Serotonin Levels in Atopic Dermatitis Patients and its Relation to Disease Severity and Depression: A Case-Control Study

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Abstract:

Background*:* Atopic dermatitis (AD) is an itchy, chronic inflammatory skin disease with frequent remissions and relapses. AD can greatly affect patients' lives by causing significant psychological distress. The neuroendocrine system and the immune system, including the skin, are connected and influenced by various mediators like Serotonin.

Aim of the Study: We aimed to estimate serum levels of Serotonin in AD patients in comparison to healthy individuals and to correlate serum Serotonin levels with patients` demographic data, clinical characteristics, and severity and depression scales.

Patients and Methods: This study included 40 (23 males and 17 females) patients with a clinical diagnosis of AD and 40 healthy volunteers. All patients were subjected to clinical examinations, evaluation of severity using scoring atopic dermatitis (SCORAD), and measuring serum Serotonin level by Enzyme-Linked Immunosorbent Assay (ELISA). For patients more than 7 years old, the 12-Item Pruritus Severity Scale and Beck Depression Inventory Scale were evaluated.

Results: Serum Serotonin level was significantly lower in AD patients than in the control group. Significant negative correlations between Serotonin level with patients' age, SCORAD, 12-Item Pruritus Severity Scale, and Beck Depression Inventory Scale were noticed.

Conclusion: Serum Serotonin level, as a marker of psychological comorbidities, is low in AD patients. Severe AD cases, especially in older age groups, are more liable to psychiatric comorbidities.

Keywords: Atopic Dermatitis, Serotonin, Depression.

Introduction:

Atopic dermatitis (AD) is a common skin disease that involves persistent inflammation, itching, and a fluctuating course [1], with a global prevalence ranging from 0.2% to 24.6% [2]. Children and females were found to be more susceptible to AD [3],[4].

Numerus comorbidities have been associated with AD, such as metabolic syndrome, obesity, anemia, sleep disorders, impaired psychosocial functions, hyperactivity, anxiety, and depression [5].

Different mediators were found responsible for the relationship between the neuroendocrine system and the skin, such as Serotonin [6],[7].

Some researchers reported that patients with severe AD have low Serotonin levels, which correlated negatively with depression scores [7],[8]. Consequently, Selective

Serotonin Reuptake Inhibitors (SSRIs) have been suggested for AD treatment [9].

So, since the previous research about serum Serotonin level in patients with AD is neither extensive nor consistent, this research was designed to explore Serotonin level in AD patients in our locality. In addition, we thought that it would be interesting to investigate the possible relation between the patient's demographic and clinical characteristics with Serotonin levels to explore the predicting value of these characteristics in determining serum Serotonin levels and, hence, the necessity for SSRIs therapy.

Patients and Methods:

This is a case-control study that was carried out during the period from May 2018 to December 2021 at the Outpatients' Dermatology Clinic in a tertiary care hospital.

The study was approved by the Research Ethical Committee, Faculty of Medicine, Assiut University, and fulfilled all the obligations of the Helsinki Declaration. Informed consent was obtained from the patients or the guardians.

Ethics Committee approval: IRB local approval number: 17100437

Clinical trial registration number: NCT03471819 on 14 /3/2018.

The sample size was calculated using G*power software 3.1.9.2. The study included 40 patients with the clinical diagnosis of AD (23 males & 17 females) and 40 age- and sex-matched healthy volunteers.

Inclusion criteria:

- All patients with the clinical diagnosis of AD.
- Age more than 2 years.

Exclusion criteria:

- Patients with any concomitant systemic or dermatological disease.
- Patients on any topical or systemic treatment during the past month before enrollment in the study.
- Uncooperative patients.

Clinical Evaluation

All patients were subjected to the following:

- Complete history taking.
- Meticulous general examination.
- Complete dermatological examination.
- All patients fulfilled the American Academy Diagnostic Criteria of AD [10].
- Severity evaluation was done by scoring atopic dermatitis SCORAD [11].

For cases older than 7 years old, the following scores were done:

- 12-Item Pruritus Severity Scale (12 PSS) [12].
- Beck's Depression Inventory (BDI) (Arabic version) [13].

Serum Serotonin levels were measured in patients and healthy volunteer controls. Blood samples (5 mL of blood per participant from a vein in the antecubital fossa without venous occlusion) were collected from the study participants to analyze the serotonin level. The detection range was 5 -180 pg/ml. All biochemistry measurements were assayed at Assiut University Hospital's clinical laboratory in the Clinical Pathology Department.

Statistical Analysis:

Data was collected and analyzed using SPSS (Statistical Package for the Social Science), version 20, IBM, Armonk, NY, USA. Chi^2-test was used to compare the nominal data of different groups in the study. Student t-tests were used to compare the mean of two groups, and an ANOVA test was used for more than two groups. Correlations were determined with Pearson and Spearman correlation tests. The level of confidence was kept at 95%. P value was considered significant if < 0.05.

Results:

This study included 40 patients with the clinical diagnosis of AD and 40 healthy volunteers. Out of 40 cases, 23 (57%) were males, while 40 controls included 15 (37.5%) males. Age in cases ranged from 2-59 years (mean 10.20 ± 11.18 SD), while in controls, age ranged from 2.5-20 years (mean 8.04 ± 4.11).

Table (1): Sociodemographic Data of Study Subjects

Personal data	Cases (n= 40)		Controls (n= 40)	
	No.	%	No.	%
Age: (years)				
Mean ± SD	10.20 ± 11.18		8.04 ± 4.11	
Range	2.0-59.0		2.5-20.0	
Sex:				
Male	23	57.5%	15	37.5%
Female	17	42.5%	25	62.5%
Residence:				
Rural	22	55.0%	19	47.5%
Urban	18	45.0%	21	52.5%
Family history				
Positive	14	35%		
Negative	26	65%		

Serotonin level in patients (505.17 ± 153.31 SD pg/ml) was significantly lower than in controls (584.44 ± 90.76 SD pg/ml) (P-value 0.006*), **Table 2.**

Table (2): Serotonin Level of Study Subjects

Serotonin level in pg/ml	Patients (n= 40)	Controls (n= 40)	P-value
Mean ± SD	505.17 ± 153.31 pg/ml	584.44 ± 90.76 pg/ml	**0.006***
Range	334.5-897.5	468.0-893.5	

The majority of cases (27 (67.5%)) had severe AD, according to SCORAD, and 13 (32.5%) were moderate. PSS and BDI scores were done only for 21 patients who were above the age of seven years. By using the PSS score, 15(71.4%) of cases were severe, and 6(28.6%) cases were moderate. BDI score showed no depression in 14(66.7%) cases, mild depression in 3(14.3%) cases, and moderate depression in 4(19.0%) cases, **Table (3).**

Table (3) Severity evaluated by scoring atopic dermatitis (SCORAD) in all 40 patients, 12-Item Pruritus Severity Scale (PSS), and Beck's Depression Inventory (BDI) in 21 patients (above the age of seven).

SCORAD severity	No. (40)	PSS severity	No. (21)	BDI severity	No. (21)
Moderate	13(32.5%)	**Moderate**	6(28.6%)	**None**	14(66.7%)
Severe	27(67.5%)	**Severe**	15(71.4%)	**Mild**	3(14.3%)
Mean ± SD	60.19 ± 17.09	Mean ± SD	14.57 ± 3.83	**Moderate**	4(19.0%)
Range	29.4-101.0	Range	7.0-20.0	Mean ± SD	4.00 ± 3.54
				Median (Range)	2.0 (0.0-11.0)

SCORAD: scoring atopic dermatitis.
PSS:12-Item Pruritus Severity Scale.
BDI: Beck's Depression Inventory.

Regarding the correlation, a significant negative correlation was found between Serotonin level and the following: Age, SCORAD score, PSS score, and BDI score, while the correlation between Serotonin level and sex and family history was insignificant. Regarding Age, it had a significant positive correlation with BDI score only in contrast to SCORAD and PSS score, which had an insignificant correlation with Age. **Table (4) and Figure 1-4.**

Table (4) Correlation between **Serotonin level** and Age, SCORAD, PSS score, BDI score, sex, and Family history. Correlation between **Age** and SCORAD, PSS score, and BDI score.

Correlation		**P-value**	**Significance**	**r-value**	**Remarks**
Serotonin level	Age	**0.02***	Significant	-0.366	Negative
Serotonin level	SCORAD	**0.046***	Significant	-0.318	Negative
Serotonin level	PSS score	**0.031***	Significant	-0.471	Negative
Serotonin level	BDI score	**0.023***	Significant	-0.493	Negative
Serotonin level	Sex	0.187	None		
Serotonin level	Family history	0.756	None		
Age	SCORAD	0.347	None		
Age	PSS score	0.113	None		
Age	BDI score	**0.010***	Significant	0.549	Positive

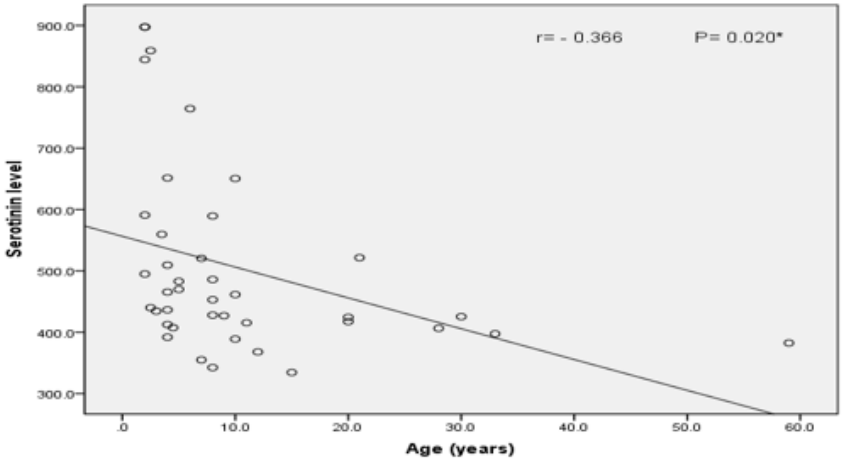

Fig. (1): Correlation between serum Serotonin level and Age.

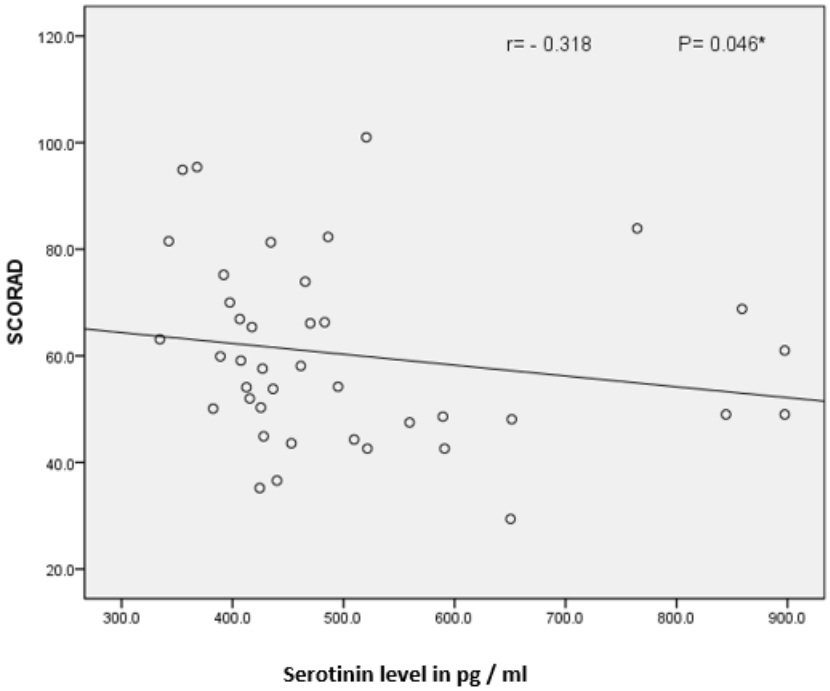

Fig. (2): Correlation of serum Serotonin level with SCORAD.

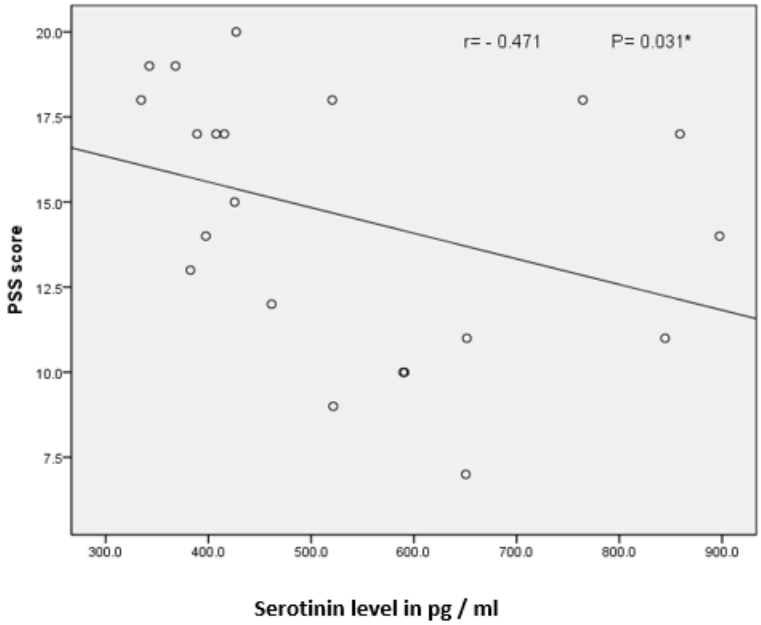

Fig. (3): Correlation of serum Serotonin level with PSS score.

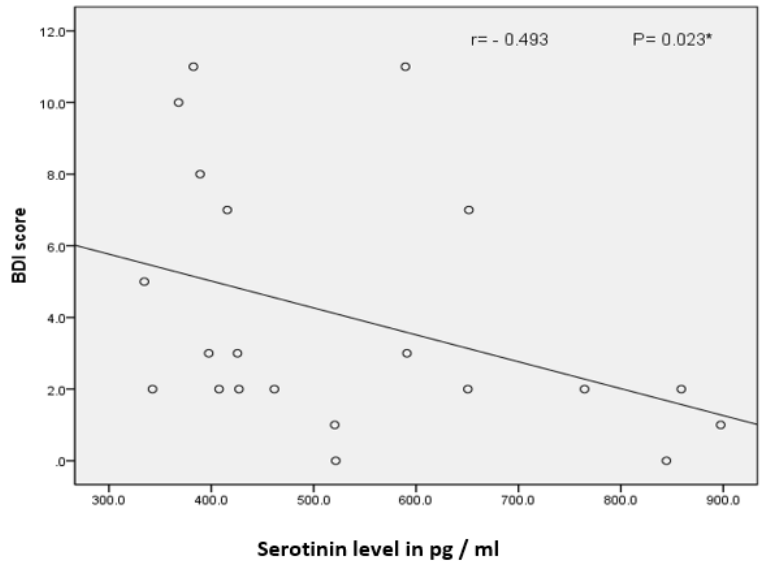

Fig. (4): Correlation of serum Serotonin level with BDI score.

Discussion

Atopic dermatitis has been linked to various comorbidities, such as hyperactivity, obesity, impaired psychosocial functions, depression, sleep disorders, anemia, and anxiety [8].

Some studies have reported lower levels of Serotonin in AD patients, which has been linked to higher depression scores. As a result, some researchers proposed that SSRIs could be used as a potential treatment option for AD patients [14],[7].

This study included patients with an average age of 10.2 ± 11.18 years, ranging from 2 to 59 years, which aligns with the age range reported in previous studies [15], [16],[17].

Forty patients were included in this study: 17 (42.5%) females and 23 (57.5%) males. However, our male predominance was in contradiction with the findings of Brew et al. (2018) [15] and Jaworek et al. (2020)[7].

Thirty-five percent of our patients reported a positive family history of AD.

However, a study by Böhme et al. (2003) found a higher percentage of 50% in their patients. This discrepancy could be due to differences in genetic backgrounds across different global regions [18].

By using SCORAD, we found that 13 patients were classified as moderate (32.5%), and 27 patients (67.5%) were classified as severe. However, ***Barbarot et al. (2018)*** reported in their cross-sectional study that 27% of their patients were mild, 52% were moderate and 21% were severe. Different environmental and genetic characteristics could be an explanation for this.

After utilizing the PSS score in this study, 6 (28.6%) patients were classified as moderate, and 15 (71.4%) patients were classified as severe.

By using the BDI score, we discovered that 3 (14.3%) patients had mild depression, and 4 (19.0%) patients had moderate depression. Noh et al. (2016) reported that 34.1% of their patients had mild depression, 35.4% had moderate depression, and 30.5% had severe depression [19]. Cheng et al. (2015) conducted a study on a group of 8208 Taiwanese adolescents and adults and revealed that AD is a risk factor for developing depressive disorders [20]. Wei et al. (2016) found that having AD in adolescence increases the risk of developing major depression and bipolar disorders in later life [21]. We believe that the lower percentage of depression in our study might be attributed to the differences in the sample sizes. Also, the perception and evolution of depressive symptoms might be different in different countries because of the diversity in the cultural, educational and economic backgrounds.

We found that serum Serotonin level was significantly lower in patients than its level in the control group ($P< 0.006$). In parallel with our findings, a significant decrease in serum Serotonin level was noticed in AD patients [7]. This finding offers a reasonable explanation of the psychiatric comorbidities of AD.

Interestingly, our study reported a significant negative correlation between serum Serotonin level and patients` Age ($p=0.02$). Also, we noted a significant positive correlation between Age and BDI score ($p= 0.010$). Jafferany et al. (2007) stated that adults with AD are more restless in their sleep, which leads to psychiatric and psychological comorbidities, such as anxiety, depression, and suicidal ideation. These findings indicate that adult patients with AD are more liable to psychiatric comorbidities [22].

In this study, a significant negative correlation was noted between serum Serotonin levels and the severity of AD as measured by SCORAD. In addition, a significant negative correlation was noted between serum Serotonin levels and PSS score. Jaworek et al. (2020) found that the intensity of skin lesions and pruritus in adult AD as measured by SCORAD correlates with the severity of depressive symptoms (Jaworek et al., 2020). So, AD patients with severe skin involvement and itching are more liable to psychiatric repercussions than mild cases. That's why significant negative correlations were noted between Serotonin levels and PSS & BDI scores in our study.

No significant relation was found between Serotonin level and sex. This was in concordance with the findings of Chang et al. (2014) [23]. Anxiety disorders, in general, manifest in women more than in men by almost twofold. Nonetheless, the expression of genes responsible for the Serotonin transporter can be influenced by sex steroids, leading to variations in the accessibility of Serotonin [24].

Family history did not have any significant impact on serum Serotonin level in this study. This finding may indicate that the familial nature of AD is irrelevant to the occurrence of psychiatric comorbidities.

We reported a significant positive correlation between Age and BDI score ($r= 0.549$ & $P= 0.010$). While age had no significant impact on SCORAD and PSS scores (P-value = 0.347, 0.113 respectively). This finding means that Age can be considered a predictive factor of depression in AD patients. Schonmann et al. (2020) stated that adults with AD are more

vulnerable to developing anxiety and depression [25].

Conclusion:

From the previous findings, we can conclude that serum Serotonin level, as a marker of psychological comorbidities, is significantly low in AD patients, especially in severe cases. So, severe cases are more liable to psychiatric comorbidities of AD. Moreover, depression and low Serum Serotonin level accompanied by AD are more marked in older age groups. So, screening for depression in adults with AD is advised.

Future studies with larger sample sizes about the evaluation of Serotonin levels in AD patients and its relation to patients' clinical data are very much warranted to explore the possibility of its involvement in the management algorithm and to determine high-risk groups of psychiatric comorbidities. Nonetheless, therapeutic clinical trials about the potential efficiency of SSRIs as possible therapeutics for AD are highly recommended.

Limitation of the Study:

We believe that the main limitation of our study is the relatively small sample size.

Conflict of Interest

The authors declare that they have no competing interests.

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