

## Role of Psychological Stress on Interferon-Gamma (IFN- $\gamma$ ) in Atopic Dermatitis

Made Wardhana\*, Sudarmajaya, Suryawati and L.M. Rusyati

Departement of Dermatology and Venereology, Faculty of Medicine,  
Udayana University-Sanglah General Hospital, Denpasar, Bali-Indonesia.

\*Corresponding E-mail: wardhanamade@unud.ac.id

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Atopic dermatitis (AD) is a chronic inflammatory skin disease, with itching predominant symptom, which usually develop in infancy and associated with an increase in serum IgE and history of atopies, such as allergic rhinitis or bronchial asthma. The etiology of AD remains unclear. However, there are many predisposing factors, such as genetic, immunological disorders, infections, foods, irritants, and psychological stress. Many research has conclude that stress is one of the risk factor for AD, but the current understanding for the underlying mechanism remain unclear. Recent research shows that stress can suppress interferon gamma (IFN- $\gamma$ ), which plays an important role in the pathogenesis of AD. This study aims to determine the role of stress and serum levels of IFN- $\gamma$  to AD. Study design using a case-control study with a sample consisting of 31 cases and 28 controls. Stress indexes were measured using Holmes & Rahe Stress Scale and serum IFN- $\gamma$  levels were examined. Statistical analysis was performed to determine the differences between the mean stress index and serum IFN- $\gamma$  level between cases and controls, the magnitude of psychological stress as a risk factor for AD, and the correlation between psychological stress and serum IFN- $\gamma$  level against the severity of AD. This study concluded that stress is a risk factor for AD with an odds ratio of 5.3, and the stress index is positively correlated with the severity of AD. Serum IFN- $\gamma$  levels were significantly lower in cases group. There was a strong negative correlation between IFN- $\gamma$  with the severity of AD ( $r = -0.905$ ;  $p < 0.05$ ). Current study conclude that psychological stress is a risk factor for AD and stress can suppress serum IFN- $\gamma$  levels.

**Keyword:** Psychological stress, Interferon gamma (IFN- $\gamma$ ), atopic dermatitis.

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Atopic dermatitis (AD) is a chronic and recidive inflammatory skin disease, with polymorphic skin disorders, accompanied by itching and other variable symptoms, precipitated by multifactorial causes. Although the exact cause is still unknown, there are many known risk factors. AD is commonly associated with atopy diatheses such as bronchial asthma, allergic rhinoconjunctivitis, genetic, immunological

abnormalities, skin barrier disorder, irritation, infection and psychological stress.<sup>1,2,3,11</sup>

AD is a major health problem worldwide, as it can affect all ages and is chronic and recidive, which markedly decrease the quality of life.<sup>4,5</sup> The role of psychological stress factor in AD has been widely investigated, that the presences of psychological stress or emotional factors increase the prevalence of AD. Cantani *et al.* (2001)

describe that stress promotes IgE production and suppresses anti-inflammatory cytokines, which lead to immunologic inflammation in AD.<sup>6</sup> Likewise, Pavlovsky *et al.* (2007), reported that psychological stress activates the production of several neuropeptides, which trigger T-helper 2 cells (Th2) to release proinflammatory cytokines, resulting in neurogenic inflammatory process in person suffering from atopic disease.<sup>3,4,10</sup>

The pathogenesis of AD is not yet known, but it has been acknowledged that this disease is associated with hypersensitivity to environmental allergens. This phenomenon is based on changes in the activity of T-helper 1 (Th1) and Th2 lymphocytes dominated by the role of Th2 cells. Th2 cells produce mediators such as immunoglobulin E (IgE), interleukin-4 (IL-4), and interleukin-5 (IL-5), all three are the main mediator in the pathogenesis of AD. Fan *et al.* (2001) suggested that the decrease in cells IFN- $\gamma$  production plays a role in the pathogenesis of AD.<sup>21</sup> Whether peripheral blood mononuclear cell (PBMC) produces IFN- $\gamma$  or reduces the production of IFN- $\gamma$  per cell, or the combination of the two remains unclear. Curtin *et al.* (2009) found that serum IFN- $\gamma$  level in controls was 128 pg/mL, which differed significantly with the level in the case group of 64.75 pg/mL. It appears that the decrease of IFN- $\gamma$  level, apart from synthesis defect by PBMC, was also associated with the risk of psychological stress.<sup>18</sup>

This study aims to determine the effect of psychological stress on AD through the level of IFN- $\gamma$  and stress index correlated with the severity of AD (assessed using SCORAD).

## METHODS

### Research Design

This study is a case-control study aiming to determine the risk of psychological stress as triggering factor for AD and the correlation with IFN- $\gamma$ . All of the cases were outpatients at dermatology and venereology clinic at Sanglah Denpasar Hospital, who were diagnosed with AD and had not received any treatment, and aged 14 to 65 year old. The diagnosis of AD is based on clinical manifestation according to Hanifin & Rajka criteria.<sup>8</sup> The control group was healthy

subjects without AD or other atopic diseases. All subjects were identified for their age, sex, family history of similar symptoms, other atopic diseases on family (such as asthma, allergic rhinitis, and hay fever), and provoking factors (such as food allergy, aeroallergen, and irritant materials). The severity of AD was assessed using Scoring Atopic Dermatitis (SCORAD) by the European Task Force on Atopic Dermatitis. The measurement of serum level of IFN- $\gamma$ , IgE, and complete blood tests were performed using blood sample from cubital vein early in the morning before daily activity. After the two groups received enough information and agreed to sign the informed consent, then a thorough anamnesis was conducted to grade the stress index using Holmes & Rahe Stress Scale to identify life events as psychological stress risk factors.<sup>7</sup>

### Statistical Analysis

All collected data were then analyzed statistically. Mean difference was analyzed using student t-test, while proportion differences and odds ratio were calculated using Chi-square and correlation analysis.

## RESULTS

There was a total of 59 samples in this study, 31 cases and 28 controls, recruited from Dermatoveneorology Clinic at Sanglah General Hospital, Denpasar, who were screened and fulfilled the inclusion criteria. Samples were outpatient from January 2011 until the end of February 2011. The characteristics of the sample can be seen in Table 1.

Table 1 shows the characteristic of research subjects. There were 31 samples in the case group, consisted of 19 males and 12 females. The control group consisted of 15 males and 13 females. On both groups, the majority of the samples were between 31-40 years old. From the case group, there were 12 samples (38.7%) with acute AD and 19 samples (61.3%) with chronic AD. The severity of AD cases was assessed using SCORAD; categorized into nine mild cases (29.1%), 17 moderate cases (54.8%), and five severe cases (16.1%). History of atopic disease on the case group was found in 20 of the cases (33.9%), while the other 11 cases did not have

a history of any other atopic diseases. In control group, five samples (8.5%) had a history of atopic disease, while the other 23 samples did not.

The serum IFN- $\gamma$  level of case group was  $4.6 \pm 6.7$  pg/mL while of the control group were  $20.0 \pm 22.8$  pg/mL. The stress indexes of the case group were  $120.0 \pm 3.5$ , whereas of the control group were  $78.5 \pm 2.5$ . The psychological stress was categorized from both of the case and control group. On the case group, there were nine samples (15.3%) and 22 samples (37.3%) with suspected stress and no stress, respectively. On the control

group, there were two samples (3.3%) and 26 samples (44.1%) with suspected stress and no stress, respectively.

**Correlation of stress level with SCORAD and IFN- $\gamma$  score**

Result from correlation test found that the correlation coefficient between the stress level and the severity of AD (SCORAD) was  $r = 0.238$  ( $p < 0.05$ ), which may be interpreted as weak positive correlation. Correlation test between stress level and IFN- $\gamma$  showed negative correlation with a coefficient of  $r = -0.305$  ( $p < 0.05$ ). Correlation test

**Table 1.** Characteristics of the samples

Characteristics	Case (%) n=31	Control (%) n=28	p -value/ Odds Ratio
Gender Distribution			
Male	19 (32.2)	15 (25.4)	p< 0.05
Female	12 (20.3)	13 (22.0)	
Age (years)			
14-30	8 (13.5)	7 (11.6)	
>31- 40	13 (22.0)	12 (20.3)	
> 40	10 (16.9)	9 (15.2)	
Atopic history			
Yes	20 (33.9)	5 (8.5)	
No	11 (18.6)	23 (38.9)	
Chronicity			
Acute	12 (38.7)	-	
Chronic	19 (61.3)	-	
SCORAD (Mean $\pm$ SD)	47.9 $\pm$ 1.2	-	
SCORAD category			
Mild (< 24)	9 (29.1)	-	
Moderate (25-50)	17 (54.8)	-	
Severe (> 50)	5 (16.1)	-	
IFN- $\gamma$ serum (pg/ml)	4.6 $\pm$ 6.7	20.0 $\pm$ 8.8	p< 0.05
Stress index (Mean $\pm$ SD)	120.0 $\pm$ 3.5	78.5 $\pm$ 2.5	p< 0.05
Stress category			
Suspected Stress	9 (15.3)	2 (3.3)	OR=5.3/p<0.05
No Stress	22 (37.3)	26 (44.1)	

**Table 2.** Correlation between stress level with SCORAD and IFN- $\gamma$

Variable	Stress Level	SCORAD	p-value
	Correlation coefficient (r)		
Scorad	0.238		0.034*
IFN- $\gamma$	-0.35		0.028*
IFN- $\gamma$		-0.905	0.000*

\*significant ( $p < 0.05$ )

between IFN- $\gamma$  and SCORAD showed a negative strong correlation ( $r = -0.905$ ;  $p = 0.000$ ). (Table 2)

**DISCUSSION**

**The role of psychological stress on atopic dermatitis**

AD is a multifactorial disease that involves the interaction between genetic, environment, immunologic, skin barrier, and psychological

stress factors. Recent research suggested that psychological stress factor may cause recurrence or worsening of AD. Previous researchers showed that psychological stress causes recurrence or worsening of AD by several mechanisms.<sup>23,25,26</sup> Various stress mechanisms increase the risk for AD, psychological stress impairs skin barrier function and also shift the immune system to Th2 cells or allergic responses. Also, patients with AD seem to have hyperreactivity to the hypothalamus-pituitary-adrenal (HPA) axis, so that the cortisol levels were lower in AD patients compared to the healthy subjects. Lower cortisol level leads to the activation of proinflammatory cytokines.<sup>16</sup> Another phenomenon that can be seen is that in psychological stress, several neuropeptides, such as norepinephrine and dopamine, which were released by the nerve endings on the skin will be directly picked up by the mast cells. The mast cells mediate neurogenic inflammation, including degranulation of mast cells. This process triggers type I allergic reaction which is the pathophysiology of AD.<sup>26,27</sup>

Holmes & Rahe Stress Scale can be used by non-psychologist to quickly assess the stress index. This method comprises of 43 questions about life events. Every life event has a certain score; for example, the death of closest relatives was scored 75, a problem with police for traffic violations was scored 15, and so forth. The total of the scores was then categorized into (1) at risk for stress if the total stress index score were 100 or higher, and (2) at no risk for stress if the total stress index score were lower than 100.<sup>31</sup> In this study, the stress index for the case and control group was  $120.0 \pm 3.5$  and  $78.5 \pm 2.5$ , respectively. These score of stress index differs significantly. On the case group, nine subjects (15.3%) were at risk for psychological stress, while 22 subjects (37.3%) were at no risk for psychological stress. Odds ratio is 5.3 (CI 95%) 1.51-13.6 with p-value < 0.005. These results were consistent with Kristina *et al.* (2005), and Jessica *et al.* (2012) studies.<sup>9,26</sup> Stress greatly contributes to the recidivism (relapse or recurrence) of AD. The mechanism was figured to be caused by the decrease of HPA responses in psychological stress, leading to lower cortisol level; whereas cortisol plays a big role in anti-inflammatory process.<sup>17</sup>

Scoring for Atopic Dermatitis (SCORAD) by European Task Force on Atopic Dermatitis was

used to determine the severity of AD; this system assess the skin condition based on affected body surface area using the rule of nine and 6 intensity items, namely (1) erythema, (2) edema/papule, (3) oozing/crusts, (4) excoriations, (5) lichenification, (6) dryness.<sup>22</sup> This dryness condition should be appreciated at best at a distance from inflammatory lesions. Additionally, patients were also evaluated for subjective symptoms, for instance, skin itching and sleep disturbances. A higher score indicates a more severe disease (Bender, 2008).<sup>18</sup> Correlation-regression analysis and scatter plot showed that increase in stress index affects the severity of AD with  $r = 0.057$ ,  $p < 0.05$ , which signify that an increment of 1 stress index unit will increase the SCORAD by 0.57.

#### **The role of psychological stress to IFN- $\gamma$**

On this study, the serum IFN- $\gamma$  level on case group was significantly lower than in control group ( $4.6 \pm 6.7$  pg/mL and  $20.0 \pm 8.8$  pg/mL). There are many assumptions on this matter Curtin *et al.* (2009) affirmed that the decrease in serum IFN- $\gamma$  level was a response to cortisol level in stress condition.<sup>7</sup> In stress condition, there was a decline in the serum level of anti-inflammatory mediator IFN- $\gamma$ , which in the long run, induced proinflammatory process.<sup>7,21</sup> There is a decline of serum IFN- $\gamma$  level in patients with panic disorder; hence it was assumed that IFN- $\gamma$  served a biomarker of stress or other mental disorder.<sup>12</sup> The decrease in serum IFN- $\gamma$  level is accordant with an increase in the severity of AD based on the SCORAD score. This study showed that there was a negative correlation between serum IFN- $\gamma$  level and psychological score,  $r=0.035$  with  $p < 0.05$ .

Byron *et al.* (1992) demonstrate that in patients with AD there was a decrease of IFN- $\gamma$  in vitro by the PBMC in response to phytohaemagglutinin (PHA) when compared to control; this seemed to be correlated with the severity of AD – the decrease of IFN- $\gamma$  provoked the severity of AD. The production of IL-12 and IL-12 induced a decrease in IFN- $\gamma$  release in blood culture from all the subjects with allergic asthma compared to healthy subjects.<sup>24</sup>

#### **Correlation between IFN- $\gamma$ level and SCORAD**

IFN- $\gamma$  played a role in inhibiting Th2 proliferation, thus leading to a decrease in IL-4, IL-5, and IL-13 production; these were cytokines that activate B cells to produce IgE, activates

mast cells and eosinophils and promote type I hypersensitivity reaction.<sup>28,13,14</sup> A study conducted by Sudramajaya in 2011 showed that the mean IFN- $\gamma$  level of patients with AD ( $0.54 \pm 0.87$  pg/mL) was lower as compared with the control group ( $0.60 \pm 0.48$  pg/mL).<sup>15</sup>

These data demonstrate that the lower the serum IFN- $\gamma$  level, the more severe the AD will be, analyzed using correlation analysis to find the linear association between IFN-g level and SCORAD score. The analysis showed that there was a strong negative correlation ( $r = -0,905$ ;  $p = 0.000$ ) between the two variables.

Several experimental findings have strongly supported the idea that the pathogenesis of AD is related to the imbalance between Th1/Th2 responses. Over the past few years, it has been shown that allergic inflammation associated with an increase in Th2 resulted in downregulation of IFN- $\gamma$ . The role of cytokines here has not been confirmed adequately, because of its pleiotropic nature. However, preliminary studies have shown substantial effects and several side effects associated with the administration of IFN- $\gamma$  to patients with AD and other allergic skin diseases. Nevertheless, based on all findings related to modulation of Th immunologic and allergic response of IFN- $\gamma$ , forthcoming possibility of immunotherapy approaches developed for allergic inflammation should consider this potent immunoregulatory property of IFN- $\gamma$ .<sup>20,28,29</sup>

The serum level of IFN- $\gamma$  was found to be different between patients with AD and patients without AD. A study by Ong *et al.* (2002) showed that the mean of IFN- $\gamma$  of a group of AD patients was  $46.3 \pm 8.1$  pg/mL, was lower compared to the control group,  $62.8 \pm 9.2$  pg/mL. While the study conducted by Hussein *et al.* (2014) found that the mean of IFN- $\gamma$  in the group of patients with AD of  $64.75 \pm 8.1$  pg/mL and the control group of  $128.8 \pm 13.6$  pg/mL.<sup>19, 30,31</sup>

In this study, the mean serum IFN- $\gamma$  level of the case group was  $0.54 \pm 0.87$  pg/mL and in the control group was  $0.60 \pm 0.48$  pg/mL ( $p = 0.062$ ). This result showed that there was a difference between the mean serum IFN- $\gamma$  level between the two groups, but it was not significant ( $p > 0.05$ ). The insignificant result might be due to the number of the sample or selection method of the patients. In this study, the number of the sample between case

and control group was disproportionate. There was also a large discrepancy in mean serum IFN- $\gamma$  level of the case group in our study in contrast to the result of studies conducted by either Ong *et al.* or Hussein *et al.*; this was probably due to a variation in reagents used to measure IFN- $\gamma$  level. Although there was a difference in mean IFN- $\gamma$  levels between the two studies, there was a similarity in the trend of IFN- $\gamma$  levels which was lower in the case group, compared to control group.

Future research suggestion should be able to evaluate not only on IFN- $\gamma$  level, but also to evaluate other inflammatory mediators such as IL-6, IL-1, etc. Also, future research must perform risk analysis of predisposing factors that play a role in the AD such as history of allergy, food, irritant, and infection.

## CONCLUSION

From this study, it can be concluded that 23.7% of AD was affected by stress. Psychological stress is a risk factor for AD, with an odds ratio of 5.3. Serum IFN- $\gamma$  levels in the case group were significantly lower compared to the control group, and serum IFN- $\gamma$  levels were negatively correlated with the severity of AD.

## REFERENCES

1. Rebeca, B, Arshdeep, S, and Mark G. "Atopic Dermatitis: An Overview", *Am Fam Physician*, **86**(1):35-42(2012).
2. Yasaman, M, and Emma G, "Immune Pathways in Atopic Dermatitis, and Definition of Biomarkers through Broad and Targeted Therapeutics", *J. Clin. Med*, **4**:858-873(2015).
3. Matteo, A, Giovina, V, Paolo, A, Marcella, R, "Cytokines and T cells in atopic dermatitis". *Eur. Cytokine Netw*, **24**(1):37-44(2013).
4. Karagiannidou, A, Botskariova, S, Farmaki, E, Imvrios, G and Mavroudi, A, "Atopic Dermatitis: Insights on Pathogenesis, Evaluation and Management", *J Allergy Ther*, **5**(6):1-9(2014).
5. Yoichi Chida, Mark Hamer, and Andrew Ssteptoe, "A Bidirectional Relationship Between Psychosocial Factors and Atopic Disorders: A Systematic Review and Meta-Analysis", *Psychosomatic Medicine*, **70**:102-116(2008).
6. Cantani, A, "Pathogenesis of Atopic Dermatitis and the role of allergic factors", *European Review for Medical and Pharmacological Sciences*, **5**: 95-117(2001).

7. Curtin, NM, Boyle, NT, Mills, KH, Connor, TJ, "Psychological stress suppresses innate IFN-gamma production via glucocorticoid receptor activation: reversal by the anxiolytic chlordiazepoxide", *Brain Behav Immun*, **23**(4):535-547(2009).
8. Hanifin, JM, and Rajka, G, "Diagnostic features of atopic dermatitis", *Acta Derm Venereol*, **92**: 44-47(1986).
9. Kristina Seiffert, Edwin Hilbert, Hartmut Schaechinger, Christos, C. Zouboulis, Hans-Christian Deter, "Psychophysiological Reactivity under Mental Stress in Atopic Dermatitis", *Dermatology*, **210**:286-293(2005).
10. Lev Pavlovsky, Alon Friedman, "Pathogenesis of Stress-Associated Skin Disorders: Exploring the Brain-Skin Axis", *Curr Probl Dermatol*, **35**: 136-145(2007).
11. Thomas H. Holmes and Richard H. Rahe, "The Social Readjustment Rating Scale", *Journal of Psychosomatic Research*, **11**:213-218(1967).
12. Rasit Tukul, Belkis Atasver Arsla, Banu Aslantas Ertekin, Erhan Ertekin, Serap Oflaz, and Arzu Ergen, "Decreased IFN- $\gamma$  and IL-12 levels in panic disorder", *Journal of Psychosomatic Research*, **73**:63-67(2012).
13. Samar, A.M.S, Heba, M.D, Ghada Fathy, Lamia, M.O. and Shereen, B, "Value of Interleukins 4, 10, 12, 18 and Interferon- $\gamma$  in Acute Versus Chronic Atopic Dermatitis", *J Egypt Women Dermatol Soc*, **7**: 56 - 60(2010).
14. Saveria Pastore, Silvia Corinti, Michelangelo La Placa, Biagio Didona, and Giampiero Girolomoni. "Interferon- $\gamma$  promotes exaggerated cytokine production in keratinocytes cultured from patients with atopic dermatitis," *J Allergy Clin Immunol*, **101**: 538-44(1998).
15. Sudarmajaya. "Kadar IFN- $\gamma$  Serum Lebih rendah pada Dermatitis Akut Dibandingkan Dermatitis Atopik Kronis Serta Berkorelasi Negatif Dengan Derajat Keparahan," Academic Thesis. Udayana University, (2011)
16. Wardhana, Suata and Suastika. "Low Plasma Cortisol Level is a Risk Factor for Adult Atopic Dermatitis and Negatively Correlated to Plasma Levels of Norepinephrine and Interleukin-4", Academic Disertation. Udayana University, (2010)
17. Wardhana. "Role of Psychological Stress on Plasma Cortisol and IL-4 in Atopic Dermatitis", *European Journal of Biomedical and Pharmaceutical Sciences*, **3**(1):1-5(2016).
18. Bender, BG, Ballard, R, Canono, B, Murphy, J.R, Leung, D.Y. "Disease severity, scratching, and sleep quality in patient with atopic dermatitis", *J Am Acad Dermatol*, **58**(3):415-420(2008).
19. Hussein, Y.M, Shalaby, S.M, Nassar, A, Alzahrani, S.S, Alharbi, A.S, Nouh, M. "Association between genes encoding components of the IL-4/IL-4 receptor pathway and dermatitis in children", *Gene*, **545**: 278-281 (2014).
20. Eva Milena Johanne Peters, Anna Michenko, Jörg Kupfer. "Mental Stress in Atopic Dermatitis -Neuronal Plasticity and the Cholinergic System Are Affected in Atopic Dermatitis and in Response to Acute Experimental Mental Stress in a Randomized Controlled Pilot Study", *PLOS ONE*, **2**: 1-17 (2014).
21. Fan Chung. "Anti-inflammatory cytokines in asthma and allergy: interleukin-10, interleukin-12, interferon- $\gamma$ ", *Mediators of Inflammation*, **10**: 51-59(2001).
22. J.F, Stalder, A. Taieb. "Severity Scoring of Atopic Dermatitis: The SCORAD index, Consensus Report of the European Task Force on Atopic Dermatitis", *Dermatology*, **186**: 23-31(1993)
23. Jessica, M.F, Hall, D.A.C, Alan Podawiltz, Diana I.Mummert, Harlan Jones, and Mark E. Mummert. "Psychological Stress and the Cutaneous Immune Response: Roles of the HPA Axis and the Sympathetic Nervous System in Atopic Dermatitis and Psoriasis", Hindawi Publishing Corporation Dermatology Research and Practice, **2**: 1-11(2012).
24. Byron, K.A, Liberatos, S, Varigos, G.A, Wootton, A.M. "Interferon-Gamma Production in Atopic Dermatitis: A Role for Prostaglandins", *Int Arch Allergy Immunol*, **99**: 50-55(1992).
25. Asmaa Almalki. "Atopic Dermatitis In Relation To Psychological Distress", *International Journal of Healthcare Sciences*, **2**(2): 276-280(2014).
26. Theoharis, T, Leena, K.S, William Boucher, Xinzhu Pang, Richard Letourneau, Elizabeth Webster, and George Chrousos. "Corticotropin-Releasing Hormone Induces Skin Mast Cell Degranulation and Increased Vascular Permeability, A Possible Explanation for Its Proinflammatory Effects", *Endocrinology*. **139**: 403-413(1998).
27. Constantin Csruntu, Daniel Boda, Sorin Musat, Ana Csruntu, and Eugen Mandache. "Stress-Induced Mast Cell Activation in Glabrous and Hairy Skin", *Mediators of Inflammation*, **22**: 1-9(2014).
28. Abramovits, W. "Atopic dermatitis", *J Am Acad Dermatol*, **53**(1):S86-93(2005).
29. Leonardo, K.T, Bruna, P.F.F, Bianca, A.B, Jao, P.B.V. "The role of IFN- $\gamma$  on immune and allergic response", *Mem Inst Oswaldo Cruz*, **100**(1):137-

- 144(2005).
30. Ong, P.Y, Ohtake, T, Strickland, I, Boguniewicz, M, Ganz, T, Gallo, R.L, Leung, D.Y. "Endogenous antimicrobial peptides and skin infection in atopic dermatitis", *N eng J Med*, **347**(15):1151-1160(2002).
31. Allen, D.K, James, C.C, Catherine, S. Richard, S.L "Comparison of two modes of stress measurement: daily hassles uplifts versus major life events", *Journal of Behavioral Medicine*, **4**(1):1-39(1981).