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The Role of Alpha Defensins in Patients with Ankylosing Spondylitis

Die Rolle von Alpha-Defensinen bei Patienten mit Ankylosierender Spondylitis

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ABSTRACT

Objectives Defensins are a family of antimicrobial peptides. Elevated levels of human neutrophil peptides (HNP 1–3) are seen in blood samples of patients with inflammatory bowel disease (IBD) and in many rheumatic diseases. It has been suggested that they may play a significant role in the progression and pathogenesis of these diseases. Therefore, we aimed to investigate the levels of HNP 1–3 in sera of patients with ankylosing spondylitis (AS) and its association with disease activity and other clinical features of AS.

Methods A total of 36 patients, who met the Modified New York Criteria for AS, and 50 healthy controls (HCs) were included in this study. The Bath AS Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Disease Activity Score (ASDAS) were used to assess disease activity. The Bath AS Radiology Index (BASRI) was used to assess radiological damage. Spinal and hip measurements were determined by the Bath AS Metrology Index (BASMI). An AS Quality of Life (ASQoL) questionnaire was administered to assess the disease-related quality of life. Serum HNP 1–3 levels were determined using the ELISA kit.

Results Mean serum HNP 1–3 levels were significantly higher in patients with AS (287.01 ± 201.307 vs. 152.09 ± 43.75 pg/ml) compared with HCs ($p = 0.001$). HNP 1–3 levels did not correlate with BASDAI ($p = 0.519$), ASDAS-CRP ($p = 0.424$), BASRI ($p = 0.280$), BASMI ($p = 0.168$), ASQoL ($p = 0.307$), ESR ($p = 0.706$) and CRP ($p = 0.157$) values.

Conclusion Elevated serum levels of HNP 1–3 may play an important role in the pathogenetic mechanisms of AS. This result may give us an opportunity to develop new treatment strategies considering the role of these peptides in the pathogenetic mechanisms of AS.

ZUSAMMENFASSUNG

Zielsetzung Defensine sind eine Familie antimikrobieller Peptide. Erhöhte Spiegel an humanen neutrophilen Peptiden (HNP 1–3) wurden in Blutproben von Patienten mit entzündlicher Darmerkrankung (IBD) und bei vielen rheumatischen Erkrankungen gezeigt. Es wurde vermutet, dass sie eine bedeutende Rolle bei der Progression und Pathogenese dieser Krankheiten spielen könnten. Daher wollten wir die HNP 1–3-Spiegel in Seren von Patienten mit ankylosierender Spondylitis (AS) und deren Zusammenhang mit der Krankheitsaktivität und anderen klinischen Merkmalen untersuchen.

Methoden Insgesamt 36 Patienten, die die modifizierten New Yorker Kriterien für AS und 50 gesunde Kontrollen (HCs) erfüllten, wurden in diese Studie eingeschlossen. Der Bath AS Disease Activity Index (BASDAI) und der Ankylosing Spondylitis

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Disease Activity Score (ASDAS) wurden verwendet, um die Krankheitsaktivität zu bewerten. Der Bath AS Radiology Index (BASRI) wurde verwendet, um radiologische Schäden zu bewerten. Wirbelsäulen- und Hüftmessungen wurden mit dem Bath AS Metrology Index (BASMI) bestimmt. Zur Beurteilung der krankheitsbedingten Lebensqualität wurde ein ASQoL-Fragebogen (AS Quality of Life) ausgefüllt. Die Serum-HNP-1–3-Spiegel wurden unter Verwendung eines ELISA-Kits bestimmt.
Ergebnisse Der mittlere HNP 1–3-Spiegel im Serum war bei Patienten mit AS signifikant höher (287,01 ± 201,307 gegenüber 152,09 ± 43,75 pg / ml) als bei HCs (p = 0,001). Die HNP 1–3-Spiegel korrelierten nicht mit BASDAI (p = 0,519), ASDAS-CRP (p = 0,424), BASRI (p = 0,280), BASMI (p = 0,168), ASQoL (p = 0,307), ESR (p =) 0,706) und CRP (p = 0,157).
Schlussfolgerung Erhöhte Serumspiegel von HNP 1–3 können eine wichtige Rolle für die pathogenetischen Mechanismen der AS spielen. Dieses Ergebnis könnte uns eine neue Gelegenheit geben, neue Therapiestrategien unter Berücksichtigung der Rolle dieser Peptide in den pathogenetischen Mechanismen der AS zu entwickeln.

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disorder which is from the spondyloarthritides (SpAs) family. It primarily affects the spine, peripheral joints and the entheses. Its extra-articular features can affect the eye, heart and the gastrointestinal tract. It has been recognized for a long while that almost 60 % of patients with SpAs develop microscopic inflammatory gut lesions [1]. Alternately, it was shown in previous studies that sacroiliac changes similar to those occurring in AS also occurred in 10 to 20 % of patients with the primary diagnosis of IBD, and 7 to 12 % of patients with IBD had the concurrent diagnosis of AS [2, 3]. Along with clinical and histopathological features, a number of genetic predispositions such as HLA B-27 positivity and common therapeutic strategies such as tumor necrosis factor (TNF) alpha blockers establish a connection between the pathogenetic mechanisms of IBD and SpAs [4–5].

Defensins are involved in a number of immunomodulatory functions including chemotactic activities, induction of proinflammatory cytokines and provision of a crucial mucosal defence [6]. Therefore, defensins play a significant role in the first defence to be provided against microorganisms [7]. Two groups of human defensins are described according to their structural characteristics, namely human α- and human β- defensins. Alpha defensins, also known as human neutrophil peptides (HNP) 1–4, are primarily released from the neutrophils [8]. Apparently, they contribute to the innate and adaptive immune response at systemic level since neutrophils have the ability to circulate around the whole body, engaging in a wide range of antibacterial activity against a number of pathogens [9, 10]. In the light of all these data, we aimed to investigate serum levels of HNP 1–3 in patients with AS and to evaluate the potential association with the disease activity and the other clinical features of AS.

Material and Methods

Thirty-six patients (27 males and 9 females) who met the Modified New York Criteria for AS and 50 healthy controls (HCs) (19 females and 31 males) were included in this study. Data on age, sex, medication and duration of symptoms were noted. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [11] and Ankylosing Spondylitis Disease Activity Score-C Reactive Protein (ASDAS-CRP) [12] were used to assess disease activity. Bath Ankylosing Spondylitis Radiology Index (BASRI) [13] was used to assess radiological damages. Additionally, Bath AS Metrology Index (BASMI) was used for the assessment of spinal mobility [14]. Ankylosing Spondylitis Quality of Life (ASQoL) questionnaire was administered to assess disease-related quality of life [15]. Furthermore, modified Schober test was performed and chest expansion was measured (▶ **Table 1**). Laboratory investigations included erythrocyte sedimentation rate (ESR) test, C-reactive protein (CRP) test, complete blood count, routine biochemical analyses and HLA-B27 analysis. Exclusion criteria were as follows: presence of systemic diseases such as diabetes mellitus and heart failure, history of acute or chronic infections and abnormality in biochemical analyses of blood. Patients who had a history of TNF-α inhibitor therapy or were administered sulphasalazine therapy over the last three months prior to the study were excluded from the study. Healthy people with no clinical evidence of rheumatic diseases or any other systemic disorders were included in the study as control subjects. Serum levels of HNP 1–3 were determined using human HNP1–3 ELISA Test Kit (Hycult biotech, Uden, The Netherlands) in both patients and HCs according to the manufacturer's protocol. All the study was carried out according to the Helsinki declaration and approved by the ethics committee of our university. Participants, who were given prior information about the study, gave their written informed consent to the study.

Statistical Analysis

Data were expressed as mean ± standard deviation (SD). Student's t test was used to test the differences between the groups in respect of variables. Mann-Whitney U test was used for comparison of serum levels of HNP 1–3 in respect of HLA-B27 positivity and disease activity. Chi-square test was used to determine frequency differences between the categorical groups. Correlation analyses were performed using the Pearson's rank correlation test. A p value of 0.05 was considered statistically significant. All the analyses were performed using the Statistical Package for Social Sciences software version 18.0 for Windows.

Results

The average age was 29.4 ± 8.2 among patients with AS and 31.7 ± 7.8 among healthy controls. No significant difference was found between the 2 groups in respect of age (p = 0.198), gender (p = 0.248) and body mass index. (p = 0.068) (▶ **Table 1**). None of the patients

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▶ **Table 1** Clinical and demographic characteristics of patients with AS and HCs.

	AS (n = 36)	HC (n = 50)	p
Age (mean ± SD year)	29.4 ± 8.2	31.7 ± 7.8	0.198
Female/male	9/27	19/31	0.248
BMI (mean ± SD kg/m²)	24.0 ± 3.8	25.7 ± 4.7	0.068
Disease duration (mean ± SD year)	5.4 ± 4.4	–	
BASDAI (mean ± SD)	4.2 ± 1.6	–	
BASRI (mean ± SD)	4.6 ± 2.1		
BASMI (mean ± SD)	2.4 ± 2.8	–	
ASQoL (mean ± SD)	8.1 ± 4.3	–	
ASDAS-CRP (mean ± SD)	2.07 ± 0.68	–	
Modified Schober (mean ± SD)	4.6 ± 1.2	–	
Chest expansion (mean ± SD)	4.5 ± 1.1	–	
HLA B-27 positive/negative	24/12		

AS: ankylosing spondylitis, HC: healthy controls, BMI: body mass index, BASDAI: Bath AS Disease Activity Index, BASRI: Bath AS Radiologic Index, BASMI: Bath AS Metrology Index, ASQoL: AS Quality of Life.

▶ **Table 2** Laboratory findings of patients with AS and HCs.

	AS	HC	p
HNP 1–3 pg/ml	287.01 ± 201.30	152.49 ± 44.44	0.001
ESR mm/h (mean ± SD)	9.88 ± 7.60	6.08 ± 5.45	0.009
CRP mg/dl (mean ± SD)	1.03 ± 1.42	0.35 ± 0.47	0.002

AS: ankylosing spondylitis, HC: healthy controls, HNP: human neutrophil peptides, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein.

has psoriasis history. One patient with ankylosing spondylitis had acute anterior uveitis and 7 patients had active peripheric arthritis. All the patients were under the non-steroidal anti-inflammatory drug treatment. The mean serum level of HNP 1–3 was 287.01 ± 201.307 pg/ml among patients with AS and 152.09 ± 43.75 pg/ml among healthy controls. The difference between the groups was statistically significant (p = 0.001) (▶ **Table 2**). Sixty-six percent of patients with AS were HLA B-27 positive. There was no significant difference between patients who were HLA- B27 positive (288.57 ± 232.37 pg/ml) and those who were HLA- B27 negative (283.89 ± 126.58 pg/ml) in serum levels of HNP 1–3 (p = 0.298). CRP and ESR values were found to be statistically higher in patients with AS compared to healthy controls (p = 0.002 and p = 0.009, respectively). There was no statistically significant difference between patients with AS (mean 7370.27 pg/ml) and healthy controls (mean 7036.66 pg/ml) in white blood cell count (WBC) (p = 0.485) No significant difference was also found in respect with neutrophil counts between 2 groups (4496.57 pg/ml vs 4378.60 pg/ml) p = 0.645. Serum levels of HNP 1–3 did not correlate with BASDAI (r = − 0.111, p = 0.519) BASRI (r = − 0.185, p = 0.280), BASMI (r = − 0.235, p = 0.168) and ASDAS-CRP (r = − 0.139, p = 0.424) (▶ **Table 3**). Furthermore, no correlation was found between neutrophil counts and serum levels of HNP 1–3 in patients with AS (r = 0.265, p = 0.123). WBC count did not correlate with serum levels of HNP 1–3 (r = 192, p = 0.262). Correlataions of HNP 1–3 with WBC, ASDAS_CRP; CRP and ESR were indicated in ▶ **Fig. 1**. The mean serum level of HNP 1–3 was 285.36 ± 196.12 pg/ml among patients with a BASDAI score of 4 and above, those with an active axial disease, vs. 288.85 ± 213.0 pg/ml among patients with a BASDAI score smaller than 4 (p = 0.537), and the difference was not statistically significant.

Discussion

Elavated levels of HNP 1–3 was found in patients with AS in this study. Any correlation between the serum levels of HNP 1–3 and disease activity was not indicated with these results. Evidence suggests that defensins play a pivotal role in the pathogenetic mechanisms of both AS and IBS. In addition, there are many pathogenic relations and therapeutic similarities between IBD and AS.

It has recently been hypothesized that microbial pathogen associated molecular patterns from urogenital and/or GI tract may trigger toll like receptors (TLRs) and lead to chronic inflammation, resulting in enthesitis or arthritis in AS [16]. Either by molecular mimicking or by triggering sensitisation to an endogenous anti-

▶ **Table 3** Correlation between clinical and laboratory findings in patients with AS.

	BASDAI r (p)	BASRI r (p)	BASMI r (p)	Modified Schober r (p)	Chest Expansion r (p)	ASQoL r (p)	HNP 1–3 r (p)	ESR r (p)	CRP r (p)
HNP 1–3	− 0.111 (0.519)	− 0.185 (0.280)	− 0.235 (0.168)	0.210 (0.219)	0.101 (0.556)	− 0.175 (0.307)	1 –	0.065 (0.706)	0.241 (0.157)

AS: ankylosing spondylitis, HC: healthy controls, HNP: human neutrophil peptides, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, BASDAI Bath AS Disease Activity Index, BASRI: Bath AS Radiologic Index, BASMI: Bath AS Metrology Index, ASQoL: AS Quality of Life.

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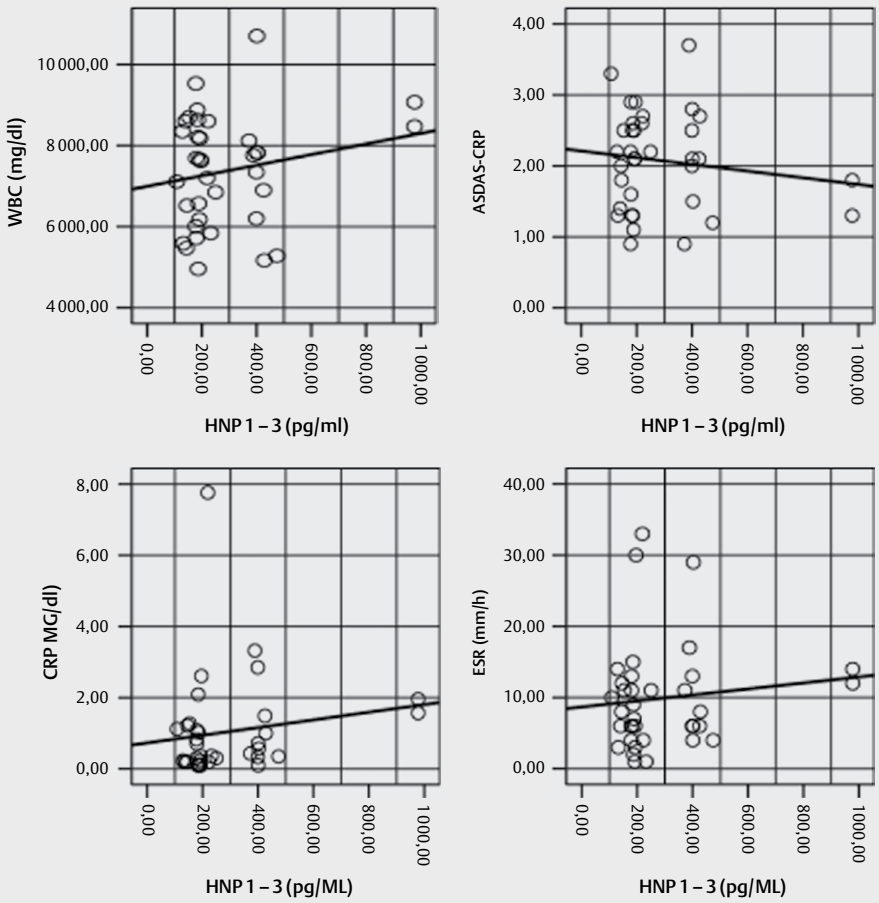

▶ **Fig. 1** Correlations of HNP 1-3 with WBC, ASDAS-CRP, CRP, ESR.

gen, bacterial components may initiate stimulation of TLRs, which activates the adaptive arm of immunity, leading to a sterile but chronic state of inflammation. Defensins play an important role in the first defence against microorganisms. In addition, defensins in the intestinal tract help restrict the invasion and adherence of pathogenic and commensal bacteria [17]. It has been recognized that almost 60 % of patients with SpA develop microscopic inflammatory gut lesions [1], and clinically, 5 to 10 % of patients with AS carry the concurrent diagnosis of IBD [1–3]. Previous studies showed similar sacroiliac changes in both diseases. Turkcapar et al. studied a group of 162 patients with IBD and found SpA in 45.7 % and AS in 9.9 % of the patients. In addition, 63 % of patients with SpA and 100 % of patients with AS were HLA-B27 positive [4]. All these data show that there may be some degree of overlap between the pathogenetic mechanism IBD and that of AS [5].

Defensins are expressed and released on bacterial stimuli that involve TLRs as well as some other stimuli such as cytokines [17]. In addition to their microbicidal activities, defensins can initiate stimulation of TNF secretion from macrophages [18]. Any imbalance in anti-microbial peptides might lead to intestinal inflammation due to their pivotal role in the first defence against microorganisms [19–20].

In a previous study, circulating HNP 1–3 levels were found to be significantly higher in patients with IBD compared to control subjects. In the same study, serum levels of HNP 1–3 significantly correlated with disease activity index scores and serum levels of CRP and TNF-α [21]. In another study, over expression of anti-microbial peptides was shown in ilea of AS patients with subclinical gut inflammation [10]. A study by Praet et al. indicated a connection among gut inflammation, duration of symptoms and disease activity in patients with axial SpA [22].

Subclinical gut inflammation might cause increased gut permeability and prolonged antigen exposure, leading to a sterile but chronic state of inflammation. This supports the hypothesis of an acquired defensin deficiency, probably caused by loss of epithelium in the course of inflammation in patients with AS [10].

It was also shown in previous studies that HNP 1–3 were expressed in intestinal epithelial cells.

Significantly increased plasma concentrations of HNP 1–3 were observed in patients with IBD compared to control subjects, which was possibly caused by increased HNP expression from circulating neutrophils [21, 23]. Furthermore, patients with rheumatoid arthritis (RA) and systemic lupus erythematosus were also shown to have elevated serum levels of HNP 1–3, and it was suggested that

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elevated serum levels of these peptides might play a significant role in progression and pathogeneses of these diseases [24–25].

In the present study, patients with AS were found to have elevated serum levels of HNP 1–3 when compared to healthy controls. In addition, WBC and neutrophil counts did not correlate with serum levels of HNP 1–3. HNP 1–3 are also expressed in intestinal epithelial cells. Previous studies described these defensins only as components of neutrophil granules; however, it is known that expression occurs in intestinal cells in case of active IBD [26]. Thus the source of elevated HNP1–3 levels might be these inflamed epithelial cells. Besides, some portion of the HNP 1–3 might be released from the infiltrating neutrophils within the affected sites into the circulation. In this study, serum levels of HNP 1–3 did not correlate with BASDAI scores or C- reactive protein (CRP) levels which were obtained to assess disease activity. This might have been caused by the small sample size of the study.

In a previous study, the authors found an association between serum levels of HNP1–3 and severe erosive joint disease in synovial fluids of patients with RA [27]. On the other hand, they found no correlation between CRP and HNP 1–3 concentrations but Okcu et al showed elevated serum levels of HNP 1–3 in patients with active rheumatoid arthritis compared to patients who are in remission [28]. We didn't find any correlation between clinical and laboratory parameters in the present study.

An interesting finding of the present study was the relatively low rate of HLA B27 positivity among patients with spondyloarthritis. In a study by some Turkish authors, 73.7 % of 262 patients with AS were HLA B27 positive, which might have been influenced by genetic factors [29].

Patients who had a history of TNF-α inhibitor therapy or were administered sulphasalazine therapy over the last three months prior to the study were excluded from the study as TNF alpha inhibitors and sulphasalzine could produce effects on inflammation in AS and IBD.

To the best of our knowledge, this is the first study in the literature which investigates serum levels of HNP 1–3 in patients with AS.

This study has some limitations. Firstly, sample size was relatively small. Larger studies are needed to evaluate the potential association between serum levels of HNP 1–3 and clinical and radiological findings. Secondly, no ileocolonoscopic research could be conducted to support our findings in patients with AS.

In the present study, patients with AS were found to have elevated serum levels of HNP 1–3 when compared to healthy controls. However, this elevation did not correlate with the disease activity. Findings concerning HNP 1–3 of the studies which investigate rheumatic diseases as well as those of the present study bring about questions about the role of HNP 1–3 in the pathogenesis of AS. Further studies are needed on the role of antimicrobial peptides in AS to achieve a better understanding of the mechanisms of AS with possible implications for future treatment strategies.

Conflict of interest

The authors declare that they have no conflict of interest.

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