al. [18] reported that Anti-PADI4 shows sensitivity of 60% and specificity of 95%. While Umeda et al. [5] reported that the sensitivity of Anti-PADI4 in serum of RA patients was 19.6% and the disease specificity was

88.5 % when compared with the healthy controls and disease controls (SLE). This discrepancy in sensitivity might reflect different cutoff levels, racial and genetic backgrounds; also, they had disease controls and healthy controls, while this study included healthy controls only.

When we correlated Anti-PADI4 with the disease activity parameters, we observed no significant correlations between Anti-PADI4 and morning stiffness, number of tender joints, number of swollen joints, modified HAQ, PGA, DAS28, CRP and ESR in RA patients. Also, there was no statistically difference in PADI4 level between both RA subgroups ($p>0.05$). In agreement with this, the study done by Umeda et al. [5] who found that the Anti-PADI4 levels were not correlated with the CRP, ESR, DAS28, MHAQ or with clinical findings. While Qian et al. [19] found that the level of Anti-PADI4 in RA patients was positively correlated with DSA28, ESR ($r = 0.24$, $P = 0.03$; $r = 0.23$, $P = 0.03$) respectively. But no positive correlations were found with number of tender or swollen joints. Our results were in disagreement with the study done by El-Hallous et al. [18] who reported significant positive correlation between the serum level of anti-PADI4 antibodies and the DAS 28 score as a measure of disease activity.

When we correlated Anti-PADI4 Abs. with RF level, we found significant positive correlation ($P <0.05$). This in agreement with El-Hallous et al. [18] who reported that anti-PAD4 antibodies show a strong positive correlation with RF. However, this finding was in disagreement with Qian et al. [19] and Umeda et al. [5] who reported that the Anti-PADI4 levels were not correlated to RF.

Limitation and Recommendations:

Further explore is required to define more precisely the role of Anti-PADI4 Abs. on RA pathogenesis. Further investigations are necessary to assess the serum the PADI4 level in RA patients compared with other autoimmune diseases. Prospective longitudinal studies are needed to investigate Anti-PADI4 Abs. in early and advanced RA patients. Level of PADI4 with different treatment modalities (DMARD and biologic) as a prognostic factor.

CONCLUSION

Our study highlighted that serum Anti-PADI4 Abs represents a useful serologic diagnostic marker in RA patients, but did not correlated with disease activity. It could be an additional diagnostic tool beside RF.

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