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Study Of Role Of Lipoxin – A4 In Psoriasis

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Abstract:

The aim of this work was to evaluate the level of lipoxin – A4 **(**LXA4) in patients with psoriasis and its correlation with clinical parameters. This study included 25 psoriatic patients who were recruited from the outpatient clinics of dermatology department, Faculty of Medicine, Beni-Suef University. In addition, 25 age and sex-matched volunteers were included as control group. Four mm punch skin biopsy will be taken from the tissue and will be kept in lysis solution for the stability of the studied parameters and will be kept frozen at -80°**C** till detection of LXA4 in tissue by real time-PCR. Peripheral blood samples for serum LXA4 are taken. Blood samples will be centrifuged and serum will be stored at 80°**C** and used for ELISA. The LPXA levels in the case ranged from 1.01 -7.8 ng/mL with a mean of 2.94 ±1.7 ng/mL. In addition, the LXA4 levels in the control ranged from 4.5 – 14.7 ng/mL with a mean of 9.45 ±2.26 ng/mL. The level of LXA4 is significantly downregulated in patients with psoriasis, compared to healthy volunteers. Moreover, the affection of LXA4 appears to be correlated with the severity of the diseases. LXA4 and its analogue may be potential therapeutic candidates for psoriasis.

Keywords: Psoriasis, LXA4, LXA4 analogue

1. Introduction:

Psoriasis is a chronic auto-immune, genetic, inflammatory, disease. It starts underneath the skin. It is estimated that the prevalence of Psoriasis varies from 2% - 3 % of the global population and increases with age [1]

A normal immune system protects the body against invaders by destroying bacteria, viruses and other foreign bodies and proteins. In person who has Psoriasis, the immune system “misfires” and inappropriately causes inflammation and an accelerated growth of skin cells[2]

Psoriasis is frequently referred to as a "T-cell mediated disease", as T-cells are a type of immune system cell (white blood cells) that are proven to be very important in the internal process of Psoriasis[3].

Psoriasis may be associated with other health conditions such as Psoriatic arthritis, cardiovascular disease, DM type II, depression and inflammatory bowel disease. The main goal of treatment is to stop the skin cells from growing so quickly [4].

Lipoxins are derived enzymatically from arachidonic acid, a W-G fatty acid. They are defined an arachidonic acid metabolite, that contain 3 hydroxyl residues A4 double bonds. This structural definition distinguish them from other SPMs (Specialized pro-resolving maresins) such as maresins, protectins and resolvins which are metabolites of omega 3 fatty acids[5] Lipoxin A4 and its analogue suppress inflammation by modulating high mobility group box 1 (HMGBI) translocation and expression in psoriasis[6].

Lipoxin A4 has a role in improvement of Psoriasis cases by many ways, as it stimulates the bacteria killing capacity of leukocytes and airway epithelial cells, it blocks production of the pro-inflammatory cytokine, TNF with increasing production of the anti-inflammatory cytokine, c-c chemochine receptor-5 (ccR5) by T-lymphocytes, and it reduce perception of pain due to inflammation[5]. They observed that LXA4and LXA4 treatment significantly attenuated the phosphorylation of ERK1/2 and nuclear NF-κB pathway effectors in the IMQ-induced skin lesions and LPS-induced NHEKs, respectively. This may be because LXA4 and LXA4suppress the expression of HMGB1, TLR4 and RAGE as well as the secretion of HMGB1. Deficiency of HMGB1, RAGE or TLR4 reduces the activation of the MAPK-ERK1/2 and NF-κB signaling pathways. These data support the notion that the activation of ERK1/2 and NF-κB pathways are mediated by HMGB1-TLR4/RAGE interactions; however, this effect may be ameliorated by treatment with LXA4and LXA4 [5]. The aim of the work is to assess the serum and tissue level of lipoxin A4 in patient of psoriasis in order to evaluate its possible role in pathogenesis of psoriasis and may be its use as therapeutic modalities.

2. Patients and Methods:

The present case-control study included 25 psoriatic patients who were recruited from the outpatient clinics of dermatology department, Faculty of Medicine, Beni-Suef University from 1May 2018 to 1 November 2018

. In addition, 25 age and sex-matched volunteers were included as control group. Verbal consents were obtained.

2.1 Inclusion criteria:

1. Age between 20 -50.
2. Patients with constant plaque psoriasis.
3. Patients not accepting psoriasis treatment for in any event three months.
4. Both males and females will be incorporated .

2.2 Exclusion criteria:

1- Age beneath 20 or > 50.
2- Patients with different kinds of psoriasis.
3- Patients getting psoriasis treatment over the last three months.

2.3 All patients were subjected to:

1. Detailed history taking.
2. Clinical assessment to determine type, extent and sites of psoriasis.
3. Four mm punch skin biopsy will be taken from the tissue and will be kept in lysis solution for the stability of the studied parameters and will be kept frozen at -80°C till detection of LXA4 in tissue by real time-PCR. Peripheral blood samples for serum LXA4 are taken. Blood samples will be centrifuged and serum will be stored at 80°C and used for ELISA.

Statistical methodology:

An Excel spreadsheet was established for the entry of data. We used validation checks on numerical variables and option-based data entry method for categorical variables to reduce potential errors. The analyses were carried with SPSS software (Statistical Package for the Social Sciences, version 24, SSPS Inc, Chicago, IL, USA). Frequency tables with percentages were used for categorical variables and descriptive

statistics (median and interquartile range [IQR]) were used for numerical variables. Independent Student t-test, paired t-test, or Mann-Whitney tests were used to compare quantitative variables, while Chi-square test or McNemar-Bowker tests were used to analyze categorical variables. A p-value < 0.05 is considered statistically significant.

3. Results:

1. The disease characteristics

Table 1: The baseline demographic characteristics of the included patients

Variables	Cases (N =25)	Control (N =25)	P-value
Age in years	48.56 ±12.2	50.24 ±7.1	0.55

1. Mean ±SD **2.** Median (range)	49 (28 -75)	52 (32-61)	
Gender - Male - Female	16 (64%) 9 (36%)	21 (84%) 4 (16%)	0.196

*Data are presented as mean ±SD, median (IQR), or number (%).

Table 2: The disease characteristics of the included patients

Variables	**Cases (N =25)**
Onset, No (%) - Sudden - Gradual	 1 (4%) 24 (96%)
Course, No (%) - Progressive - Remission - Stationary - Regressive	 6 (24%) 15 (60%) 2 (8%) 2 (8%)
Duration, in months - Mean ±SD - Median (Range)	 121.3 ±86.2 120 (1 – 260)
Variables	Cases (N =25)
PASI **3.** Mean ±SD **4.** Median (range)	 7.624 ±6.5 5 (0.9 -28.5)

Table 3: The precipitating factors of the included patients

Variables	Cases (N =25)
Precipitating Factor, No (%)	
- Cold	8 (32%)
- Stress	13 (52%)
- Stress, cold	3 (12%)
- Sun	1 (4%)

*Data are presented as mean ±SD, median (IQR), or number (%).

2. Lipoxin A4

Table 4: Comparison of LXA4 between cases and controls

Variables	Cases (N =25)	Control (N =25)	P –value
Tissue Lipoxin A4 (ng/ml)			
- Mean ±SD	2.94 ±1.7	9.45 ±2.26	<0.001
- Median (Range)	2.4 (1.01 -7.8)	9.1 (4.5 – 14.7)	
Serum Lipoxin A4 (ng/mg protein)			
- Mean ±SD	1.73 ±0.67	8.99 ±2.15	<0.001
- Median (Range)	1.5 (1.01 -3.01)	9.4 (4.6 – 13.1)	

*Data are presented as mean ±SD and median (IQR).

Table 5: Correlation analysis between Lipoxin A4 and age, PASI, and duration.

	Tissue Lipoxin A4		Serum Lipoxin A4	
	r	**P-value**	**r**	**P- Value**
Age in years	0.045	0.755	0.104	0.473
PASI	0.277	0.197	0.49	0.013
Duration in months	-0.108	0.606	0.101	0.632

*Data are presented as correlation coefficient (r)

4. Discussion:

Psoriasis is a chronic, inflammatory skin condition that affects between 2–4% of the general population, with recent estimates suggesting over one hundred twenty-five million patients worldwide. It is associated with a number of comorbidities as well as a high socioeconomic burden.

Psoriasis patients also experience a decreased quality of life as a result of this disease. The pathogenesis of psoriasis is currently under active investigation, with studies aiming to identify genetic susceptibility loci for psoriasis in order to detect novel targets for systemic therapy. While the exact pathogenesis of psoriasis is not fully understood, basic and translational investigations have led to a renewed understanding of Th-17 and Th-1 pathways involved in the development of psoriasis[8].

On the other hand, lipoxin A4 (LXA4), an endogenous lipoxygenase-derived eicosanoid mediator, has potent dual pro-resolving and anti-inflammatory properties. LXA4 has been found to suppress leukocyte-mediated injury, promote chemotaxis of monocytes and phagocytosis of apoptotic neutrophils, and inhibit the production of proinflammatory cytokines and cell proliferation[6].

Over the past few years, a growing body of evidence has suggested that modulation of Inflammation by lipid mediatiors in patients with psoriasis is dysregulated and, thus, LXA4 is signisifcantly downregulated in patients with psoriais[7].

Nevertheless, there is a scaricty in the published literature regarding the role of LXA4 in the pathogensis of psoriasis and its protective effects. Therefore, we conducted the present prospective, case-control, study in

order to evaluate the level of LXA4 in patients with psoriasis and its correlation with clinical parameters.

The present study includes included 25 psoriatic patients who were recruited from the outpatient clinics of dermatology department, Faculty of Medicine, Beni-Suef University. In addition, 25 age and sex-matched volunteers were included as control group.

The current body of evidence shows that psoriasis often develops between the ages of fifteen and thirty-five , but it can develop at any age. Moreover, it has previously been speculated that women have less severe psoriasis, as men are overrepresented in psoriasis registers and consume more care [9].

In the present study, the age of the included patients ranged from 28-75 years old with a mean age of 48.56 ±12.2 years old. In term of gender distribution, 64% of the cases were males, compared to 36% who were females

In line with our findings, **Kimball and colleagues (2014)** evaluated the demographic and disease characteristics in patients enrolled in the Psoriasis Longitudinal Assessment and Registry (PSOLAR). A total of eleven thousand nine hundred patients were enrolled at three hundred one sites in North America, Europe, and Latin America. Over half of the PSOLAR population (54·7%) is male, with a mean age of 48.6 years [10].

Similarly, **Truong and colleagues** (**2015**) conducted a prospective study to identify and compare demographics, clinical disease characteristics, and quality of life (QoL) scores in a large cohort of psoriasis patients. A total of five hundred sixty-eight patients were enrolled in the database. The mean age of psoriasis patients was 48 years and the majority of them were males[11].

Recently, **Ghazy et al.,** (**2020**) conducted a case-control study included one hundred Egyptian psoriatic patients and one hundred age and sex-matched healthy controls. They reported that 62% of the patients were males[12].

From a clinical perspective, psoriasis can be seen as a wide spectrum of various skin manifestations at any given time. The onset of psoriasis is usually gradual but occasionally explosive; while the course of psoriasis is variable depending upon the type of psoriasis[13].

In term of clinical characteristics of the included patients, all patients had a gradual onset of disease, except one patient (4%) who had a sudden onset. The course of the disease was progressive in 6 (24%) patients, stationary in 2 (8%) patients, regressive in 2 (8%) patients, and in remission in 15 (60%) patients.

In agreement with our findings, **Kojanova and colleagues** (**2017**) described the characteristics of patients with psoriasis at the time of enrollment between May 2005 and May 2015. A total of 1412 psoriatic patients initiating biological treatment were included with a predominance of males (63.4%). The

majoirty of the patients had gradual onset of the disease [14].

Many exogenous or endogenous factors can trigger the eruption of psoriasis. Known exogenous triggers are skin aggression, infections, alcohol and tobacco, stress, drugs (lithium, beta-blockers, antimalarials, ACE-inhibitors, NSAIDs). Endogenous triggers are hormonal changes and allergies[4].

Our results showed that the most commonly encountered precipitating factor was stress (52%), followed by cold (32%), stress and cold (12%), and sun (4%).

In line with these findings, **Xhaja and colleagues** (**2014**) conducted a cross-sectional study to evaluate the role of trigger factors and the impact on quality of life in a sample of psoriasis patients. A transversal study performed in 90 patients affected by psoriasis between January and November 2012 at the "Nene Tereza" University Hospital, Tirane, Albania, based on two scored questionnaires. The most commonly encountered risk factor was stressful events, followed by smoking and alcohol [15].

Similarly, **Islam and colleagues** (**2011**) performed **a** cross-sectional study on 102 cases having clinical manifestation of psoriasis with a view to evaluate the epidemiological determinants of psoriasis. Regarding precipitating factors, psoriasis was developed after stressful condiction in majoiry of cases, followed by infection and alcohol [16].

Psoriasis is a multidimensional diseases with a strong genetic component. The genetic basis of psoriasis is recognized based on family aggregation studies, epidemiological studies, association studies with human leucocyte antigens (HLAs), genome-wide linkage scans and candidate gene studies. According to the population based epidemiologic studies approximately 40%of patients with psoriasis have a family history for either of thesein first-degree relatives[17].

In the present study, only 3 (12%) patients had a positive family history of psoriasis.

In contrary to our findings, **Affandi and colleagues** (**2018**) evaluated the epidemiology and clinical characteristics of patients with psoriasis who seek treatment in outpatient dermatology clinics throughout hospitals in Malaysia. Data were obtained from the Malaysian Psoriasis Registry (MPR) with a total of 15,794 patients. 23.1% of patients had positive family history of psoriasis[18].

Similarly, **Iskandar and colleagues** (**2015**) described the demographics, disease severity and comorbidities of patients with psoriasis on enrolment into BADBIR, and to highlight differences in those commencing biologics compared with those on conventional systemic therapies. Baseline data were collected from 151 dermatology departments in the U.K. and Republic of Ireland. Descriptive analysis was conducted. As of August 2014, 8399 patients were registered. Nearly half (46.7%) of the patients enrolled

reported a family history of psoriasis in a first-degree relative[19].

Regarding the primary outcomes of the present study, the tissue LPXA levels in the case ranged from 1.01 -7.8 ng/mL with a mean of 2.94 ±1.7 ng/mL. In addition, the tissue LXA4 levels in the control ranged from 4.5 – 14.7 ng/mL with a mean of 9.45 ±2.26 ng/mL. The mean serum LXA4 level in the patients and control groups was 1.73 ±0.67 and 8.99 ±2.15ng/mg, respectively. The association analysis showed statistically significant association between disease and LXA4 levels (P <0.001). Psoriasis patients had significantly lower tissue and serum LXA4 levels.

To the best of our knowledge, this is the first study that evaluated the in-vivo level of LXA4 in psoriasis patients. However, previous reports have shown that LXA4 can ameliorate the inflammatory response in psoriasis.

For example, **Liu and colleagues** (**2017**) investigated the effects of LXA4 on the HMGB1 signaling cascade and inflammation in lipopolysaccharide (LPS)-induced keratinocytes and imiquimod (IMQ)-induced psoriasiform dermatitis in mice. The authors found that treatment with LXA4 attenuated the development of IMQ-induced psoriasiform dermatitis. Furthermore, treatment with LXA4 inhibited HMGB1 translocation from the nucleus to cytoplasm and downregulated the expression of toll-like receptor 4 (TLR4), receptor for advanced glycation end products (RAGE), p-ERK1/2, nuclear NF-κB p65, and proinflammatory cytokines *in vivo* and *in vitro*. Such findings indicate that LXA4 and its analog may be potential therapeutic candidates for psoriasis because of their ability to modulate the translocation and expression of HMGB1[6].

Similarly, **Lewandowska-Polak and colleagues** (**2018**) assessed if the influence of LXA4 on inhibition of synthesis of pro-inflammatory cytokines by peripheral blood mononuclear cells (PBMNCs) of patients with psoriatic arthritis. The study group consisted of 10 patients with psoriatic arthritis and 5 healthy controls. Incubation of cells with LPS, increased production of all cytokines assessed either in patients with psoriatic arthritis or in healthy controls. In PBMCs from patients, incubation of cells with LXA4 decreases production of proinflammatory cytokines.

In conclusion, there is a significant dysregulation of lipid mediators in patients with psoriasis. The present study showed that the level of LXA4 is significantly downregulated in patients with psoriasis, compared to healthy volunteers. Moreover, the affection of LXA4 appears to be correlated with the severity of the diseases. Our findings highlight LXA4 and its analog may be potential therapeutic candidates for psoriasis. Nevertheless, further trials that

assess the usefulness of LXA4-based therapeutic options are still needed.

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5. Conflict of interest:

There are no conflicts of interest.

6. References:

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