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A Useful marker in the assessment of remission and activation of disease in patients with rheumatoid arthritis: Serum human neutrophil peptides 1-3

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Abstract.
AIM: Rheumatoid arthritis (RA) is a chronic disease of unknown etiology. Various cellular and molecular immunological factors are involved in the pathophysiology of RA. Recent studies suggest that neutrophils and alpha-defensins released from the neutrophils assume significant roles in the pathogenesis of RA. The aim of this study was to investigate the potential association between serum alpha-defensin levels and disease activity, functional status, radiological damage and several laboratory parameters in patients with RA.
MATERIAL AND METHOD: A total of 42 patients with established RA who presented to the outpatient clinics of rheumatology of Dicle University Hospital and 38 healthy control subjects were included in this study. Disease activity was assessed by using the Disease Activity Score 28 (DAS28). Quality of life was assessed by using the Rheumatoid Arthritis Quality of Life (RAQoL) Questionnaire and the Nottingham Health Profile (NHP). Functional status was assessed by using the Stanford Health Assessment Questionnaire (HAQ). Laboratory examinations included the following tests: CBC, ESH, CRP, and HNP 1-3.
RESULTS: Patients with active disease exhibited higher HNP 1-3 levels compared to patients in remission. At a cut off value of 708 pg/ml, sensitivity and specificity of the tests for HNP 1-3 were 72% and 70.6%, respectively.
CONCLUSION: In the present study, patients with an active disease had significantly higher serum HNP 1-3 levels compared to patients in remission. In this respect, serum HNP 1-3 can be a useful marker in the assessment of disease activity and remission in patients with RA.

Keywords: Rheumatoid arthritis, human neutrophil peptides, disease activity

1. Introduction

Defensins are a family of anti-microbial peptides [1]. They are involved in a number of immunomodulatory functions including chemotactic activities, induction of

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proinflammatory cytokines and provision of a crucial mucosal defence [2]. Alpha defensins, also known as human neutrophil peptides (HNP) 1-4, are primarily released from the neutrophils [3]. They contribute to the innate and adaptive immune response at systemic level [4,5]. They are small cationic peptides containing 29–35 amino acids that are present in considerable quantities in the azurophil granules of polymorphonuclear cells. They can kill a wide range of Gram-positive and Gram-negative bacteria, fungi, and protozoa [6,7]. In addition to their microbicidal activities, defensins can initiate stimulation of TNF secretion from macrophages [8].

Rheumatoid arthritis (RA) is a chronic joint disease causing severe erosion of the adjacent bone, which is not observed in patients with osteoarthritis (OA). Although an inflammatory process is present in the OA synovial tissue, RA patients demonstrate a higher state of synovial tissue inflammation compared to OA patients. In the pathophysiology of RA, T cells, B cells, macrophages, fibroblasts, and osteoclasts play prominent roles. In addition, neutrophils are important mediators of tissue inflammation in RA, and neutrophils are the most abundant cell type in the synovial fluid [9]. In many studies, there is evidence demonstrating that neutrophils play a critical role in the pathophysiology of RA [10–12].

Recently, alpha-defensins have been implicated in the pathogenesis of autoimmune diseases. In order to investigate the potential role of these defensins in the pathogenesis and progression of RA, we aimed to determine whether or not altered serum levels could be found in patients with RA.

2. Material and method

A total of 46 patients diagnosed with RA according to the ACR 1987 Revised Rheumatoid Arthritis Classification Criteria [13] who went to the outpatient clinics of rheumatology of Dicle University Hospital were included in this study. The control group consisted of 38 subjects who presented to the outpatient clinics of physical medicine and rehabilitation of Dicle University Hospital for other reasons than rheumatic disorders at various dates. Exclusion criteria included the following: administration of biological agents or corticosteroids at a dose of greater than 7.5 mg/day; presence of inflammatory bowel disease, malignancies, overlap syndrome, autoimmune or auto inflammatory disorders, diabetes mellitus, acute infectious conditions or thyroid dysfunction; and history of cerebrovascular events or joint contractures due to a previous trauma.

All the patients, who had been provided with detailed information about the study, gave verbal and written informed consent to the study. The study was approved by the local ethics committee (approval no: 317, approval date: September 2nd, 2014) and performed in compliance with the Helsinki Declaration.

Demographic features of the study subjects were noted. Patients' body weights were noted in terms of kilogram and their heights in terms of centimeter. Body mass index (BMI) was calculated by dividing body weight in kilogram by the square of height in meter. In addition to tender and swollen joints, physician and patient global assessment scores were noted. Laboratory examinations included the following: routine biochemical tests, hemogram, ESR, CRP, anti-CCP, RF, and HNP 1-3. Disease activity was determined by DAS 28 and patient and physician global assessment scores. Patient global assessment score was calculated by asking the patient to select one of the numbers from 1 to 5 (1 = asymptomatic (no disease-related symptom), 2 = mildly active, 3 = moderately active, 4 = very active, 5 = extremely active). Physician global assessment score was also determined by asking the physician to select one of the above numbers.

The Rheumatoid Arthritis Quality of Life Scale (RAQoL) [14] and the Notthingham Health Profile (NHP) [15,16] were used to assess the quality of life; the Stanford Health Assessment Questionnaire [17,18] was used to assess the functional status.

Two-sided radiograms involving both hands and feet were taken to determine the radiographic involvement and erosion. The radiograms were interpreted by two independent radiologists using the Larsen method, and the total score was calculated [19].

A DAS 28 score of < 2.6 was considered to represent disease remission; 2.6–3.2 mild disease activity; 3.2–5.1 moderate disease activity; and > 5.1 high disease activity [20].

Serum HNP 1-3 levels were studied by using the Human HNP 1-3 ELISA Test Kit (Hycult biotechnology, Uden, Netherlands) according to the protocol described in the user's manual provided by the manufacturer.

3. Statistical analysis

Normally distributed data were presented as mean and standard deviation. Non-normally distributed vari-

Table 1
Demographic and clinical properties of the RA and control groups

	RA	Control	P
Age (years) (mean ± SD)	47.1 ± 12.6	32.6 ± 8.2	< 0.001
BMI (mean ± SD)	26.7 ± 4.0	25.9 ± 5.2	0.460
ESR (mean ± SD)	**17.8 ± 10.5**	–	–
WBC count (mean ± SD)	**8.6 ± 2.4**	–	–
Neutrophil count (mean ± SD)	**5.4 ± 2.3**	–	–
CRP (mean ± SD)	1.7 ± 3.1	–	–
HNP1-3 (mean ± SD)	821.9 ± 540.6	835.5 ± 505.8	0.908
Disease duration (months) (mean ± SD)	65 ± 56	–	–
Morning stiffness (minutes) (mean ± SD)	35.3 ± 62.0	–	–
Health assessment qustionnaire score (mean ± SD)	16.2 ± 13.6	–	–
RAQoL score (mean ± SD)	17.4 ± 10.6	–	–
NHP total score (mean ± SD)	49.6 ± 34.5	–	–
NHP energy (mean ± SD)	70.6 ± 41.7	–	–
NHP pain (mean ± SD)	56.9 ± 38.0	–	–
NHP emotional (mean ± SD)	53.9 ± 40.7	–	–
NHP sleep (mean ± SD)	45.7 ± 36.7	–	–
NHP isolation (mean ± SD)	25.7 ± 34.2	–	–
NHP physical (mean ± SD)	46.2 ± 37.9	–	–
Number of Anti ccp positive /Anti ccp negative patients	18/24	–	–
Swollen joint (mean ± SD)	0.6 ± 1.3	–	–
Number of RF +/RF – patients	17/25	–	–
Mean DAS 28 score (mean ± SD)	3.3 ± 1.4	–	–
Number of DAS 28 < 5.1 /DAS 28 > 5.1 patients	34/8	–	–
Tender joint (mean ± SD)	4.1 ± 6.6	–	–
Anti-ccp (mean ± SD)	27.8 ± 68.6	–	–
RF (mean ± SD)	66.2 ± 155.4	–	–
Patient global (mean ± SD)	2.4 ± 1.1	–	–
Physician global (mean ± SD)	2.3 ± 0.9	–	–

BMI: Body mass index; ESR: Erythrocyte sedimentation rate; WBC: White blood count; CRP: C reactive protein; HNP: Human neutrophil peptide; RAQoL: Rheumatoid arthritis quality of life; NHP: Nottingham Health Profile.

ables were expressed as median and 25%–75% percentiles [interquartile range (IR)]. Student's t test was used for the comparison of study parameters that met the parametric test criteria while Mann Whitney-U test was used for those that did not. Chi-square test was used to determine the frequency differences between the categorical groups. Correlation analyses were performed by using the Pearson's rank correlation test. A p value smaller than 0.05 was considered statistically significant. The discriminatory power for each putative marker was described via the area under the curve (AUC) in the receiver operating characteristic (ROC) analysis. All statistical computations were performed with SPSS (Statistical Package for Social Sciences) for Windows Version 18.0 software package.

4. Results

A total of 46 RA patients who presented to the outpatient clinics of rheumatology and 38 healthy control subjects who presented to the outpatient clinics of physical medicine and rehabilitation of Dicle University Hospital were included in this study. Two subjects were later excluded due to missing medical data. A subject was excluded for being diagnosed with and followed up for spondyloarthropathy and another for being diagnosed with lung cancer later in the course of the study. As a result, a total of 42 RA patients remained in the final analysis. The patient group consisted of 37 (88%) women and 5 (12%) men, and the control group consisted of 16 (42.1%) women and 22 (57.9%) men. The patient group and the control group had a mean age of 47.1 ± 12.6 and 32.6 ± 8.2 years, respectively (Table 1). The two groups were significantly different with respect to both mean age ($p < 0.001$) and gender distribution ($p < 0.001$)

There was no significant difference between the groups with respect to BMI (26.7 vs. 25.9 for RA and control groups, respectively; $p = 0.460$).

There were no significant differences between the two groups with respect to HNP 1-3 levels ($p = 0.908$). (Table 1). RA patients were further categorized into active disease and disease remission groups based on a DAS 28 score threshold of 2.6. As a result, 17 of 42 RA patients were found to be in remission and 25

Table 2
Some parameters of RA patients by disease activity

	DAS 28 < 2.6 $n = 17$	DAS 28 > 2.6 $n = 25$	P
HNP 1-3 median (25–75 IQR)	396.7 (203.93–1036.99)	851.76 (606.5–1382.0)	0.028
Age median (25–75 IQR)	46.0 (34.0–59.5)	46.0 (40.5–59.5)	0.512
BMI median (25–75 IQR)	25.5 (23.3–28.5)	27.6 (24.8–29.6)	0.154
Disease duration (months) median (25–75 IQR)	48 (15–96)	60 (12–102)	0.979
ESR median (25–75 IQR)	15.0 (7.5–17.5)	19 (13–28.5)	0.037
CRP median (25–75 IQR)	0.41 (0.17-0.73)	1.13 (0.42–2.59)	0.005
WBC median (25–75 IQR)	8.0 (5.9–9.0)	8.7 (7.5–11.2)	0.060
Neutrophil count median (25–75 IQR)	4.2 (3.1–5.4)	5.5 (4.6–7.5)	0.006

HNP: Human neutrophil peptides; IQR: Interquartile range; BMI: Body mass index; ESR: Erythrocyte sedimentation rate; CRP: C reactive protein; WBC: White blood cell.

Table 3
The correlations between HNP 1-3 level and other laboratory parameters

	ESR	WBC count	Neutrophil count	CRP	Anti-CCP
	p (r)	p (r)	p (r)	p (r)	p (r)
HNP 1-3	0.130	**0.038**	0.074	0.146	0.330
	0.238	**0.321***	0.278	0.228	−0.154

had active disease. The comparison of serum HNP 1-3 levels between the two subgroups of RA patients revealed that the active group had significantly higher HNP 1-3 levels than the remission group ($p = 0.028$) (Table 2). The negative and positive predictive values of HNP 1-3 were calculated as 63.2 and 78.3, respectively. As to the prediction of disease activity, A ROC determined a cut-off value of 708 pg/ml for HNP 1-3. For that value, the test had a sensitivity of 72% and a specificity of 70.6% for prediction of active disease. ROC AUC was 0.70 between the patients with an active disease and those in remission (Fig. 1). ROC AUC of the CRP level and sedimentation rate were 0.76 and 0.69, respectively. In addition, neutrophil count was also higher in the active patient group ($p = 0{,}06$).

In the RA group, serum HNP 1-3 levels did not show any significant correlation with ESR ($p = 0.130$), neutrophil count ($p = 0.74$), CRP ($p = 0.146$), and anti CCP ($p = 0.330$) values whereas it had a positive correlation with WBC count ($p = 0.038$) (Table 3). On the other hand, HNP 1-3 levels correlated significantly with HAQ ($p = 0.033$), RAQoL ($p = 0.051$), and NHP Total scores ($p = 0.028$) (Table 4).

HNP 1-3 levels did not demonstrate any significant correlation with the Larsen total score, a marker of radiographic injury ($p = 0.419$, $r = -0.128$)

There were no significant differences between RF positive and RF negative RA patients with respect to median serum HNP 1-3 levels (749.8 (IR 467.3–1260.4) and 690.1 (IR 238.5–1051.3), respectively; $p = 0.254$). Similarly, there were no significant differences between the two groups with respect to Larsen score ($p = 0.918$), ESR ($p = 0.918$), CRP ($p = 0.356$), WBC count ($p = 0.363$), and neutrophil count ($p = 0.144$).

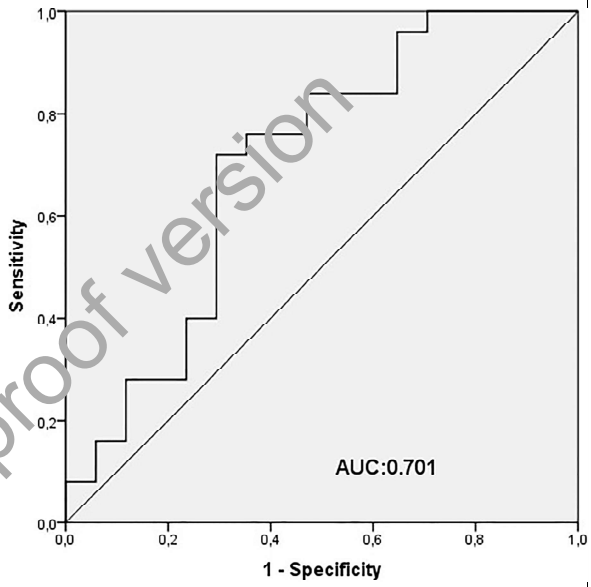

Fig. 1. ROC AUC was 0.70 between the patients with an active disease and those in remission.

There were no significant differences between anti-CCP positive and anti-CCP negative patients with respect to serum median HNP 1-3 levels (745.1 (IR 522.3–1569.0) and 732.8 (IR 236.1–1019.7), respectively; ($p = 0{,}213$)).

5. Discussion

In the present study, there was no significant difference between RA patients and control subjects with respect to serum HNP 1-3 levels. Furthermore, no significant correlation was found between neutrophil count and HNP 1-3 levels. However, HNP 1-3 levels were significantly higher in patients with an active disease

Table 4
The correlations between HNP 1-3 level and quality of life and physical functioning scales in RA patients

	HAQ	RAQOL	NHP Total	NHP Energy	NHP Pain	NHP Emotion	NHP Isolation	NHP Physical	NHP Sleep
	p (r)	p (r)	p (r)	p (r)	p (r)	p (r)	p (r)	p (r)	p (r)
HNP 1-3	0.033	0.051	0.028	0.350	0.005	0.098	0.162	0.017	0.042
	0.330*	0.303	0.339*	0.148	0.423*	0.259	0.220	0.368*	0.315*

compared to those in remission. RA patients having considerable quantities of neutrophils in the joint space containing considerable quantities of alpha defensins, which have the ability to modulate inflammation and immune response [21], led us to investigate the role of defensins in the pathogenesis of RA.

Several previous studies reported a significant correlation between RA and alpha defensins. Ahn et al. studied 51 patients with RA and 21 patients with osteoarthritis and found a significantly higher synovial fluid alpha defensin levels in the RA group compared to the OA group (39.3 ± 3.5 ng/ml vs 18.0 ± 5.6 ng/ml, respectively, $p = 0.002$). They also determined that that difference was more prominent in RF positive subjects compared to RF negative ones [21].

Bokarewa et al. studied blood and synovial fluid samples from 67 RA patients with acute arthritis and blood samples from 22 healthy volunteers. They detected 10–60 times higher HNP 1-3 levels in the synovial fluid compared to matched blood samples. A significant correlation was detected between HNP 1-3 levels and radiological joint destruction [22]. In the present study, on the other hand, no correlation was found between HNP 1-3 and CRP.

Ahn et al. also found a significant increase in IL-6, IL-8, MMP-1 (matrix metalloproteinase) and MMP-3 mRNA expression after applying alpha defensins to fibroblast-like synovial cells in RA. By using C-Jun N-terminal kinase (JNK) and extracellular signal-regulated kinase (ERK) inhibitors, it was also shown that alpha defensins cause IL-6, IL-8, MMP-1 (matrix metalloproteinase) and MMP-3 release. The authors concluded that alpha defensin played a role in the RA pathogenesis by regulating IL-6, IL-8, MMP-1 (matrix metalloproteinase) and MMP-3 production, and these processes acted in relation with JNK and/or ERK and NF-kB pathways [21].

In a study among 14 RA patients and 7 healthy controls, Bovin et al. detected an increased gene expression of alpha defensins 1 and 3 in RA patients compared to healthy controls [23].

The lack of synovial fluid analysis can be considered a limitation of the present study. There are only a limited number of studies investigating alpha defensin levels in RA patients. Our pubmed search also failed to lead us to a study that investigates alpha defensin levels, functional status, disease activity, quality of life, and radiological erosion in RA patients. Unlike the previous studies, administration of TNF alpha inhibitors or corticosteroids at a dose greater than 7.5 mg/day was accepted as an exclusion criterion in this study. Exclusion criteria list was more extensive than those of the previous studies. As a result of a stricter exclusion procedure and various other reasons, sample size remained small, which can also be considered a limitation. In the present study, higher serum HNP 1-3 levels and neutrophil count were found in RA patients with an active disease compared to those in remission. In addition, there were significant correlations between HNP 1-3 and HAQ, NHP total, and WBC count.

Simultaneous elevations in HNP 1-3 levels and neutrophil count can be explained by neutrophils being the source of HNP 1-3. Transfer of HNP 1-3 into systemic circulation from the synovial fluid of the inflamed joints may account for the significantly higher HNP 1-3 levels in RA patients with an active disease compared to those in remission.

The test was determined to have a sensitivity of 72% and a specificity of 70.6% at the specified cut-off value. ROC AUC was 0.70 between the RA patients with an active disease and those in remission. ROC AUC of the CRP level and sedimentation rate were 0.76 and 0.69, respectively. Thus, HNP 1-3 levels might have a high discriminatory power for estimating the activation/remission of the disease in patients with RA.

In the present study, HNP 1-3 levels correlated significantly with the quality of life scores, namely NHP and RAQoL scores, and the physical function scores, namely HAQ scores. Such a correlation may be explained by the reduced quality of life and limited physical function in RA patients with an active disease compared to those in remission [24]. In this context, this correlation supports the elevation in HNP 1-3 levels in patients with an active disease. In addition, a significant difference was observed between the two groups with respect to age and gender distribution; however, this was not considered to have an influence on study results since no study to date has reported HNP 1-3 levels varied by age and gender [25].

The significant correlation between HNP 1-3 levels and HAQ and NHP total scores, which was coupled with higher serum HNP 1-3 levels in patients with an active disease compared to those in remission, suggests that HNP 1-3 levels may be used as a parameter of disease activity or remission. Etiology and pathogenesis of RA are of great interest to the investigators as they are yet to be fully revealed. In this respect, further large-scale randomized clinical trials involving examination of synovial fluid are needed to fully reveal the role of alpha defensins in RA.

Conflict of interest

None to report.

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