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Serum concentrations of antimicrobial peptide cathelicidin LL-37 in patients with bacterial lung infections

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Abstract

Nowadays, data indicate that antimicrobial peptides play an important role in immunological defense. Human cathelicidin LL-37 possesses a broad spectrum of antimicrobial properties against Gram-positive and Gram-negative bacteria, and is thereby an important component of defense mechanisms within the respiratory tract. In this study, we determined the LL-37 serum level in patients with pneumonia caused by different bacteria species in comparison with healthy subjects. Twenty-two patients with pneumonia caused by coccal Gram-positive bacteria (I), 16 patients with pneumonia caused by Haemophilus influenzae (II), 29 patients with pneumonia caused by members of the Enterobacteriaceae (III), 13 patients caused by non-fermenting Gram-negative bacteria (IV), and 30 healthy controls were enrolled in the study. Serum LL-37 concentration was measured using an enzyme-linked immunosorbent assay (ELISA). The mean LL-37 concentration in pneumonia patients was significantly higher in group I ($p = 0.0032$), group II ($p = 0.0022$), and group III ($p = 0.019$), and significantly lower in group IV ($p = 0.000004$) as compared with healthy volunteers. Our data suggest that LL-37 plays an important role in defense mechanisms during pneumonia. The reduced level of this peptide in subjects with pneumonia caused by opportunistic bacteria may reflect weakened immune system reactivity in these patients.

Key words: *pneumonia, immune system, antimicrobial peptides, cathelicidin LL-37, host defense.*

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Introduction

The main function of the immune system is to protect the host against different pathogens, such as bacteria, viruses, and fungi. In response to infection, first mechanisms of innate immunity are involved, in which different body cells such as neutrophils, macrophages, NK cells, dendritic cells, mast cells as well as various humoral factors, i.e. complement proteins, acute phase proteins, and cytokines, play roles. Acting together, these cells and humoral factors produce an inflammatory response to eliminate the invading microorganisms. Without a doubt, in antimicrobial defense, an extremely important role is played by the adaptive immunity mechanisms, in which B cells, different subsets of T lymphocytes, and antibodies are involved. Nowadays, more and more data indicate that in antimicrobial defense some small molecules, such as cathelicidins and defensins, take part. From among these antimicrobial peptides, cathelicidin LL-37, the only known member of the cathelicidin family expressed in humans, has essential importance [1].

Peptide LL-37 is produced by mucosal epithelial cells, neutrophils, monocytes, macrophages, mast cells, NK cells, T and B lymphocytes, adipocytes, and keratinocytes. Its expression is regulated by various endogenous factors, including proinflammatory cytokines, growth factors, as well as an active form of vitamin D. Cathelicidin LL-37 possesses a broad spectrum of antimicrobial properties against Gram-positive and Gram-negative bacteria with microbicidal activity against many different species and strains. It exhibits antiviral activity and acts against fungal infection, as well. Peptide LL-37 directly kills pathogens by disrupting their membranes and participates in the neutralization of biological activity of bacterial endotoxins. Furthermore, it can re-engineer bacterial biofilms and may prevent their formation. Additionally, LL-37 strongly affects inflammatory processes, as acts as a chemoattractant for neutrophils, monocytes, macrophages, eosinophils, and

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mast cells [1-3], stimulates chemokine production, increases chemokine receptor expression, and induces interleukin (IL)-1b generation by monocytes. In concert with IL-1b, peptide LL-37 promotes the inflammatory response of macrophages and directs their differentiation toward macrophages with a proinflammatory signature [4]. Moreover, peptide LL-37 influences innate and adaptive immune responses developed in response to infection. It restrains programmed cell death by enhancing expression of the anti-apoptotic BcL-xl protein [5], and by blocking the activity of caspase-3 activity [6]. This results in the suppression of neutrophil apoptosis, which extends the neutrophil lifespan and increases phagocytosis. LL-37 up-regulates the autophagy-related gene expression in macrophages and induces autophagosome formation to promote the killing of intracellular bacteria, as well [7]. Peptide LL-37 affects the Toll-like receptor (TLR)-mediated response and transports self-DNA into monocytes and plasmacytoid dendritic cells, leading to activation of TLR9 and production of type I interferons (IFNs) [8, 9]. This peptide may modulate dendritic cell differentiation and dendritic cell-induced T-cell polarization [10] and can up-regulate CD86 and HLA-DR expression in dendritic cells [11]. LL-37 significantly increases migration of $CD4^+$ T cells, as well [12].

Cathelicidin LL-37 is produced by airway epithelial cells and immune cells that are resident in or recruited to the respiratory tract. The presence of LL-37 in bronchoalveolar lavage (BAL) fluid, nasal lavage, tracheal aspirate samples obtained from new-born children, sputum, and saliva was documented. Thus, it is obvious that this peptide contributes to the barrier function of intact respiratory epithelia and it is an important component of defense mechanisms within the respiratory tract. Hence, it can be assumed that LL-37 might be involved in the immune response in the course of lung bacterial disease. The exact role of this peptide in defense mechanisms against bacteria within the respiratory tract is not well known and the data are not entirely clear. Therefore, in this study, we sought to determine the cathelicidin LL-37 serum level in patients with lung infection caused by different varieties of bacteria and to compare them with those of healthy subjects.

Material and methods

Study participants

Eighty adult patients with pneumonia symptoms and 25 healthy adult volunteers were included in this study. Subjects were selected from the patients of the Pulmonary Disease Hospital in Lodz. All individuals were subjected to an initial evaluation that included: a clinical examination, radiological findings, basic laboratory blood parameters including alanine aminotransferase (ALAT), aspartate aminotransferase (AspAT), total bilirubin, urea, creatinine, glucose, C-reactive protein (CRP), white blood cell (WBC) count, and microbiology standard laboratory methods. Exclusion criteria were as follows: taking antibiotics for last three months, taking immunosuppressive or antihistamine agents, chronic inflammatory diseases, systemic diseases, immunological disorders (AIDS, allergy), and neoplastic processes. Patients were divided into four clinical groups, according to their lung infectious agent. The groups were the following: subjects with pulmonary infection caused by coccal Gram-positive bacteria, i.e. *Staphylococcus aureus* ($n = 17$), *Streptococcus pneumoniae* ($n = 4$), or *Streptococcus pyogenes* ($n = 1$) (group I); subjects with pneumonia caused by *Haemophilus influenzae* ($n = 16$; group II); subjects with pneumonia caused by members of the *Enterobacteriaceae*, i.e. *Escherichia coli* ($n = 12$), *Enterobacter cloacae* ($n = 5$), *Klebsiella pneumoniae* ($n = 3$), *K. mobilis* ($n = 1$), *K. oxytoca* ($n = 3$), *Serratia liquefaciens* ($n = 1$), *Raoultella terrigena* ($n = 1$), *Raoultella ornithinolytica* ($n = 1$), *E. aerogenes* ($n = 1$), *Proteus mirabilis* ($n = 1$) (group III); and subjects with pneumonia caused by non-fermenting Gram-negative bacteria, i.e. *Pseudomonas aeruginosa* ($n = 10$), *Stenotrophomonas maltophilia* ($n = 2$), *Acinetobacter baumannii* ($n = 1$) (group IV). Twenty-five healthy subjects were randomly selected from a control group (group V). All subjects were informed about the aims and methods of the study and expressed their written informed consent for participation in the study. The study protocol was approved by the Bioethics Committee of the Medical University of Lodz (approval no. RNN/785/13/KB).

Laboratory measurements

Blood samples were obtained from all the patients before the commencement of the treatment and from the control subjects. Blood samples were collected between 8 am and 9 am after ensuring at least 8 h overnight fasting. WBC count was determined using a Sysmex XS-1000i TM automated hematology analyzer (Sysmex Corporation, Japan) in blood samples collected into tubes with an anticoagulant. For LL-37 and CRP measurement blood samples were collected directly into serum separator tubes and centrifuged (10 min, 3500 rpm). Immediately, after the centrifugation process, CRP serum levels were determined using a latex-enhanced immunoturbidimetry and automatic analyzer, Dirui CS-400 (Dirui, China). For LL-37 measurement, all serum samples were kept frozen at $-80^{o}C$ until analysis. The concentration of LL-37 in serum was assessed using an ELISA kit (MyBioSource, USA).

Statistical analysis

The statistical analysis was performed using Statistica 12.5 (StatSoft Inc., USA). Simple descriptive statistics (means, standard deviation (SD)) were generated for LL-37, WBC and CRP variables. Normality of distribution was tested with the Shapiro-Wilk test. Serum concentration

Table 1. Demographic and clinical characteristics of the study population

	Group I	Group II	Group III	Group IV	Control group
n	22	16	29	13	25
Age (years)	65 ±15	70 ±14	70 ±8	74 ±9	44 ±13
Gender (M/F)	16/6	13/3	15/14	10/3	12/13
ALAT (U/l)	23.68 ±14.73	15.87 ±5.79	24.17 ±12.96	17.33 ±8.64	24.44 ±12.57
AspAT (U/l)	21.86 ±10.39	21.13 ±8.42	24.59 ±15.36	16.58 ±5.04	22.48 ±5.71
Total bilirubin (mg/dl)	0.39 ±0.18	0.45 ±0.13	0.46 ±0.28	1.06 ±1.95	0.56 ±0.22
Urea (mg/dl)	37.34 ±11.91	35.29 ±17.47	32.32 ±17.08	41.43 ±9.20	25.66 ±5.68
Creatinine (mg/dl)	0.93 ±0.24	0.86 ±0.17	0.85 ±0.23	1.37 ±1.44	0.81 ±0.15
Glucose (mg/dl)	102.64 ±17.87	98.67 ±12.05	101.39 ±15.30	102.54 ±16.08	79.16 ±14.16

Values expressed as mean ±SD, M – male, F – female, AspAT – aspartate transaminase, ALAT – alanine transaminase, WBC – white blood cell count, CRP – C-reactive protein

of LL-37 and CRP, as well as WBC count, were compared using the Mann-Whitney U test. The relationships between the serum concentrations of LL-37 and CRP in all groups were expressed as Spearman's correlation coefficients. $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics of the study subjects are shown in Table 1. In group I, the mean (±SD) age was 65 ±15 years, and the male/female ratio was 16/6. In group II the mean age ±SD was 70 ±14 years, and the male/female ratio was 13/3, and in the *Enterobacteriaceae* group (III) the mean age ±SD was 70 ±8 years, and the ratio was 15/14. In group IV, the mean age ±SD was 74 ±9 and there were 10 men and 3 women. In the control group the mean age ±SD was 44 ±13 years and the proportion of men and women was as 12 to 13. Age and gender distributions were not statistically different between the groups. The levels of basic laboratory parameters, including AspAT, ALAT, total bilirubin, urea, creatinine, and glucose, in all groups were within normal ranges.

The serum levels of LL-37 in patients infected with Gram-positive bacteria (group I), patients with pneumonia caused by *H. influenzae* (group II), patients with infection caused by *Enterobacteriaceae* family pathogens (group III), and patients infected with Gram-negative nonfermenting rods (group IV) ranged from 0.11 to 90.59 ng/ml, from 0.09 to 33.27 ng/ml, from 0.11 to 86.12 ng/ml, and from 0.10 to 0.77 ng/ml, respectively. In healthy subjects, LL-37 concentration in serum ranged from 0.25 to 12.79 ng/ml. The mean concentrations of serum LL-37 in groups I, II, III, and IV were 5.25 ±19.25 ng/ml, 3.79 ±8.89 ng/ml, 8.92 ±19.65 ng/ml, and 0.29 ±0.20 ng/ml, respectively. The mean concentration of LL-37 in healthy individuals was 2.71 ±3.57 ng/ml (Table 2). Statistical analysis revealed statistical differences in group I ($p = 0.0032$), group II ($p = 0.0022$), group III ($p = 0.019$), and group IV ($p = 0.000004$) as compared with healthy volunteers. What is more, there were no significant differences in LL-37 concentration between groups I, II, III and IV.

Table 2. LL-37, WBC, and CRP values of the pneumonia patients and control subjects

	LL-37 (ng/ml)	WBC (× 10^9/l)	CRP (mg/l)
Group I	5.25 ±19.25	9.12 ±2.70	70.14 ±81.57
Group II	3.79 ±8.89	9.36 ±4.31	59.10 ±79.10
Group III	8.92 ±19.65	8.99 ±3.36	46.60 ±79.71
Group IV	0.29 ±0.20	12.53 ±9.87	50.30 ±37.27
Control group	2.71 ±3.57	5.72 ±1.29	1.38 ±1.23

Values expressed as mean ±SD; WBC – white blood cell count; CRP – C-reactive protein

There were significant differences for WBC between study groups and healthy controls (I vs. V – $p = 0.000001$; II vs. V – $p = 0.0016$; III vs. V – $p = 0.000008$; IV vs. V – $p = 0.0032$). Similarly, there were significant differences for CRP concentration between study groups and healthy controls (I vs. V – $p = 0.000000$; II vs. V – $p = 0.000000$; III vs. V – $p = 0.000000$; IV vs. V – $p = 0.0000000$) (Table 2). Significantly higher levels of CRP and WBC in the patients from groups I, II, III, and IV, compared to the control group, confirmed the ongoing infection. Spearman's correlation tests revealed no statistically significant correlations between LL-37 and CRP serum levels and LL-37 serum levels and WBC count ($p > 0.05$).

Discussion

Data relating to cathelicidin LL-37 expression in the course of bacterial infections are scarce. It was shown

that neonates with congenital pneumonia had significantly higher serum concentrations of LL-37 [13], and newborn infants with pulmonary infections exhibited elevated LL-37 levels in tracheal aspirates [14], as compared with healthy controls. It was documented that circulating levels of LL-37 in children with post-infectious bronchiolitis obliterans were higher than in healthy subjects [15]. Moreover, elevated circulating LL-37 levels in adult patients with pulmonary tuberculosis, in comparison with healthy subjects, were noted [16]. In our previous studies, we also observed significantly higher concentrations of this peptide in the serum of adult patients with pulmonary tuberculosis [17]. Significantly elevated LL-37 levels in bronchoalveolar lavage (BAL) fluid of children with pulmonary tuberculosis were noted, as well [18]. Visser *et al.* [19] documented higher levels of this peptide both in serum and cerebrospinal fluid of children with tuberculous meningitis compared with those of patients with bacterial and viral meningitis. Elevated LL-37 levels in gingival crevicular fluid (GCF) [20] and in saliva [21] of patients suffering from periodontitis were also reported. It should be emphasized that a significant elevation of LL-37 gene expression in blood of patients with active pulmonary tuberculosis, compared with those in subjects with latent tuberculosis and healthy individuals, was observed [22]. Additionally, it was stated that expression level of cathelicidin mRNA in the skin of patients with infective cellulitis was elevated, as compared with the expression in the skin of healthy volunteers [23]. On the other hand, in diabetic foot ulcer biopsies, the LL-37 expression level was low or zero in comparison with healthy skin, and cultured epidermal cells from these biopsies infected with *S. aureus* showed lower LL-37 expression compared with cell cultures from healthy donors' skin [24]. It was also observed that *Neisseria gonorrhoeae* infection caused downregulation of LL-37 transcript and peptide levels in the cervical epithelial cell line [25]. Decreased circulating LL-37 levels in patients with leprosy [26] and in the course of septic shock [27, 28] were documented, as well.

In this study we evaluated the serum levels of peptide LL-37 in patients with pneumonia caused by different bacterial pathogens, i.e. some Gram-positive bacterial species (*S. aureus*, *S. pneumoniae*, *S. pyogenes*), *H. influenzae*, various species of the *Enterobacteriaceae* family (*E. coli*, *E. cloacae*, *K. pneumoniae*, *K. mobilis*, *K. oxytoca*, *S. liquefaciens*, *R. terrigena*, *R. ornithinolytica*, *E. aerogenes*, *P. mirabilis*), and some species of opportunistic bacteria (*P. aeruginosa*, *S. maltophilia*, *A. baumannii*). For comparison, we checked LL-37 concentrations in serum of healthy individuals. We demonstrated that serum concentrations of LL-37 in subjects with pneumonia caused by different bacterial species were significantly higher than in healthy controls. It should be noted that there were no statistically significant differences in LL-37 level in patients with pneumonia caused by the different etiological agent. Moreover, we have observed that in patients with opportunistic bacterial infection the circulating level of this cathelicidin was significantly lower than in healthy subjects.

The respiratory tract is especially exposed to contact with different pathogens entering via inhalation and through nasal and oral mucosal surfaces. Thus, the innate and adaptive immune responses within the respiratory system are very important. Growing evidence indicates that antimicrobial peptides, including cathelicidin LL-37, take part in the pathomechanism of various respiratory diseases [29-31], i.e. cystic fibrosis [32], interstitial lung disease [33], and bronchiolitis [34, 35]. Furthermore, as LL-37 has a broad spectrum of antimicrobial activities [36, 37] and can directly kill various Gram-positive and Gram-negative bacteria [38-40], one can assume that it plays an important role in defense mechanisms during lung infectious diseases. Our observation that in the course of bacterial pneumonia caused by various pathogenic bacteria strains the LL-37 level is raised seems to confirm such a suggestion. The reduced level of this peptide in subjects with pneumonia caused by opportunistic bacteria may reflect weakened immune system reactivity in these patients. However, further studies are needed to clearly explain the role of cathelicidin LL-37 in defense mechanisms in the course of infectious diseases within the respiratory system.

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The authors declare no conflict of interest.

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