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Relation of Serum Lipocalin-2 Level and Itching Severity in Patients with Psoriasis and Atopic Dermatitis

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Psoriasis (PS) is an immune-mediated skin disease characterized by skin lesions. Atopic dermatitis (AD) pruritic inflammatory skin condition in children and results in significant morbidity. Itch causes distress in patients with psoriasis and atopic dermatitis, not only by impairing quality of life but also by aggravating exanthema due to scratching. This study aimed to early detect the itching severity in psoriasis and atopic dermatitis by serum Lipocalin-2 (LCN2).A case-control study with a target sample comprised 54 subjects of age ranging from 6 to 60 years selected randomly from those admitted to the Dermatology Outpatient Clinics of Zagazig University Hospital. They divided into three groups: Group (I) included 18 volunteers' patients without dermatitis symptoms included as control group, group II included 18 patients with psoriasis and group III included 18 patients with atopic dermatitis (AD). All patients included in this study were subjected to the following: complete history taking, clinical examination, laboratory investigations and measurement of serumlipocalin-2There were no statistical significant differences between the three studied groups in sex distribution, but there was a statistical significant decrease in mean age among atopic dermatitis group compared to control and psoriasis groups. The PASI score among psoriasis patients ranged from 12.3 to 49.3 with mean 24.44. Also, SCORAD score among AD patients ranged from 20.1 to 84.21 with mean 48.21.Serum LCN2 levels were higher in patients with psoriasis and atopic dermatitis than those in healthy controls. Also our study showed a close relationship between the degree of itch and serum LCN2 level in patients with psoriasis.

Keywords: Psoriasis, Atopic dermatitis, Lipocalin-2 and Itching.

INTRODUCTION

Psoriasis (PS) is a common, chronic, relapsing/remitting, immune- mediated skin disease characterized by skin lesions including red, scaly papules, plaques and patches, which usually itch. It affects 2–4% of the general population (Shlyankevich et al. 2014). The etiology of psoriasis remains unclear, although there is evidence for genetic predisposition; genetic susceptibility factors strongly contribute to the predisposition to psoriasis (Harden et al. 2015). Psoriasis pathogenesis implies that a pathogenic cross-talk between epithelial and immune cells sustain the aberrant immune and epidermal response seen in PS (Lowes, 2013). Treatment modalities are chosen on the basis of disease severity, relevant comorbidities, patient preference (including cost and convenience), efficacy, and evaluation of individual patient response (Elmets et al. 2019).

Atopic dermatitis (AD) is a common, chronic, relapsing, highly pruritic inflammatory skin condition and is one of the most common skin disorders of children. The disorder results in significant morbidity and adversely affects quality of life (Krakowski et al.2008). According to the current consensus nomenclature by the World Allergy Organization (WAO), the term atopy is

tightly linked to the presence of allergen-specific IgE antibodies in the serum, as documented by positive fluorescence enzyme immunoassays (previously radio allegro sorbent test) “RAST” or skin prick tests (Fuiano and Incorvaia, 2012). Approximately half of children with disease onset during the first 2 years of life develop allergen-specific IgE antibodies by 2 years of age. About 60% of infants and young children with AD go into remission by 12 years of age, but in others disease activity persists into adolescence and adulthood (Esaki et al. 2016). Atopic dermatitis is a disease that can be controlled effectively with topical and/or systemic treatments and fortunately spontaneously disappears with age. Only in some cases are they very resistant to therapies (Saeki et al. 2009).

Lipocalin 2 (LCN-2) is a small extracellular protein, expressed by neutrophils and originally presenting itself in complex with neutrophil gelatinase, also known as matrix metalloproteinase 9 (MMP-9). LCN-2 has been classified as transport proteins of lipophilic molecules. LCN-2 additionally plays a role in inflammatory conditions and immune response, including the synthesis of prostaglandins (Gwira et al.,2005).While the LCN-2-Fe complex appears to be biologically active, the empty protein (apo-NGAL) in humans is functional as well. When the “naked” LCN-2 is internalized by receptor-induced endocytosis, it associates with a siderophore in the cell, accepts intracellular iron, and transfers it to the extracellular space. This process generates an intracellular deficiency of iron, which signals the cell to undergo apoptosis (Devireddy et al. 2005).Although the relationship between neutrophils and itch has not been fully determined, neutrophil activities have been associated with several pruritogens such as tumor necrosis factor (TNF-α) and substance-P (SP). TNF-α produced by epidermal keratinocytes is required in the expression of acute and chronic itch in mice (Miao et al.2018). Thus, the present study aimed to early detect the itching severity in psoriasis and atopic dermatitis by serum Lipocalin-2 (LCN2).

MATERIALS AND METHODS

This study was a case-control study. The target sample comprised 54 subjects of age ranging from 6 to 60 years selected randomly from those admitted to the Dermatology Outpatient Clinics of Zagazig University Hospital. The study had been approved by the local ethics committee on research involving human subjects of Faculty of Medicine, Zagazig University Hospital.

The studied subjects were divided into three groups according to the following inclusion criteria: Group I included 18 volunteers' patients without skin diseases and without personal history of dermatitis symptoms will be included as control group, group II included 18 patients with psoriasis and group III included 18 patients with atopic dermatitis (AD).

All patients included in this study were subjected to the following: complete history taking, clinical examination, laboratory investigations and measurement of serumlipocalin-2.

Full history taking:

Various demographic data were recorded, including age, gender, skin disorders and occupation (indoor oroutdoor). As well, course and duration of skin disease in the patients. Detailed disease and family histories were obtained from all subjects.

Clinical examination:

Psoriasis disease severity were assessed by measuring psoriasis area and severity index score (PASI; 0-72 points) (Fredriksson and Pettersson, 1978), When PASI ≥ 15; patients will be defined assevere.

Blood Sampling:

Peripheral blood samples were obtained from all studied subjects. The blood samples were allowed to clot for 30 minutes before centrifugation. Serum samples were collected and stored at≤−20°C.

Enzyme-Linked Immunosorbent Assay (ELISA):

Serum LCN2 concentrations were measured in all studied subjects using specific ELISA kits (R and D Systems, Minneapolis, MN, USA), according to the manufacturer's instructions.

Statistical analysis

The collected data were computerized and statistically analyzed using SPSS program (Statistical Package for Social Science) version 18.0. Qualitative data were represented as frequencies and relative percentages. Chi square test was used to calculate difference between qualitative variables. Mann Whitney (MW) test was used to calculate difference between quantitative variables in 2 groups in not normally distributed data. Kruskal Wallis test was used to

calculate difference between quantitative variables in groups in not normally distributed data.

RESULTSAND DISCUSSION

In our study, serum samples were obtained from 18 patients with psoriasis (8 females and 10 males; mean ±SD age 33.72±17.75 years, range 7 - 66), 18 patients with AD (7 females and 11 males; age 9.5 ± 2.46 years, range 6 - 14) and 18 healthy controls (10 females and 8 males; age 28.33 ± 6.16 years, range 19 -42) (Table 1).

The results in Table (2) shows the two cases groups as regards disease duration or VAS score. The PASI score among psoriasis patients ranged from 12.3 to 49.3 with mean 24.44. Also, SCORAD score among AD patients ranged from 20.1 to 84.21 with mean 48.21

In the present study, there was a statistical significance increase in Lipocalin-2 level among the two cases groups compared to control group (Figure 1). A statistical significance positive correlation between lipocalin-2 level and VAS score among the psoriasis group but not in atopic dermatitis group, Also there was no statistical significance correlation between lipocalin-2 level and PASI score in psoriasis group and SCORAD score in atopic dermatitis group (Figure 2).

Regarding relation between sex and Lipocalin-2 among the three studied groups, there was a statistical significance increase in Lipocalin-2 among female compared to male in atopic dermatitis group while no significance differences among controls or psoriasis group as shown in Table (3).Psoriasis is a chronic autoimmune condition that causes skin lesions characterized byred, scaly papules, plaques and patches of skinvaries in severity from small, localized patches to complete body coverage (Rendon and Schäkel, 2019). Lipocalin-2 (LCN-2), also known as neutrophil gelatinase-associated lipocalin (NGAL) belongs to the lipocalin family. It is highly accumulated in the human kidney cortical tubules, blood and urine, after nephrotoxic and ischaemic injuries (Ding et al.2015). Serum LCN-2 concentration was shown to be higher in psoriatic patients and it may contribute to the pathogenesis of psoriasis by modulating neutrophil activities, including neutrophil infiltration, migration, and activation, inducing neutrophils to release proinflammatory mediators (Wieser et al.2016).

However, the relationship between LCN-2 and itch in patients with psoriasis and atopic dermatitis remains unclear. Therefore, to more extent the present study aimed to estimate lipocalin-2 level and correlates its level by itching severity in psoriasis and atopic dermatitis.

In our study, there were no statistical significant differences between the three studied groups regarding sex distribution, but there was a statistical significant decrease in mean age among AD group compared to control and psoriasis groups because AD more common in pediatric age group. Also, a statistical significant increase was foundin LCN-2 among females compared to males in atopic dermatitis group which may be explained by presence hormonal correlation with LCN-2 in females but not in males.

In the current study,there was a statistical significant increase in LCN-2 level among the two cases groups (982.20 ± 650.45 in psoriasis group and 685.78± 291.96 in atopic dermatitis group) compared to control group (71.16 ±14.60) this confirm that LCN-2 has a role in the pathogenesis of both diseases.

This study in agreement with Aizawa et al. (2019) who examined the correlation between serum LCN-2 levels in patients with psoriasis and AD. They showed that serum LCN-2 concentrations were significantly higher in patients with psoriasis (80.08 ± 51.3 ng/ml) and AD(78.32± 43.42 ng/ml) than those in healthy controls (59.07 ± 20.18 ng/ml, P < 0 05 each), but there was no significant deference in serum LCN2 levels between psoriasis and AD patients.

Similary, Kamata et al. (2012) who found that serum LCN-2 levels were significantly higher in patients with psoriasis than in healthy controls (41.1 ± 14.9 vs. 30.7 ± 8.1 ng ⁄ mL). But in contrast the patients with AD had significantly lower serum LCN-2 levels than did healthy controls (13.3 ± 4.00 vs. 30.7 ±8.10 ng ⁄ mL), indicating the possibility that the AD microenvironment might suppress LCN-2 production.

Also, Shiratori-Hayashi et al.(2015) they has been recorded Serum LCN-2 concentration higher in patients with psoriasis, but incontrast lower in patients with AD, than that in healthy controls.

Table 1: Comparison of demographic data of the three studied groups:

Variable	Group I (control) (n=18)		Group II (Psoriasis) (n=18)		Group III (Atopic dermatitis) (n=18)		p
Age (years) Mean ± SD Median Range	28.33 ± 6.16 28 19 – 42		33.72 ± 17.75 34 7 – 66		9.5 ± 2.46 9 6 – 14		<0.001 **
	No	%	No	%	No	%	p
Sex							
Female	10	55.6	8	44.4	7	38.9	0.59
Male	8	44.4	10	55.6	11	61.1	NS

NS: Non significant (P>0.05) **: Highly significant (P<0.01) P1:Group I versusGroupII,P2: Group I versus Group III, P3: Group II versus Group III

Table (2): Clinical data of the two cases groups

Variable	Group II (Psoriasis) (*n*=18)	Group III (Atopic dermatitis) (*n*=18)
Duration (years) Mean ± SD Median Range	7.10 ± 9.53 4 5 m - 40	4.83± 2.87 4.5 1 – 13
VAS score: Mean ± SD Median Range	5.67 ± 2.83 6 0 – 9	5.33 ± 2.68 5.5 1 – 9
PASI score: Mean ± SD Median Range	24.44 ± 9.99 22.95 12.3 – 49.3	-------
SCORAD score: Mean ± SD Median Range	------	48.21 ± 18.69 46.4 20.1 – 84.21

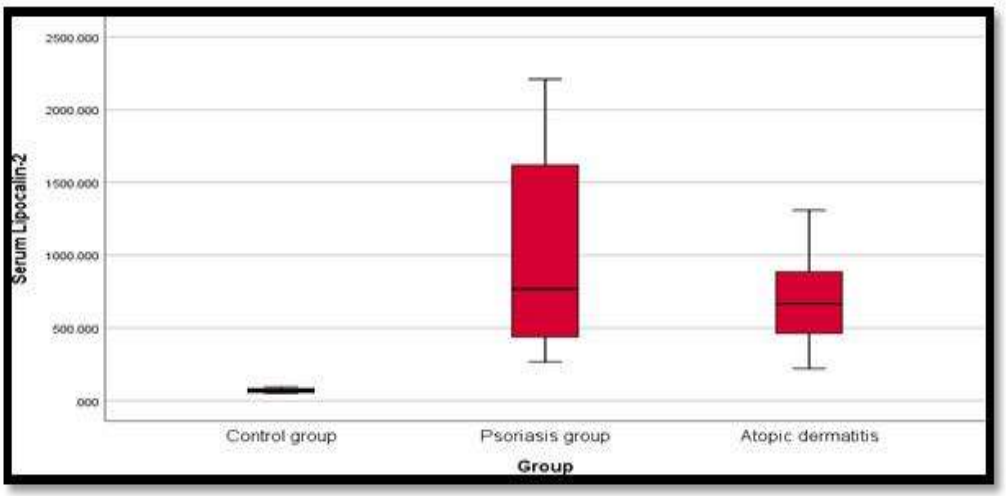

Figure 1: Lipoclain-2 among the three studied groups

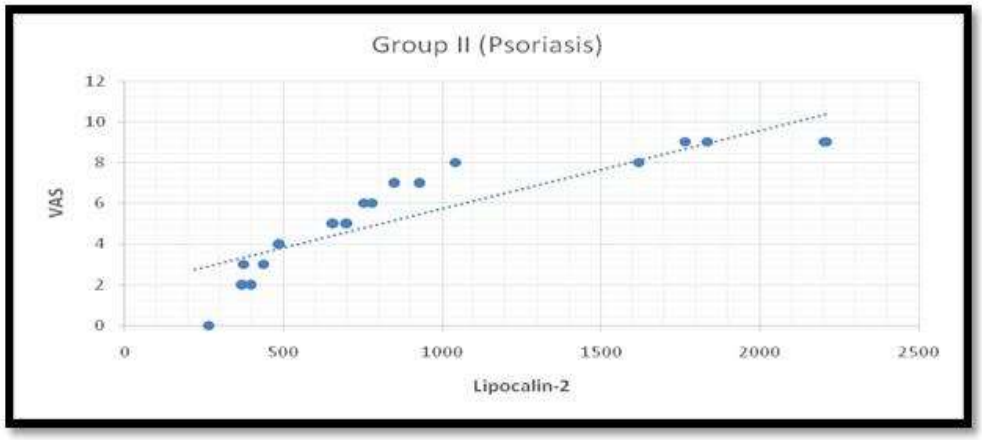

Figure 2: Correlation between Lipoclain-2 and VAS score among the patients with Psoriasis.

Table 3: Relation between sex and Lipocalin-2 among the three studied groups

Group	Sex	No	Lipocalin-2					MW	p
			Mean	Sd	median	Range			
I	Female	10	69.11	15.92	64.7	52.25	94.5	0.80	0.42
	Male	8	73.73	13.36	71.4	52.35	96.12		NS
II	Female	8	1098.71	726.6	841.6	375.08	2205.08	0.62	0.53
	Male	10	888.99	605.6	739.50	266.46	2209.41		NS
III	Female	7	875.02	230.6	854.01	619.31	1309.56	**2.14**	**0.03***
	Male	11	565.36	268.3	574.45	221.1	963.14		

SD:Standarddiviation, MW: Mann Whitney test, NS: Non significant (P>0.05), *: Significant

LCN2 was found to be upregulated in spinal astrocytes in a mouse model of AD, indicating itch sensitization at the spinal level. Wang et al. (2019) explored the association of serum LCN-2 concentrations with psoriasis. They indicated that serum LCN-2 concentrations are higher in psoriasis patients than controls.

In the current study there was no statistical significance positive correlation between LCN-2 level and PASI score in psoriasis group and SCORAD score in atopic dermatitis group, which indicates initiation of the diseases.

In agreement with this study Kamata et al. (2012)who found that serum LCN-2 levels did not correlate with PASI score, indicating that extracutaneous tissues might be the source of serum LCN-2 protein in patients with psoriasis, although there is a possibility that this result could be due to small sample size or the effect of treatment. In fact, serum LCN-2 seems to be a general indicator for systemic inflammation in psoriasis. Also, Aizawa et al. (2019) found that serum LCN-2 levels did not correlate with PASI score in psoriasis and SCORAD score in atopic dermatitis.

In contrast, Romaní et al. (2013) reported a positive correlation between LCN-2 and PASI score. These discrepancies may be due to factors such as disease duration, type of psoriasis and previous medical history and treatment.

We detected a statistical significant positive correlation between LCN-2 level and VAS score among the psoriasis group but not in atopic dermatitis group which may explained by present other factors more involved to itching in AD.

With this study of Aizawa et al. (2019) who showed that serum LCN-2 concentration is associated with the degree of itch in patients with psoriasis but not in AD which may be explained by differences in the local and systemic effects of LCN-2 in the patients with psoriasis and AD.

Based on our results, it can be assumed that the decrease of serum LCN-2 levels represents the improvement of itch and serum LCN-2 level may be a useful clinical marker for the evaluation of itch in atopic dermatitis and psoriasis patients.

CONCLUSION

Serum LCN2 levels were higher in patients with psoriasis and atopic dermatitis than those in healthy controls. Also our study showed a close relationship between the degree of itch and serum

LCN2 level in patients with psoriasis.

So, we found that serum LCN-2 level involved in the pathogenesis of psoriasis and atopic dermatitis and is responsible for occurring of itching in psoriasis which may be good substance for therapy in the future.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

All author contributed in all parts of the paper.

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