

The relation between atopic dermatitis and depressive symptoms

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ABSTRACT

Introduction: Atopic dermatitis (AD) is characterized by chronic itching, presenting with fluctuating evolution, resulting in sleep disorders and social stigmatization due to the presence of visible and recurrent lesions, that might become progressively lichenified. Factors such as those mentioned and others associated, such as incapacity for work, lack of concentration throughout the day and isolation have profound impacts on the patient's mental health, resulting in low self-esteem, depression and frustration. In addition, it is known that AD is essentially an inflammatory disease. And, recent studies demonstrate the role of inflammatory cytokines in the development of depressive syndromes, therefore may be a causal correlation between the conditions by inflammatory pathways. **Objectives:** This systematic literature review aimed to analyze a relationship between atopic dermatitis and depressive symptoms, identifying mechanisms responsible for this connection. **Methods:** The research was carried out between 11/17/2020 and 11/18/2020 following the PRISMA model and using PUBMED, Virtual Health Library (VHL) - IBECs, LILACS and CUMED - and EMBASE databases. Keywords "Depression" and "Atopic Eczema", along with its MeSh and DECS terms, were used and associated using the Boolean method. Inclusion criteria were defined as articles that are clinical or observational trials involving a group of patients with atopic dermatitis and a control group, which could be constituted by the group with atopic dermatitis itself, however, after an intervention. The depressive symptoms had to be measured by scales or, at least, the criteria for diagnosis of depressed syndrome must have been established. **Results:** In the end, fifteen studies remained, which were classified among those that compare treatments and their outcomes related to depression and AD, those that propose AD as an aggravator of depressive symptoms, those that propose depressive symptoms as an aggravating factor for AD and those that bring statistical analysis without clearly establishing where the causality relation resides. **Conclusion:** Several studies have presented a relationship between the condition of AD and depressive symptoms in distinct pathways, or analyzing AD as an aggravating factor for depressive symptoms or vice-versa. From this perspective, there may be a cyclical bidirectional causality, in which constant positive feedback generates worsening of both conditions until the adequate approach is taken, highlighting the importance of the multidisciplinary propaedeutics for these patients. **Keywords:** Atopic eczema, Atopic dermatitis, Depression, Depressive symptoms.

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INTRODUCTION

Atopic dermatitis (AD) is an inflammatory dermatological disease, with a clinical presentation characteristically marked by intermittent and chronic itching due to the presence of visible and recurrent lesions with a tendency to a progressive lichenification, may result in social stigmatization and modifications in sleep pattern¹. Other disease-associated factors may cause low self-esteem, depression and frustration, such as the incapacity for work, lack of concentration throughout the day and isolation^{2,3}. Furthermore, whereas atopic dermatitis is a comorbidity marked by chronic inflammation of the skin through Th2 pathways, recent studies demonstrated that its inflammatory characterization may have a systemic character⁴, in the same way, that growing evidence indicate the role of inflammatory cytokines in depression^{5,6,7}. On the other hand, considering that it is not yet possible to establish clearly where resides the relation of causality between AD and psychiatric disorders, at the same time that is already well verified the existence of relation between them, there is a possibility of mechanisms secondary to mental diseases accentuate the dermatosis^{4,8}. The exact magnitude of this association still needs to be elucidated.

Moreover, it is essential to emphasize the differences between sadness and depression to better define what is being addressed. The first is related to a momentary emotional state that, in general, has triggering events, such as losses, deceptions, health disorders and others. On the other hand, the second one is a clinical syndrome characterized by symptoms such as apathy, hopelessness, indifference and mood predominantly depressed by, at least, two weeks⁹.

Although there are several distinct scales capable to measure the levels of depressive symptoms, the diagnosis of unipolar depression, according to the Diagnostic and Statistical Manual of Mental Disorders 5^a Edition⁹, is established in the presence of specific criteria that goes beyond mood swings and include, for example, cognitive and psychomotor aspects. From this pathological perspective, depression may present itself in many ways, such as major depressive disorder and dysthymia, or may present itself inside other clinical conditions, such as bipolar disorder⁹.

Given such evidence, this systematic literature review intended to analyze the relationship between atopic dermatitis and depressive symptoms, identifying possible mechanisms responsible for this connection.

MATERIAL AND METHODS

Information sources and search strategies

The study is a systematic review of the literature regarding the relations between atopic dermatitis and depressive symptoms, based on the PRISMA¹⁰ methodology, without a registered protocol. In the stage of identification, the articles were found using databases of PUBMED, Virtual Health Library (VHL) - IBECs, LILACS and CUMED - and EMBASE for studies able to analyze patients with atopic dermatitis at the same time that it was verified the diagnostic criteria for depression or if depressive symptoms were measured. The Keywords included were "Depression" and its respective MeSh and DECS terms associated with each other with the Boolean operator "OR". Similarly, the term "Atopic Eczema" and its respective MeSh and DECS terms were submitted to the described operator and through the operator "AND", the two sets explained their intersection of results.

Eligibility Criteria

Observational studies or clinical trials that investigated the relationship between atopic dermatitis and depressive symptoms or depression were included, based on the presence of individuals with AD, which the levels of depressive symptoms were quantified by scores and compared to a control group or to the group itself after an intervention. There were no criteria based on publication dates, size of the studies, age of patients or status of the publication. The following criteria were considered for exclusion: there are no AD patients among the individuals studied, scores of depressive symptoms are not quantified or criteria for diagnosis of depression or depressive syndrome are not established and literature that was not in portuguese or english or articles that were not clinical trials or observational studies.

Selection of studies and data extraction

Based on the eligibility and exclusion criteria, the studies selection was made in two steps, being the first reading the title and abstract and the second reading the full text. All the stages were performed simultaneously

and individually by all the authors. Disagreements were debated and defined by consensus.

Outcomes relating to AD and depression, by statistical analysis or causal relationship were extracted from included studies. The characteristics of the selected studies, such as reference, diagnosis criteria or AD stratification, type of study, number of analyzed individuals, scales of quantification for depressive symptoms and outcomes were summarized in the tables along this article. The literature search and selection flowchart is described in figure 1.

Bias Analysis

For assessing bias analysis of the included clinical trials, the use of the *Risk of bias for non-randomized studies of interventions* (ROBINS-I) for non-randomized trials and *Cochrane risk-of-bias tool for randomized trials* (RoB 2)¹¹ for those that were randomized was chosen, evaluating the risk of randomization, allocation problems, blinding of the participants and the staff, blinding of the outcomes, missing data and other factors.

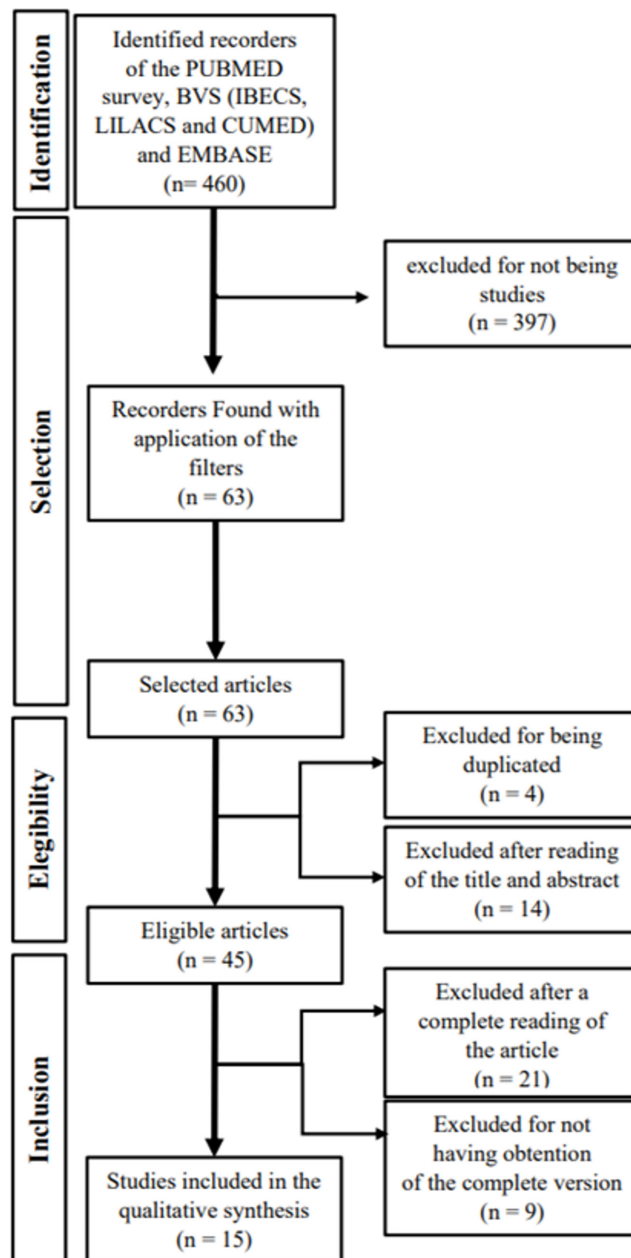


Figure 1. Flowchart of the search and selection of the studies for atopic dermatitis and depressive symptoms.

On the other hand, aiming to stratify the observational studies risk of bias, the method *Newcastle-Ottawa Scale* (NOS)¹² was used, which utilizes parameters of selection, comparison and exposure or outcome, depending on the kind of methodology. Articles with low quantitative-qualitative significance were those that presented high risk of bias in any of the

algorithms used, being the inferior cut off point for the NOS the obtention in zero stars in, at least, one of the qualified domains or the presence of red score in, at least, one of the domains of the RoB 2 and ROBINS-I.

All the authors made the evaluation independently, and disagreements were solved by consensus. Outcomes were summarized in the tables 1 and 2.

Table 1. Risk of bias for observational studies

Reference	Newcastle-Ottawa Scale			Risk of bias
	Selection	Comparability	Exposure	
Arima et al. (2005) ¹³	**	*	**	Moderate
Dalgard et al (2015) ¹⁴	**	*	*	Moderate
Zachariae et al. (2012) ¹⁵	**	*	**	Moderate
Brenaut et al. (2019) ¹⁶	**	*	***	Moderate
Lind et al. (2014) ¹⁷	**	*	**	Moderate
Simpson et al. (2018) ¹⁸	****	*	**	Low
Sicras-Mainar et al. (2018) ¹⁹	**	**	***	Moderate
Poot et al. (2011) ²⁰	**	**	***	Moderate
Kim S-H et al. (2015) ²¹	****	*	***	Low
Eckert et al. (2019) ²²	**	*	**	Moderate

Notes: The criteria for determining the low risk of bias was 3 or 4 stars in the domain of selection + 1 or 2 stars in the domain of comparability + 2 or 3 stars in the domain of exposure; for determining the risk of moderate bias it is necessary 2 stars in the domain of selection + 1 or 2 stars in the domain of comparability + 2 or 3 stars in the domain of exposure; for determining the high risk of bias, it is necessary 0 stars in at least one of the domains.

Table 2. Risk of bias for clinical trials

Reference	D1	D2	D3	D4	D5	D6	D7	Results
Cork et al. (2020) ²³	Green	Green	Green	Green	Green	Green	Green	Low risk
de Bruin-Weller et al. (2018) ²⁴	Green	Green	Green	Green	Green	Green	Green	Low risk
Simpson et al. (2016) ²⁵	Green	Green	Green	Green	Green	Green	Green	Low risk
Simpson et al. (2016) ²⁶	Green	Green	Green	Green	Green	Green	Green	Low risk
Hedman-Lagerlöf et al. (2019) ²⁷	Green	Green	Yellow	Green	Green	Red	Green	High risk

Notes: Only the Hedman-Lagerlof et al. Study was not randomized; and, thus, was analyzed by the ROBINS I. D1: Risk of bias through the randomization process by the RoB2 and risk of bias of confusion to ROBINS I; D2: Risk of bias due to deviations of the intended intervention for RoB2 and risk of bias in the selection of participants for ROBINS I; D3: Risk of bias due to the lack of data of the outcomes for the RoB2 and risk of bias in the na classification and interventions for ROBINS I; D4: Risk of bias in the outcome measures and risk of bias due to deviations of the intended intervention for ROBINS I; D5: Risk of bias in the selection of the presented outcomes and risk of bias due to the missing data for ROBINS I; D6: does not apply to the Rob2 and risk of bias for outcome measures; D6: does not apply to the Rob2 and risk of bias in the selection of the presented outcomes for ROBINS I. The green color represents a low risk of bias, the yellow color represents a moderate risk of bias and the red color represents a high risk of bias.

Analysis of outcomes

The prioritized conclusions to be discussed were those that compared the levels of depression and/or depressive symptoms between patients with AD and patients without AD or between patients with AD at different levels of severity, between patients with AD before and after the treatment or that measure the relation between related physiological variables to AD and depressive symptoms. Statistically relevant results are those that present significance inferior to 5% within a confidence interval of 95% in its measures of association.

Outcomes

Initially a total of 460 articles were found, remaining 63 after the first filter was applied; from these, 4 were excluded by being duplicated and 14 after a title and abstract reading, considering the criteria of eligibility. In the penultimate stage there were 45 articles, of which 15 were included after a qualitative analysis of the review after the complete reading of the articles, besides the exclusion of those which were not obtained a complete version of the manuscript. After the selection process, as presented in figure 1, the studies were summarized and classified as those that compared treatments and its outcomes related to depression and AD, those that proposed AD as aggravating of depressive symptoms, those that presented depressive symptoms as aggravants of the AD and those that bring statistical analysis without establishing clearly where lays the relationship between the two conditions (Table 3).

Outcome of AD and depressive symptoms after therapeutic approaches

Some of the selected articles presented variables liable to comparisons between the presentation of eczema and depressive symptoms before and after therapeutic approach. It is possible to observe, in general, concomitant reduction in the severity of both. Thus, besides the control group being defined by specific criteria of each study, the trials tested different doses of the therapeutic approach, obtaining, this way, one graduation on eczema, that was measured by scores and could be investigated for the presence of depressive symptoms in different degrees of severity. The outcomes and selected articles for this subgroup were summarized by reference, criteria for definition or gradation of atopic dermatitis, type of study, sample size, criteria for measuring depressive symptoms or definition of depressive syndrome, and outcome gathered in table 4.

All the pharmacological analyzed interventions presented the human monoclonal antibody dupilumab as a therapeutic approach. This substance acts in the alpha receptor of interleukin (IL)-4, inhibiting the signaling of IL-4 and IL-13, which have a pathophysiological role in the development of AD. The patients submitted to the treatment showed a reduction of the levels of lymphocyte markers Th2, having medical utility for other atopic comorbidities that act by this pathway²³.

In the analysis of the clinical trials SOLO1 and SOLO2²³, comparing the outcomes of the use of dupilumab applied in the dose of 300 mg subcutaneously weekly (qw) and in every two weeks (q2w) in relation to the use of placebo in patients with atopic dermatitis,

Table 3. Classification of articles regarding the outcomes

Outcome	Number of articles
AD outcomes and depressive symptoms after therapeutic approaches	5
Depressive symptoms as aggravating the AD	1
AD as aggravating the depressive symptoms	3
Isolated statistic relation	6
Total	15

Table 4. Characteristics of the selected studies for the comparative outcome of the AD and depressive symptoms after therapeutic approaches.

Reference	Criteria for atopic dermatitis	Type of study	Sample size	Criteria for depressive symptoms	Outcome
Cork et al. (2020) ²³	IGA; EASI; SCORAD; POEM.	Randomized clinical trial	1379	EQ-5D-3L HADS	Reduction of depressive and eczematous symptoms after the use of dupilumab.
de Bruin-Weller et al. (2018) ²⁴	EASI; IGA	Randomized clinical trial	318	HADS	Reduction of depressive and eczematous symptoms after the use of dupilumab.
Simpson et al. (2016) ²⁵	IGA; EASI; SCORAD; POEM.	Randomized clinical trial	380	HADS EQ-5D-3L	Reduction of depressive and eczematous symptoms after the use of dupilumab.
Simpson et al. (2016) ²⁶	IGA; EASI; SCORAD; POEM.	Randomized clinical trial	1379	EQ-5D-3L HADS	Reduction of depressive and eczematous symptoms after the use of dupilumab.
Hedman-Lagerlöf et al. (2019) ²⁷	Williams et al. SCORAD	Open pilot trial	9	MADRS-S	Cognitive therapy reduced AD symptoms, but did not modify the MADRS-S.

NOTES: IGA: Investigator's Global Assessment ; EASI: Eczema Area and Severity Index ;ESCORAD: Scoring Atopic Dermatitis; POEM: Patient-Oriented Eczema Measure; EQ-5D-3L: Three Level EuroQol five-dimensional descriptive system ;HADS: Hospital Anxiety Depression Scale Inventory; MADRS-S: Montgomery Åsberg Depression Rating Scale Self-Report.

and measuring the effects on the depressive symptoms, it was found that, compared to placebo, the drug reduced itching in a significant way in two days, measured by *Severity Scoring of Atopic Dermatitis index Visual Analogue Scale (SCORAD VAS)*²⁸. In general, AD symptoms, measured by the *Patient Oriented Eczema Measure (POEM)*, were reduced in relation to placebo. Concomitantly, anxiety levels and depression, measured by the *Hospital Anxiety and Depression Scale (HADS)*, were decreased, being possible that the depressive syndrome is related to the eczematous presentation either due to the psychological effects arising from the dermatological aspect, but also directly by inflammatory cytokines acting on the nervous system, as suggested by studies that indicate greater levels of pro-inflammatory cytokines, although not necessarily modulated by the Th2 pathway, associated with depression, anxiety and autism³⁻⁸.

Similarly, the analysis of effectiveness and security of concomitant use of dupilumab and topical corticosteroids in adults with escore of *Eczema Area and Severity Index (EASI)* ≥ 20 with inadequate or insufficient response to cyclosporine A, revealed a greater proportion of patients achieving smaller EASI scores in the week 16 between the treated with dupilumab qw + topical corticosteroid and q2w + topical corticosteroid *versus* placebo + corticosteroid (59,1% and 62,6% *versus* 29,6% respectively, $p < 0,0001$) at the same time in which there was a

bigger proportion of patients that reached HADS-D < 8 between them in use of dupilumab²⁴.

By observing the outcomes of dupilumab in 380 adults with severe AD and index *Investigator Global Assessment (IGA)* ≥ 3 , presenting involvement of at least 10% of the body surface, not being controlled with topical corticosteroids, the drug presented a reduction in itch in relation to placebo, so that the dose 300 mg qw presented the greatest reductions ($p < 0,0001$)²⁵. All the doses of dupilumab, except 100mg q4w, presented significant reduction of other dermatological symptoms in relation to placebo after 16 weeks ($p < 0,0001$) measured by the score POEM. Concomitantly, a reduction was observed in HADS score either in anxiety and depression subscale. Similarly, patients who reported to be moderate to severely anxious or depressives in the baseline of the scale EQ-5D-3L, had a greater improvement in the dose of 300mg qw; only 19,4% remained anxious or depressive compared to 76% of the patients taking placebo⁹. It is possible that, in addition to the improvement of the life quality due to the reduction of dermatological symptoms, the inhibition of the Th2 pathway improves the mood by direct neurological effects, although the role of this pathway is still not clear. Studies about other cytokines, such as the tumor necrosis factor (TNF) in psoriasis, revealed that modulation of the inflammation influences mood²⁹.

On the other hand, analysing psychoterapeutic repercussions on AD, Hedman-Lagerlöf et al²⁷ developed one type of cognitive-behavioral treatment in 10 sessions during 10 weeks with psychological and clinical AD assessments and with 6 months of follow-up. Such strategy consisted of reducing momentary symptomatic relief acts (scratching for example) to avoid trauma and increase the itching threshold. Furthermore, distraction methods were applied in these situations. Using the *Severity Scoring of Atopic Dermatitis index* (SCORAD)²⁸ as instrument to determine the symptomatic outcome and the *Montgomery Åsberg Depression Rating Scale Self-report* (MADRS-S), method of good diagnostic accuracy in depressive conditions³⁰, it was observed no significant changes in the depressive symptoms and reduction in the PO-SCORAD (self-reported), but without changes in the measures of 6 months of follow-up. It is important to highlight that due to the high risk of bias of this study, especially because of not having randomization or control group, the outcomes must be considered cautiously.

Depressive symptoms as aggravating factor of atopic dermatitis

One of the analyzed articles, proposed explicitly, the possibility of exacerbating the AD symptoms in the presence of mental distress, as depressive symptoms.

Using the *Beck depression inventory* (BDI) for measuring depressive symptoms and the

Yoshiike score for the eczematous symptoms, psychosomatic characteristics were found in patients with AD¹³. In the outcomes, it was observed rates of depression significantly higher between patients with AD in relation to the control group; 53% of the patients with AD reported exacerbation of the clinical presentation in the presence of mental stress; between patients with the same AD degree it was observed more marked levels of anxiety and depression the lower the serum IgE levels, measured by the *RadioImmunoSorbent Test* (RIST), but with no statistically significant differences. Additionally, Hashizume et al.³¹ observed that the administration of anxiolytic agents improved the itch and the skin injuries in some patients with AD, suggesting a psychosomatic causality relationship.

Atopic dermatitis as aggravating factor of depressive symptoms

Three studies presented atopic dermatitis as an aggravating factor of depressive symptoms, either through broad psychosocial pathways or through inflammatory phenomena that still need more elucidations. The outcomes and the selected articles for this subgroup were summarized by reference, criteria for definition or graduation of atopic dermatitis, type of study, sample size, criteria for measuring the depressive symptoms or definition of the depressive syndrome and outcome gathered in table 5.

Table 5. Characteristics of the studies that found atopic dermatitis as an aggravating factor of depressive symptoms

Reference	Criteria for atopic dermatitis	Type of study	Sample size	Criteria for depressive symptoms	Outcome
Dalgard et al (2015) ¹⁴	Diagnosis and severity found by dermatologist	Multicentric observational study	4994	HADS	Higher prevalence of depressive symptoms in patients with AD. Suicidal ideation related to skin condition in the group of AD (self-reported)
Zachariae et al. (2012) ¹⁵	SCORAD ISS	Observational study	103	BDI	The severity of the itching, broadly, had predictive positive value for severity of depressive symptoms
Brenaut et al. (2019) ¹⁶	DLQI	Observational cross-sectional study	4994	HADS EQ-5D-3L	Prevalence statistically relevant higher of patients with depression and suicidal ideation between those with AD compared to the control

NOTES: ESCORAD: Scoring Atopic Dermatitis; ISS: Itch Severity Scale; DLQI: Dermatology Life Quality Index; HADS: Hospital Anxiety Depression Scale; BDI: Becker Depression Inventory; EQ-5D-3L: Three Level EuroQol five-dimensional descriptive system.

In an observational study, involving 13 countries with 3635 patients from dermatological clinics and 1359 controls, it was found that, among the individuals affected by AD, there was a relation of 10,1% *versus* 4,3% from the control group for depression, according to HADS scale ($p < 0,001$) and 15% had suicidal ideation ($p < 0,002$) *versus* 8,3% from the control group, so that being the group with major prevalence between groups of dermatoses studied¹⁴. Of the patients who reported general suicidal ideation, 53,6% described that these thoughts arise from their skin condition, in a way that inside the subgroup of patients with AD and ideation, 68% declared the same.

After analysing the impact of itching in the quality of life of 3635 patients of dermatologic ambulatories together with 1359 controls, it was observed that 10,1% (16/158) of the patients with AD suffered from depression. The used criteria included 27 patients with itching. Such statistics were associated to the general measures of itching, once that HADS demonstrated the presence of a depressive condition in 29,6% of the pruritic patients against 4,3% of the controls ($p < 0,001$), while under evaluation by dermatologists, it was observed such condition in 21,7% *versus* 13,5% ($p < 0,22$); such heterogeneity was given due to the low accuracy of diagnostic for psychiatric disorders made by

dermatologists with one rate of real positives of 50% for anxiety and 20% for depression¹⁶. In a general way, a significant impact of the itching in life quality was observed, with a high frequency of anxiety, depression and suicidal ideation.

Therefore, by associating the intensity of itching as a psychosocial aggravant factor of depressive symptoms, observationally it could also be shown that, from the measurement of the depressive levels by BDI, those of itching by *Itch Severity Scale* (ISS) and the severity of AD symptoms by the SCORAD, the severity of itching, broadly, had predictive positive value with the severity of depressive symptoms¹⁵.

Isolated statistical relation

Some of the analyzed studies did not establish a clear relation of causality between AD and depressive symptoms, or vice versa, performing a purely statistical analysis that aid in the formulation of hypotheses about this possible association. The outcomes and selected articles for this subgroup were summarized by reference, criteria for definition or graduation of atopic dermatitis, type of study, sample size, criteria for measurement of depressive symptoms or definition of depressive syndrome and outcome and gathered in table 6.

Table 6. Characteristics of the studies that found isolated statistical relation between atopic dermatitis and depressive symptoms

Reference	Criteria for atopic dermatitis	Type of study	Sample size	Criteria for depressive symptoms	Outcome
Lind et al. (2014) ¹⁷	Diagnosis by a doctor	Longitudinal observational study	3406	HADS	It was observed a major rate of depression in AD patients and asthma in relation to the control group
Simpson et al (2018) ¹⁸	SCORAD	Observational cross-sectional study	1519	HADS	Symptoms of anxiety or depression were higher in patients with AD moderate/severe compared to mild
Sicras-Mainar et al. (2018) ¹⁹	Hanifin and Rajka	Multicentric longitudinal and observational study	6156	ICPC-2	Statistical association between AD and depression
Poot et al. (2011) ²⁰	SCORAD	Study of multicentric control-case	106	GHQ-12	Major prevalence of depression in patients with AD compared to the control group
Kim S-H et al. (2015) ²¹	Criteria from Military Manpower Administration from South Korea	Cross-sectional observational study	1517	KMPI	The prevalence of each type of psychological suffering was significantly higher in the population with AD
Eckert et al. (2019) ²²	DLQI	Cross-sectional observational study	1860	SF-36v2-MCS	Major prevalence of depression in AD that in controls

NOTES: ESCORAD: Scoring Atopic Dermatitis; DLQI: Dermatology Life Quality Index; HADS: Hospital Anxiety Depression Scale; ICPC-2: International Classification of Primary Care, 2nd edition; GHQ-12: General Health Questionnaire; KMPI: Korean Military Multiphasic Personality Inventory; SF-36v2-MCS: 36 Item Short Form Health Survey version 2 – Mental Component Summary.

In one observational study, accomplished in the Swedish province of Västerbotten, searched the relation between asthma/allergy and psychological stress, with a random sample of 8600 individuals, of which 3406 volunteered for analysis, being that 530 had the diagnostic of allergic asthma, non-allergic asthma, allergic rhinitis and/or atopic dermatitis by a doctor¹⁷. Among these, 132 had more than one of the four diagnoses and were excluded. Of the remaining 398, 76 had allergic asthma, 86 had non-allergic asthma, 190 had allergic rhinitis and 46 had atopic dermatitis. Using 2876 that did not have the mentioned comorbidities as the control group, several psychological tests were applied, being the HADS and its subscales the chosen method for measuring levels of depression and anxiety. As a result, there was a strong tendency ($p < 0,07$) for group differences regarding the subscale of depression HADS, appearing with higher levels between groups with allergic asthma and atopic dermatitis; these two groups did not differ significantly from each other, but considerably among the others¹⁷.

In order to establish a relation between the psychological stress and the presentation and severity of the AD, one cross-sectional study used data of men about 19 years old from the South Korean army in the recruitment between 2008 and 2012, involving 120508 recruits, Among which 1517 (1,2%) presented AD²¹. The Korean Military Personality Multiphase Inventory (KMPMI), a revised version of the Minnesota Multiphasic Personality Inventory adjusted for the Korean population, was used to measure levels of depression and anxiety. It was seen that the proportion of individuals with at least one type of psychological suffering was higher in the population with AD than in the population without AD (18,7% e 8,9%, respectively). The prevalence of each type of psychological suffering, as depression, anxiety and somatization was significantly higher in the population with AD. Also, significant relations between AD and depression, anxiety and somatization was observed in the univariate analysis.

The Eckert et al.²² study brought together individuals from France, Germany, Italy, Spain and the United Kingdom, which were identified, by self-report, presence of AD and self-reported presence of one medical diagnostic. For measuring the levels of anxiety and depression, the *Dermatology Life Quality*

Index (DLQI) was chosen, in which ten specific questions for dermatology were addressed. As a result, depression was more prevalent in patients with AD, affecting 25,8% and 36,2% of those with AD and inadequate control of AD (IC-AD), respectively, compared to 12,9% of the controls without AD. The rate of anxiety was also major in patients with AD than the controls without AD (31,9% against 14,4%, respectively), particularly on those with IC-AD (51,7%) *versus* controls without AD and patients with control of AD (31,6%), establishing then a visible increase in the prevalence of symptoms of depression and anxiety in patients with AD.

Simpson et al.¹⁸ conducted a cross-sectional study in clinical practices of 6 medical centers in the USA through a self-applicable questionnaire that analyzed 1519 adults with AD. A stratification of severity based on the PO-SCORAD was performed, among which identified 830 moderate/severe and 689 mild. Symptoms of anxiety or depression were reported, based on the HADS scale, by 417 (50,2%) patients with AD moderate/severe *versus* 188 (27,3%) with mild ($p < 0,001$), in which the higher scores (8 or more) were more frequent in patients with AD moderate/severe in relation to those with mild disease (all $p < 0,001$).

Poot et al.²⁰ approached, in one multicentric control-case study, the familiar genetic influence in some skin diseases in 59 patients (11,9% with AD) and 47 controls. Using the *General Health Questionnaire* (GHQ-12), which measures disorders of anxiety or depression, the prevalence of anxiety and/or depression were 71,4% in the AD and 43,3% in the general cutaneous cases.

Sicras-Mainar et al.¹⁹, in one retrospective observational study, analyzed comorbidities, medications used and costs related to health in 215634 medical records from the region of Catalonia, Spain. The international classification of primary attention and the codes of the International Disease Classification acted as the instruments for tracking AD, its severity and comorbidities. 6287 cases were found cases of AD in the place, among which 6186 were used in the synthesis of the article, once applied to the criteria of exclusion. In total, 19,9% of AD cases fit in the depressive syndrome. In addition to this, 55,7% of the patients fit as mild AD (14,4% with depression), 38,2% as moderate (25,1% with depression) and 6,1% as severe (36,3% with depression) ($p < 0,001$, in all of them).

DISCUSSION

As demonstrated in the results, several studies presented a relationship between AD and depressive symptoms, existing divergences on where is the cause of this relation. Under a perspective in which the increase of psychosocial stress levels results in an aggravation of the eczematous condition of AD¹⁹, pathways related to inflammasomes may have an essential role in their mechanism⁵, added to the hypothalamic-pituitary-adrenal axis levels and the sympathetic nervous system, that also have immunomodulatory functions³². Studies with rats indicate that animals exposed to chronic stress activate inflammasomes of the type NOD-, LRR- and *domain containing protein 3* (NLRP3), which act in response to the *damage-associated molecular pattern* (DAMPs)³³. Some indications of the increase of inflammatory proteins in patients with depression, including NLRP3, corroborate this hypothesis^{6,7,10}.

Such as in neurotransmission, there are ways in which inflammatory molecules can influence the availability of monoamines, which have an elementary role in the development of depressive symptoms. The cytokine IL-1 β and the TNF may increase the reception of serotonin in the synaptic cleft³³, which reduces its availability and induces depressive behavior, having the possibility of other inflammatory pathways being involved.

From this perspective, it is possible the existence of a cyclic bidirectional causality, in which the pathway "A" AD accentuates the depressive symptoms, at the same time in that, in "B",

depressive symptoms reinforce the eczematous symptoms (Figure 2).

One of the pathophysiological mechanisms in which A and B pathways act concomitantly may be due to the increased number of inflammatory cytokines, due to AD and also the depressive symptoms^{5,34,35}. Lindqvist et al.³⁶ found levels significantly higher of interleukin-6 in individuals that tried suicide. Even though the role of cytokines from Th2 pathway is not clear in the development of depression, dupilumab may have reduced depressive symptoms through the inhibition of interleukins that may act in this direction, in addition to its direct role in the improvement of life quality due to the reduction of AD symptoms.

A possible psychosomatic causality of atopic dermatitis may also be suggested due to the observation of reduction of itching after the administration of anxiolytics in these patients²⁷, although it is not possible to report the role of depression in this situation, if it exists.

Another possibility in which A pathway can act is due to psychosocial factors, departing from social stigmatization of itching and sleep deprivation, as suggested in studies in which patients affirmed to have suicidal thoughts arising from their skin condition or in other studies that analyzed the burden of the AD on diverse social aspects, from laboral to family aspects.^{2,3} So that, the inhibition caused by dupilumab can act indirectly on depression through B pathway, with reduction of the symptoms of atopic dermatitis, of the psychosocial factors and a posterior decrease in depressive symptoms, besides acting directly on the cytokines through A pathway.

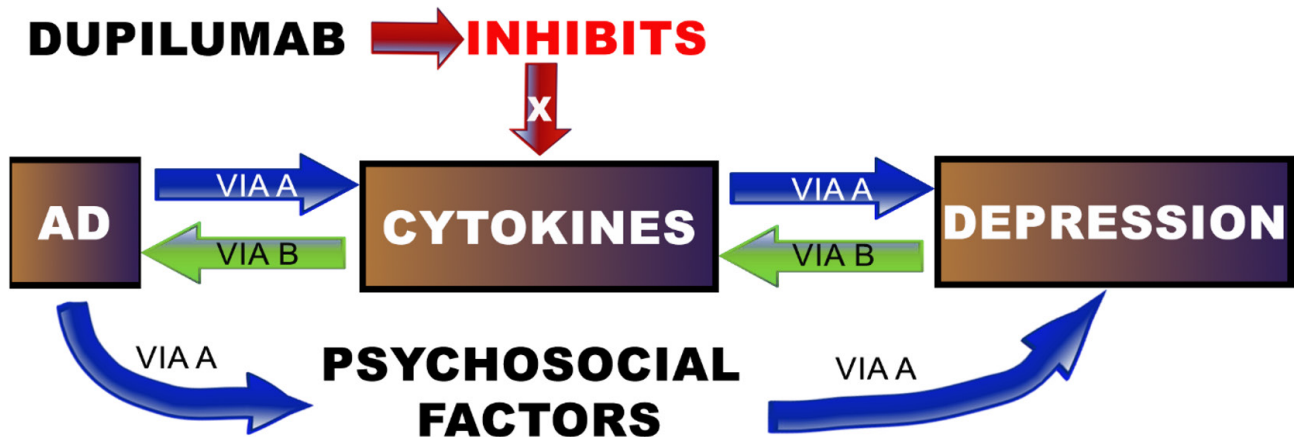


Figure 2. Bidirectional Cyclic causality between atopic dermatitis and depression, with possible inhibitory effect by the dupilumab.

It is also fundamental to highlight that this systematic review presents limitations: i) Although all the searching processes made on based on databases, some complete articles could not be addressed leading to the exclusion of studies that could present relevant information to the qualitative discussion; ii) Only articles in English were selected, what may have narrowed the found results; iii) Only studies that expose quantitatively, through scores, depressive symptoms were selected, what at the same time turns easier the systematic organization of the discussion, and ends up excluding studies with other approaches, but that also have a capacity of adding to the theme.

CONCLUSION

It is assumed, therefore, that the prevalence of depressive conditions is increased in patients with AD. The data available in the literature approached the theme in different ways, but reaffirm themselves in the point in which they interrelate possible psychological and inflammatory mechanisms in the synthesis of the clinical presentations of both conditions. So that, new studies about the intersection of the approached diseases are fundamental to clarification of the diagnostic perspectives, therapeutic and, mainly, pathophysiological, since they can develop techniques and comprehension turned specially to the described mechanism, improving the multidisciplinary propaedeutics in these patients.

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Author Contributions:

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MVMS: Busca sistemática, redação de manuscrito, formulação de hipóteses

TRMOF: Redação e revisão do artigo

Funding Sources

There was no funding for this study.

Conflict of interests

None of the authors declare a conflict of interest.

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Editor:

Prof. Dr. Felipe Villela Gomes

Received: may 02, 2021

Approved: aug 02, 2021
