JIMR - Journal of Islamic Medicine Research
Published by Faculty of Medicine, Universitas Islam Malang
Email: jimr@unisma.ac.id
Home Page :http://riset.unisma.ac.id/index.php/fk
E-ISSN: 2580 927X
Pages: 65 – 73

Correlation between LL-37 Levels and *Scoring of Atopic Dermatitis* (SCORAD) in Atopic Dermatitis in dr. Saiful Anwar General Hospital Malang

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ABSTRACT

Introduction: *Atopic dermatitis (AD) is a chronic, recidive inflammatory skin disease that is associated with hyper-reactivity of the immune response to environmental allergens. LL-37 is an antimicrobial peptide which plays an important role in the pathogenesis of AD. Several studies conducted to find out LL-37 expression on the skin of patients showed varying and contradictory results. Studies aimed to find out the association of LL-37 levels in circulation with AD degree of severity are still very limited. The aim of this study are to determine the relationship between serum LL-37 levels and Scoring Atopic Dermatitis (SCORAD) score and to determine the relationship between serum LL-37 levels and the severity of atopic dermatitis.*

Method: *This study is analytic observational cross sectional study. The subjects are 30 patients with AD who came to Outpatient Care for Dermatovenereology and Outpatient Care for Pediatric Allergy in dr.Saiful Anwar General Hospital (RSSA) Malang and fulfilled the inclusion and exclusion criteria. The subjects are grouped into 2 groups based on AD severity, i.e. mild and moderate-severe based on SCORAD index. The measured variable is serum LL-37 levels with enzyme-linked immunosorbent assay (ELISA) method.*

Results: *The mean serum LL-37 levels are 12.4±6.7 ng/ml for mild degree AD and 9.4±6.06 ng/ml for moderate/severe degree AD. Statistical analysis using Pearson parametric statistic test shows no significant correlation (p> 0.05) between serum LL-37 levels and SCORAD score in patients with AD. Serum levels of LL-37 in this study are lower than the normal score in circulation.*

Conclusions: *LL-37 serum levels in AD do not experience an increase and is not related to SCORAD score.*

Keywords*: Atopic Dermatitis, LL-37, SCORAD*

INTRODUCTION

Atopic dermatitis (AD) is a chronic residive skin inflammatory disease associated with hyper reflexibility of the immune response to environmental allergens (1). Based on the records of the Indonesian Pediatric Dermatology Study Group, AD cases in 2013 were 11.8% (2). Based on the data obtained from the medical record of Outpatient Care for Dermato-venereology of dr. Saiful Anwar General Hospital Malang from 2009-2013, the percentages of patients with AT reached 2.14% of all patients (Unpublished). Atopic dermatitis is a disease that has psychosocial and economic impact, and it also has considerable contribution in health

financing (3,4). AD pathogenesis is the result of a complex interaction between genetic and environmental factors, exacerbated by defects in the skin barrier and dysregulated immune responses (5). Inflammation in AD lesions is biphasic with the dominance of Th-2 immune responses in the acute phase, followed by the dominance of Th-1 immune responses in chronic phase (1). Initiation of inflammation in AD is not clearly known. The presence of lesion in the epidermis due to scratching, exposure to environmental allergens, and microbial colonization leads to inflammation(6). Dysregulation of the immune response in the acute phase affects the expression of LL-37, an antimicrobial peptide considered to have an important role in the pathogenesis of AD(7,8). Several studies aimed to determine the relationship between LL-37 expression in skin tissue and the severity of AD lesions have been done with varying, and sometimes, contradictory results. So far, researches that aim to determine the relationship between LL-37 levels in the circulation and the degree of severity of AD are still very limited. To the extent of the author's knowledge, studies aimed to determine the relationship between serum LL-37 levels and severity of AD in Indonesia have not been found.

SUBJECTS AND METHODE

The research design used in this research is analytic observational cross sectional which aims to determine the relationship between serum LL-37levelsand SCORAD score in AD. Research sample in this research is all research population that fulfilled inclusion and exclusion criteria and visited Outpatient Care for Dermatovenereology and Outpatient Care for Pediatric Allergy of dr.Saifulanwar General Hospital Malang.

Procedures in Measuring Degree of Severity

The diagnosis of AD and the determination of the degree of severity were performed by anamnesis, physical examination with typical clinical features according to Hanifin Rajka and SCORAD criteria by two consecutive examiners on the same day (9,10).

Specimen Collection and Handling Procedures

Collect blood samples in tubes containing citrate, heparin or EDTA. Centrifuge for 10 minutes at 1,000X g in 30 minutes. The plasma samples must be tested immediately or stored in temperatures <-20°C. Avoid repeated freezing cycles. The plasmaspecimen should be clear and not hemolytic.

Measurement Procedure of Serum LL-37 Level

Serum LL-37 level is determined from 5 ml of veined blood sample using venoject and vaccutainer from the median cubital vein. The blood sample is then centrifuged; the serum is taken and measured using ELISA kit.

Processing and Data Analysis Technique

After filling the data on the data collection sheets, the data is then processed using Statistical Package for Social Sciences (SPSS) version 15. The correlation is tested using the Pearson test formula if the distribution is normal and homogeneous. If the distribution is abnormal and not homogeneous, then a non parametric statistical test is performed by using Spearman test(11).

RESULTS

Subject Basic Data

To determine whether or not there is a difference in subject basic data based on DA category, cross tabulation (crosstab) followed by T test and Mann-Whitney test is carried out to find out the homogeneity of the data. Table 1 shows that the characteristics of the subjects which consist of age, gender, SCORAD score and its components in mild category and moderate/severe category are significantly different.Meanwhile, the result of measurement of total serum IgE level and peripheral blood eosinophil percentage does not show significant difference between 2 study groups.

Table1. Subject Basic Data by Category of Atopic Dermatitis

Characteristics	DA n(%)		Total	*p* value
	Mild (n=14)	Moderate/Severe (n=16)		
Age (year)	21.14 ±7,24	21.56±7, 38	21.37 ±7,19	0.877*
Gender Male female	4(28.6) 10(71.4)	6(37.5) 10(62.5)	10(33.3) 20(66.7)	0.697**
SCORAD	21.29 ±3.3	38.50±6.89	30.47 ±10.28	0.000**
Extension	10.71 ±7.22	26.50±17.29	19.13 ±15.56	0.003**
Lesion width	3.43± 0.51	6.13±1.41	4.87± 1.74	0.000**
Subjective symptoms	6.71± 3.02	11.81±3.49	9,433 ±4,13	0,000**
Total serum IgE level	170(43.76-2579)	316,75(72.43-4495)	-	0.240*
Peripheral Eosinophil Percentage	3.41± 1.82	4.28±2.65	3.88± 2.30	0.312**

*p<0,05 used *Mann-Whitney*
** p<0,05 used *T-test*

The measurement result of serum LL-37 levels in 2 study groups shows a statistically insignificant difference, with the mean in mild DA group being relatively higher than the mean in moderate/severe group.

Table 2. The Measurement Result of Serum LL-37 Levels

serum LL-37 level (ng/ml)	DA n=3	
	Mild n=14	Moder
Mean	12.4	
SD (standard deviation)	6.7	

* p<0,05 used *T-test*

Correlation between Serum LL-37 Levels and SCORAD Score and Its Components

The relationship between serum LL-37 levels and SCORAD score is tested by the Pearson Correlation test (Table 3). Based on the results of Pearson test analysis, correlation coefficient of-0.238 with p = 0.205 is obtained, so it can be concluded that there is no relationship between serum LL-37 levels and SCORAD score.

Table 3. Correlation between Serum LL-37 Level and SCORAD Score and Its Components

Characteristics	serum LL-37 levels	
	R	*p*
SCORAD category	-0.238	0.205
Lesion width	-0.264	0.159
Lesion intensity	-0.358	0.052
Subjective symptoms	-0.092	0.628

Correlation between LL-37 Serum Levels and Several Clinical and Laboratory Parameters

In this study, LL-37 levels are also correlated with age, gender, total serum IgE levels and percentage of eosinophil in peripheral blood. The result of Pearson correlation test shows that there is a significant relationship between age and serum LL-37 levels with correlation coefficient of 0.405 with p = 0.026.

Table 4. Correlation between Serum

LL-37 Levels and Several Clinical and Laboratory Parameters

Characteristics	serum LL-37 levels	
	R	*p*
Gender	-0.317	0.088
Age	0.405	0.026
Total serum IgE levels	-0.215	0.254
Eosinophil count	-0.094	0.621

The study involved30ADpatients with ages ranging from 9 to 35 years, and the highestpercentageis in the age group17-25 years old (56.67%). The number of female subjects is higher when compared to male subjects in mild and moderate/severe AD groups. The ratio of women is bigger than men because most subjects are in 17-25 age group. In general, the incidence of ADin female is higher than that in male with a ratio of 1.3: 1.0 (5). A research conducted by Silverberg & Haniffin (12) found that AD prevalence in adult was 3.2% with female having bigger ratio than male. The relationship between gender and the prevalence of AD is not clearly known(13). It is thought that the high prevalence of ADin women isdue to differences in patterns of genetic interaction with the environment during childdevelopment. Another factor is the possibility of a misdiagnosis in cases of allergic contact dermatitis or irritant contact dermatitis commonly occurs in girls, resulting in a prevalence bias(14). Differences in the prevalence of AD in each region in the world are related to the magnitude of environmental influence on the development of AD(4). The grouping ofresearch subjects based on mild and moderate-severe AD categories is due to the disproportionate number of subjects related to the sampling method used(11). A study conducted by Willemsen, et al (2009)(15) on the severity of AD found that most AD patients were included in mild AD category. In this study, 1 severe AD subject, 15 moderate AD subjects, and 14 mild AD subjects were obtained. In the sampling for research on seasonally-influenced diseases, it is recommended to have a longer period(16). This study was conducted within 3 months with patients having atopic dermatitis with clinical manifestations influenced by climate and environment as the research subjects(17).

Atopic dermatitis is considered as skin manifestation of a systemic abnormality characterized by elevated

DISCUSION

Serum IgE levels and peripheral eosinophilia(6). The measurement of total serum IgE levels is a rough screening method for detecting AD, and it is important to measure the severity of the disease and the evaluation of the result of therapy(18,19). Eosinophil is one of the factors that influence the mechanism of inflammation in AD skin lesions. The dominance of Th-2 immune response in AD is characterized by an increase in IL-5 secretion that triggers formation, activation, and chemotaxis, as well as eosinophil apoptosis deceleration(20). Eosinophil cell infiltration in AD skin lesions triggers IL-12 secretion that affects the process of immune response switching in acute and chronic AD lesions. An increase in eosinophil count in the circulation may be related to the degree of AD severity, but may also be considered as a variable of laboratory parameter(21). In AD the dysregulation of immune response is indicated by the increase of total serum IgE(19). In this study, measurement of total serum IgE levels and eosinophil count in peripheral blood are conducted. Increased serum total IgE levels were obtained in 73.3% of subjects, with moderate/severe AD group being relatively higher than mild AD group, but not statistically significant. The measurement of eosinophil count in peripheral blood between mild AD group and moderate AD group was not

significantly different. In a research conducted by Ahmed & Nasreen (2007)(18)in child population, it was found that elevated serum IgE levels were obtained in 70% of subjects, and were associated with the severity of the disease. In a literature review, it was found that elevated IgE levels were obtained in 80% of patients with AD. Increased levels of IgE can be found in individuals without AD. On the contrary, normal IgE levels can be found in patients with AD(18). A study aimed at finding out the relationship between peripheral eosinophilia and the degree of AD severity still has a contradictory result. This study was similar to that of Jerenowicz (2007)(21) where no significant correlation was found between the percentage of eosinophil in peripheral blood and the degree of AD severity. The examination result of two laboratory parameters in this study is a variable of laboratory parameters or secondary phenomenon in AD.

This study aims to determine the relationship of LL-37 levels in circulation and SCORAD score in patients with AD. The result shows that serum LL-37 level in mild AD group is relatively higher than L serum L-37 level in moderate/severe AD group although it is not statistically significant. There is no statistically significant correlation between serum LL-37 level and SCORAD score which depicts the severity of AD (r=-0.238, p=0,205), so it is concluded that Ho is accepted. Based on previous research, the role of LL-37 in pathogenesis of AD is not clearly known. A study conducted by Goo et al (2010)(22) aimed to determine the basal expression of LL-37 in the skin of AD patients. The result showed that basal LL-37 expression in the skin of AD patients was not different from normal individual skin. The study by Mallbris et al (2009)(23) aimed to determine the expression of LL-37 in skin lesions of AD patients compared to normal individuals and psoriasis sufferers. Psoriasis is a skin inflammatory disease whose pathogenesis is associated with LL-37 expression. The result showed that LL-37 expression in skin lesions of AD patients was lower when compared to skin lesions of psoriasis patients, whereas LL-37 expression on skin without lesions was almost the same among AD patients, psoriasis sufferers, and normal individuals. Lesion in the epidermis can cause low LL-37 expression in AD skin due to the dominance of Th2-immune responses that suppress pro-inflammatory activities of LL-37. A research conducted by Ballardini et al (2009)(24) indicated that LL-37 expression increased in the skin of patients with lesions, which was related to the process of tissue re-epithelialization.

A previous research aimed to determine the association of LL-37 levels in circulation with the degree of severity by Leung et al. in 2012, showed a significant correlation between serum LL-37 levels with total SCORAD score ($r = 0.181$; $p = 0.030$) and objective SCORAD ($r = 0.207$; $p = 0.013$) in children subjects. Therefore, it is concluded that serum LL-37 levels can be used as a marker of ADseverity(25). LL-37 has complex functions and roles. The role of LL-37 in the inflammatory process is influenced by the type of cell and the underlying disease. Activation of LL-37 as an immunomodulator is mediated by several different pathways. Until now, it is very difficult to conduct research that aims to determine the role of LL-37 separately because of its activities that overlap and run simultaneously(7,26).

LL-37 is expressed in tissue and circulation. In vitro studies to measure LL-37 expression in keratinocyte cell culture have some limitations with respect to the process of cell differentiation(22). The mechanism of LL-37 induction in

tissue or circulation is still uncertain. Both local and systemic infections and inflammations can induce LL-37 expression in the tissues and circulation (7). Some local and systemic inflammatory diseases are associated with LL-37 expression, for example psoriasis vulgaris, rosacea, lupus erythematosus, hidradenitis suppurative, and rheumatoid arthritis. Other inflammatory conditions that can affect the expression of LL-37 are periodontitis, gastrointestinal infections, urinary tract infections and genital tract, as well as respiratory tract infections. The expression of LL-37 is set in a balanced condition to maintain homeostasis. Some physiological conditions may also affect the expression of LL-37, such as the conceptus, childbirth, and the overgrowth of the body's microflora(27). In this study local and systemic inflammatory diseases are excluded by the criteria of sample rejection, but some uncontrollable physiological conditions may affect the results of the study. Psychological stress may decrease antimicrobial peptide levels in the skin through endogenous glucocorticoid secretion (28). The mechanisms underlying the influence of psychological stress on antimicrobial peptide expression are unclear. Psychological stress may increase endogenous glucocorticoid levels which in turn lead to inhibition of epidermal lipid synthesis which affects the production of lamellar bodies in the epidermis, thus suppressing the level of LL-37 in the skin (28). The relationship between LL-37 expression in tissue and circulation is still unclear. Until now there has not been any study that compares basal expression of LL-37 in circulation with various physiological and pathological conditions.

Levels of LL-37 obtained in this study ranged from 9.40±6.06 ng/ml to 12.4±6.7 ng/ml, lower when compared to normal levels in circulation (plasma = 50-80 ng/ml)(29,30). The type of sample is presumed to have an effect on the research result. Several coagulation factors are not obtained in serum samples. In a literature it is said that the components of proteins in the blood can be affected by the loss of several coagulation factors. However, until now there has not been any data on the effect of this type of sample on LL-37 circulation(31).

In some literature studies it is known that elevated serum total IgE levels and peripheral blood eosinophil counts may reflect increased expression of Th-2 immune response in AD, but it is said that this condition is inconsistent (32,33). Th-2 cytokines i.e. IL-4 and IL-13, are cytokines that play a role in IgE secretion. It is considered that serum IgE levels can be used as a marker of the expression of Th2 cytokines (IL-4 and IL-13). In this study there is no significant correlation between serum LL-37 levels and total serum IgE levels and the percentage of eosinophil counts in peripheral blood, so it can be concluded that the effect of Th2 immune response on circulation is not related to total serum IgE levels and peripheral blood eosinophil percentage. The result shows that there is a statistically significant correlation between serum LL-37 levels and age of the subjects, with r=0.405, p=0.026. In a literature study, it is known that LL-37 levels in saliva are directly proportional to the age of individuals (27)jk. So far the researchers have not found any studies that examine the correlation between serum LL-37 levels and age of the subjects. Further research is needed to determine the effect of age on LL-37 circulation expression.

Biological factors affecting regulation of LL-37 expression are enormous, thus resulting in considerable bias in this study. In AD there are several abnormalities in the immune system, both systemic and specific to the skin (6). Genetic diversity in AD is one of the

causes of the limitations in this study. The proportion of unbalanced subjects with a relatively small number of subjects may influence the results of the study. The method used to measure some parameters can also be the cause for bias in the research results because the element of subjectivity and accuracy is not high enough.

CONCLUSION

From the results of this study it can be concluded that serum LL-37 levels are not related to SCORAD score in AD, so they can not be used to assess the degree of severity of AD.

FUTURE DIRECTIONS

Research with more proportional subjects using more representative methods is needed to obtain more significant data and may reduce the bias in the study.

ACKNOWLEDGEMENT

We acknowledge Badan Penelitian dan Pengabdian kepada Masyarakat Medical Faculty Brawijaya University which have provided funding of this research from the Hibah Kompetitif DPP/SPP scheme.

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