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KORELASI ANTARA KADAR INTERLEUKIN 13 SERUM DAN SKOR SCORAD PADA PENDERITA DERMATITIS ATOPIK

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CORRELATION BETWEEN INTERLEUKIN 13 SERUM LEVELS AND SCORAD INDEX IN PATIENTS WITH ATOPIC DERMATITIS

ABSTRACT

Background: *Atopic dermatitis is one of the most common inflammatory skin disorders with increasing prevalence. AD is a multifactorial disease influenced by a complex relationship between genetic and environmental factors. Genetic predisposition for atopic diseases may cause an expansion of Th2 cells activities, and IL-13 is an important mediator in Th2 immunity response. IL-13 has a role in the abnormal immune response against pathogens and decreased skin barrier function, two major predisposing factors for AD. The purpose of this study is to prove that there is a correlation between IL-13 serum levels and AD disease severity measured by the SCORAD index.*
Method: *This is a cross-sectional analytic observational study. Research subjects are 37 patients with atopic dermatitis and 16 healthy controls. Serum samples were processed and analyzed at the GAKI Laboratory of Dr. Kariadi General Hospital Semarang.*
Results: *There is a significant difference of IL-13 serum levels between patients with atopic dermatitis and healthy control (p=0.0001), and between the study group with mild, moderate and severe atopic dermatitis (p=0.0001). Analysis found a significant and very strong positive correlation (p=0.0001; r=0.911) between IL-13 serum levels and SCORAD index.*
Conclusion: *There is a significant positive correlation between IL-13 serum levels and atopic dermatitis disease severity, which means that IL-13 serum level will increase with increasing disease severity of atopic dermatitis.*

Key words: *IL-13, SCORAD index, atopic dermatitis.*

ABSTRAK

Latar belakang: Dermatitis atopik merupakan jenis penyakit inflamasi kulit yang paling sering ditemui dan prevalensinya terus mengalami peningkatan. DA bersifat multifaktorial dan dipengaruhi oleh hubungan yang kompleks antara faktor genetik dengan lingkungan. Predisposisi genetik untuk penyakit atopi dapat menyebabkan ekspansi aktivitas sel Th2, dan IL-13 merupakan mediator penting pada respon imunitas Th2. IL-13 berperan dalam terjadinya kelainan respon imunitas terhadap patogen dan gangguan sawar kulit yang merupakan faktor predisposisi utama dari DA. Tujuan penelitian ini adalah membuktikan adanya korelasi antara kadar IL-13 serum dan derajat keparahan penderita dermatitis atopik yang dinilai dengan SCORAD.
Metode: Penelitian ini merupakan penelitian analitik observasional dengan pendekatan *cross-sectional*. Subyek penelitian terdiri atas 37 orang penderita dermatitis atopik dan 16 orang kontrol sehat. Sampel serum diolah dan diperiksa di Laboratorium GAKI RSUP Dr. Kariadi Semarang.
Hasil: Ditemukan perbedaan kadar IL-13 serum yang bermakna antara pasien dengan dermatitis atopik dan kontrol sehat (p=0,0001), serta antar kelompok subyek penelitian dengan dermatitis atopik derajat ringan, sedang dan berat (p=0,0001). Dari uji korelasi diperoleh adanya korelasi positif sangat kuat yang bermakna (p=0,0001; r=0,911) antara kadar IL-13 serum dan skor SCORAD.
Simpulan: Terdapat korelasi positif yang bermakna antara kadar IL-13 serum dan derajat keparahan dermatitis atopik, yang berarti bahwa kadar IL-13 serum akan makin meningkat seiring dengan bertambah beratnya derajat keparahan penyakit dermatitis atopik.

Kata kunci: IL-13, skor SCORAD, dermatitis atopik.

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PENDAHULUAN

Atopic dermatitis (AD) is a chronic inflammatory skin disorders characterized by erythematous and pruritic skin lesions with excoriation in the acute stage and lichenification in the chronic stage. Patients with this disorder may also have asthma and allergic rhinitis as part of the atopic march.[1-7]

Atopic dermatitis is one of the most common inflammatory skin disorders and can be found in 10–20% children and 1–3% adults globally.[8-10] The prevalence of AD has increased in the last decade.[4,11] There were 1261 patients with AD at the dermatology and venereology clinic of Dr. Kariadi General Hospital Semarang between 1996–2000, where 770 were new cases. Of all pediatric patients, the highest incidence was found in the less than 5 years old age group (62.6%; 123/197), followed by 5–14 years old (37.4%; 74/197).[12] Based on the recapitulation done by the Pediatric Dermatology Study Group (KSDAI) in five largest cities in Indonesia in 2000, AD was the most common (23.67%) pediatric skin disorders in ten largest hospitals from these cities. In 2005, AD was 36% of all dermatitis cases in Indonesia.[13]

The pathogenesis and etiology of AD is not fully understood, however this disease is likely multifactorial and may be influenced by a complex relationship between genetic and environmental factors.[5,8,11,14] The genetic predisposition for atopic disorders may cause an expansion in Th2 cells activities, and will increase the secretion of Interleukin-5 (IL-5), IL-4, IL-13, IL-3, IgE, mast cells and cause eosinophilia.[15] There is a correlation between immune disorders and decreased epidermal barrier function in AD, which means that several cytokines that play a role in AD, such as IL-4, IL-13 and IL-22, may inhibit the production of skin barrier protein (FLG and LOR).[5]

The effects of Interleukin 13 on the Th2 inflammation may play an important role in asthma and AD. These effects are the ability to induce IgE production, CD23 expression, endothelial P-selectin and vascular cell adhesion molecule-1 expression, and to inhibit eosinophil apoptosis.[16] IL-13 also reduce the expression of antimicrobial peptide in eczematous skin, which will make the skin more prone to recurrent infections.[17-19]

A study in the United States found that IL-13 may induce dermal inflammation and remodeling in transgenic mice with AD.[17] Another study also found that IL-13 is a potent mediator for pathologic fibrosis in AD,20 and IL-13 may induce AD and atopic march through a TSLP-dependent mechanism.[21] Another study in Italy found a dominant Th2 profile in the blood of children with AD, and IL-13 is correlated with AD disease severity.[22] These studies showed that IL-13 levels is correlated with the disease activity of atopic dermatitis.

Studies assessing the relationship between IL-13 serum levels and AD disease severity measured by SCORAD index are lacking. This encourages us to do a research on this topic.

MATERIALS AND METHOD

This is a cross-sectional analytic observational study. Research subjects are 37 patients with atopic dermatitis treated at the dermatology and venereology clinic of Dr. Kariadi General Hospital Semarang that met the inclusion criteria and 16 healthy controls. Subjects are selected using the consecutive sampling method from January 2015 to March 2015.

Atopic dermatitis disease severity was assessed using the Scoring for Atopic Dermatitis (SCORAD) index. The score is calculated based on the intensity of eczematous lesion such as redness, swelling, oozing, scratch marks, lichenification (skin thickening), and skin dryness (assessed in area where there is no inflammation) in nine body areas *(rule of nine)*. Subjective symptoms such as itch and sleeplessness will also be assessed. Higher score showed more severe atopic dermatitis.

Venous blood sample were taken from every subject to analyze the IL-13 serum levels. This analysis was done using ELISA IL-13 examination kit from R&D Quantikine® at GAKI Laboratory of Dr. Kariadi General Hospital Semarang. This study has been approved by the ethic committee of Faculty of Medicine Diponegoro University / Dr. Kariadi General Hospital Semarang.

Statistical analysis was done using Statistical Programs for Social Science (SPSS) 15.0. The correlation between IL-13 serum levels and SCORAD index is considered significant when $p<0.05$ and the correlation coefficient (r) is close to +1.

RESULTS

This study obtained 37 subjects with atopic dermatitis (AD) that met the inclusion criteria with the age between 16 to 86 years old (mean ± SD, 38.57 ± 20.26 years old). Seventeen (45.9%) subjects are male and 20 (54.1%) female. Highest level of education for most subjects are graduate degree (51.4%), and the most frequent occupation are college student (35.1%) and private employee (32.4%). Subjects in this study shoved varied duration of disease, between 0.5 to 50 years (mean ± SD, 14.27 ± 12.78) (Table 1).

Tabel 1. The characteristic of study subjects

Characteristic	Mean ± SD	*n* (%)
Age (year)	38.57 ± 20.26	
Sex		
Male		17 (45.9%)
Female		20 (54.1%)
Education		
Elementary school		2 (5.4%)
Junior high school		6 (16.2%)
Senior high school		7 (18.9%)
Academy		2 (5.4%)
Graduate		19 (51.4%)
Post-graduate		1 (2.7%)
Occupation		
Student		2 (5.4%)
College student		13 (35.1%)
Private employee		12 (32.4%)
Entrepreneur		5 (13.5%)
Driver		2 (5.4%)
Retired		1 (2.7%)
Not working		2 (5.4%)
Onset (year)	24.74 ± 19.73	
Duration of disease (year)	14.27 ± 12.78	

Among the 37 study subjects, 21 (56.75%) has history of atopic disease other than atopic dermatitis, mostly allergic rhinitis in 12 (32.4%) subjects, and asthma, conjunctivitis and urticaria in 4 (10.8%), 4 (10.8%), and 8 (21.6%, respectively. The most common precipitating factors causing recurrence of atopic dermatitis are cold weather (56.8%), shrimp (27.0%), dust (27.0%), stress (24.3%), and fish (16.2%). There are no significant correlation between precipitating factors of atopic dermatitis and disease severity measured by the SCORAD index. The SCORAD index from 37 study subjects are between 10.5–53.4 (mean ± SD, 30.82 ± 13.96). Subject with mild atopic dermatitis has mean SCORAD index of 17.23 ± 3.56, moderate 36.95 ± 6.96, and severe 51.82 ± 1.12 (Table 2). Based on the SCORAD index, there are 16 (43.3%) subjects with mild atopic dermatitis, 15 (40.5%) with moderate atopic dermatitis, and 6 (16.2%) with severe atopic dermatitis.

Tabel 2. The result of SCORAD index assessment

Study subject	SCORAD index	
	Min-max	Mean ± SD
All subject (*n*=37)	10,5–53,4	30,82 ± 13,96
Mild AD (*n*=16)	10,5–23,4	17,23 ± 3,56
Moderate AD (*n*=15)	27,6–48,6	36,95 ± 6,96
Severe AD (*n*=6)	50,4–53,4	51,82 ± 1,12

Mean IL-13 serum level in this study is 12.38 pg/mL for patients with atopic dermatitis and 2.55 pg/mL for healthy control. Analysis found a significant difference between mean IL-13 serum levels in patients with atopic dermatitis and healthy control (p=0.0001). (Table 3).

Tabel 3. Mean IL-13 serum levels in study subjects

Study subject	Mean IL-13 serum levels	*p* value
Atopic dermatitis patients (*n*=37)	12,38 ± 7,19	0,0001*
Healthy control (*n*=16)	2,55 ± 1,31	

*Mann Whitney test

In this study, IL-13 serum level in patients with atopic dermatitis is between 3.67 pg/mL to 30.00 pg/mL (mean ± SD, 12.38 ± 7.19). Subjects with mild atopic dermatitis had IL-13 serum level between 3.67–9.64 pg/mL (mean ± SD, 6.51 ± 2.03), moderate between 10.09–19.80 pg/mL (mean ± SD, 13.31 ± 2.68), and severe between 11.01 30.00 pg/mL (mean ± SD, 21.57 ± 7.08) (Table 4).

The data normality for IL-13 level was analyzed using Saphiro-Wilk test. Because the data showed normal distribution, we analyze the difference of mean IL-13 serum levels between AD disease severity groups using One-way ANOVA test. The test showed p value of 0.0001. Because $p < 0.05$ then we concluded that there is a significant difference in IL-13 serum levels between study subjects with mild, moderate and severe atopic dermatitis.

Tabel 4. IL-13 serum levels based on AD disease severity

Study subjects	IL-13 serum levels			
	Mean ± SD	Median	Minimum	Maximum
Control group	2,55 ± 1,31	2,75	0,46	4,59
Mild AD (*n*=16)	6,51 ± 2,03	6,42	3,67	9,64
Moderate AD (*n*=15)	13,31 ± 2,68	13,08	10,09	19,80
Severe AD (*n*=6)	21,57 ± 7,08	20,40	11,01	30,00
Total subject (*n*=37)	12,38 ± 7,19	11,01	3,67	30,00

Post Hoc test was used to analyze the difference of mean IL-13 serum levels between two subject groups based on AD disease severity. This analysis showed a significant difference in mean IL-13 serum level between study subjects with mild and moderate AD (p=0.0001), mild and severe AD (p=0.0001), and moderate and severe AD (p=0.005) (Table 5).

Tabel 5. Differences of IL-13 serum level between study subjects

Study subjects	Moderate AD (*n*=15)	Severe AD (*n*=6)
Mild AD (*n*=16)	0.0001*	0.0001*
Moderate AD (*n*=15)	–	0.005*

*Post Hoc test

Normality test for IL-13 serum levels and SCORAD index showed data with abnormal distribution, thus Spearman test was used to analyze the correlation between these variables. Analysis found a significant and very strong positive correlation (p=0.0001; r=0.911) between IL-13 serum levels and SCORAD index.

DISCUSSION

The study subjects consisted of 17 male and 20 female patients with atopic dermatitis with varied duration of disease, but most of them have had this disease for more than 1 year. Atopic dermatitis (AD) is a chronic inflammatory skin disorder with frequent recurrence or remission.[3,6,7] Studies from several countries have found equal incidence of AD in male and female patients.[23,24]

Atopic dermatitis usually manifested in infancy (45% case showed onset during the first 6 month after birth), and 70% children had this disease before the age of 5. Atopic dermatitis may also have an adult onset.[11] Along with the increasing prevalence of AD for the last decades, the prevalence for adult onset AD was also increased to 1–3% in several countries.[25] Prevalence of AD in these countries may be influenced by race, genetic, and geographic factors.[23] In this study, the age of the study subjects are between 16 to 86 years old.

The etiology if AD is not fully understood, but there are several factors that may play a role in AD, such as food allergen, aeroallergen, autoallergen, skin infection, or stress.[26] In this study, the most common precipitating factors causing recurrence of atopic dermatitis are cold weather (56.8%), shrimp (27.0%), dust (27.0%), stress (24.3%), and fish (16.2%).

A study found that 83% AD patients reported cold weather as a precipitating factor. Cold weather may reduce air humidity, thus making the skin dry and inducing pruritus.[27] Exacerbation of AD was also reported in patients with house dust mite exposure. Epicutaneous aeroallergen (such as house dust mite, grass, animal dander, and fungus) given using atopic skin prick test may induce eczematoid reaction in 30–50% patients with AD. Study found that an effective measures to reduce house dust mite exposure may reduce AD symptoms. The degree of IgE sensititation is directly proportional to AD disease severity.[28]

Food that often become a precipitating factor for atopic disease (asthma, allergic rhinitis, atopic dermatitis) in adults are seafood, especially shrimp, lobster, crab, and fish.[29] Aside from cold weather, food and dust, psychological stress is also an important precipitating factor that may induce an exacerbation of AD. Stress may cause disturbance in hypothalamus-pituitary-adrenal axis and blocking Corticotropin Releasing Factor (CRF), which in return will reduce Th1 activity and push the Th1/Th2 balance toward Th2.[30] This study found no

significant correlation between precipitating factors and AD disease severity.

The duration of disease for patients with AD in this study is between 6 months to 50 years (mean 14.27 years). Previous studies found that AD disease severity assessed using SCORAD index will increase with longer duration of disease.[31,32] A study in Poland found a significant correlation between duration of disease and SCORAD index in patients with AD.[32]

Patients with atopic dermatitis in this study also reported history of another atopic disease such as allergic rhinitis and asthma. A study in the United States found that IL-13 played a role in inducing atopic march and AD through a thymic stromal lymphopoietin (TSLP)-dependent mechanism.[21] IL-13 plays a role in the regulation of respiratory tract inflammation, IgE synthesis, eosinophil infiltration, mucus hypersecretion, respiratory hyper-response, subepithelial fibrosis, and bronchoconstriction. These processes play an important role in the pathogenesis of allergic rhinitis and asthma.[33,34]

Th2 inflammation is a major component of AD, especially during the early phase of disease progression.[17] IL-13 is a major stimulator of the inflammatory process and tissue remodeling in Th2 inflammation. Selective IL-13 expression on the skin of transgenic (Tg) mice with AD resulted in skin inflammatory phenotype characterized by an increase in eosinophil, mast cell, activated Langerhans cells, T CD4+ cell, and significant remodeling of the skin.[20] IL-13 is increasing the production of IgE and inducing the expression of MDC chemokine (CCL22) in primary human keratinocyte and activating matrix metaloproteinase-9, which in return may induce leukocyte migration to the epidermis.[35,36] IL-13 may also reduce the expression of fillaggrin and human beta-defensin-3 in vitro, so this cytokine may play a role in decreasing the skin barrier function.[36]

This study found a significant difference of IL-13 serum levels between subjects with atopic dermatitis and healthy control. The mean serum levels of IL-13 in 37 study subjects with AD are 12.38 ± 7.19 pg/mL, higher than the observed IL-13 serum level in healthy control (2.55 ± 1.31 pg/mL). Consistent with the result obtained in this study, a previous study in Egypt also found that AD patient has a significantly higher IL-13 mRNA expression and IL-13 levels compared with normal control.[37]

This study found a significant difference in mean IL-13 serum levels between study subjects with mild, moderate and severe atopic dermatitis. We also found a significant positive correlation between IL-13 serum levels and AD disease severity measured by SCORAD index. A previous study in an outpatient clinic in Italy also observed similar results. They found a significant relationship between CD4+IL-13+ levels with AD disease severity measured by SCORAD index. These cells is considered as an excellent biologic marker for atopic dermatitis because we can observe a dynamic changes in CD4+IL-13+ levels with AD disease progression.[22] Another study in Egypt assessing IL-13 levels in AD patients before and after topical treatment also found a significant correlation between the levels of this cytokine and disease severity measured by SCORAD index. They observed a significant decrease in IL-13 levels after treatment.[38]

The results of this study in conjunction with the previous studies described above showed that IL-13 plays a role in decreased skin barrier function and chronic inflammation through several cellular or molecular mechanism thus considered to also play an important role in the pathogenesis of AD and as a potential therapeutic target for AD in the future.[17,36] Treatment using topical IL-13 antisense oligonucleotide with cationic elastic liposome (IL-13 ASO/cEL complex) in mice was reported to reduce clinical symptoms of AD, thus this formulation is considered a potential therapeutic tool for the treatment of AD in human.[39] There are several anti-interleukin 13 drugs developed for the treatment of AD in human, such as Dupilumab, Lebrikizumab, and Pitrakinra, which currently being tested in a phase II/III trials with promising results.[40,41,42]

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