Sleep Disturbance, depression, anxiety and perceived stress in adult atopic dermatitis patients, and their relationship with objective and subjective disease severity

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Abstract

Background: Atopic dermatitis (AD) is a chronic inflammatory skin disease often associated with non-atopic comorbidities. Recently, a severity-dependent relationship between AD with sleep and mental health diseases has been proposed, but few studies investigated this topic through validated questionnaires. Therefore, the present study aimed to: (i) assess the impact of AD on sleep and psychological disorders using validated instruments and (ii) estimate the association of AD severity with sleep disorders and psychological symptoms distinguishing between clinical-oriented and patient-oriented measures. **Methods:** We conducted a cross-sectional, case-control study, recruiting 57 adult AD patients matched for age and sex with 57 healthy adults. To investigate the differences in sleep quality, insomnia, depression, and anxiety between the two groups, we performed independent samples t-tests. Moreover, we conducted several univariable linear regression analyses to examine the relationship between objective/subjective severity of AD and sleep quality, insomnia, and psychological symptoms. **Results:** AD patients presented poorer sleep quality and more severe symptoms of insomnia and depression than healthy adults. Objective and subjective AD severity were similarly associated with worse sleep quality, anxiety, and self-perceived stress. However, subjective AD severity was more strongly associated with insomnia and depressive symptoms than clinical-oriented AD severity. **Conclusions:** The study demonstrated poor sleep quality and high levels of insomnia, depression, and perceived stress in AD patients, with an aggravated psychological status for adults with more severe disease. We suggest implementing a multidisciplinary approach to AD management and treatment that considers objective and subjective measures of disease severity.

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease affecting the pediatric and adult population with a lifetime prevalence of up to 20%[1]. It is characterized by recurrent itchy eczematous lesions, papulation, and lichenification, with high heterogeneity of clinical manifestations and diffuse dry skin as an expression of skin barrier dysfunction[1].

Aside from the cutaneous signs and symptoms of AD, several atopic and non-atopic comorbidities can occur in AD patients[1–3]. Not surprisingly, the severe, persistent, and debilitating itch, typical of AD, causes sleep deprivation, anxiety and depression, and reduced quality of life and productivity[2,3].

Sleep disturbances are one of the most relevant non-atopic comorbidities, reported by 33 to 87.1% of adults with AD[4,5], a much higher percentage than the prevalence in the general population (7–48%)[6]. AD patients report lower sleep quality and more insomnia symptoms, experiencing difficulty in falling asleep, increased

frequency and duration of nocturnal awakenings, and shorter sleep duration, which can lead to excessive daytime sleepiness, fatigue, and dysfunction[3–9]. Overall, sleep disorders significantly impact the general health and quality of life of AD patients[10], impairing work and home functioning and interpersonal relationships[6] and playing a critical role in the development of cardiovascular[11], metabolic[12], and psychiatric diseases[13].

Psychological disorders represent another common comorbidity in the AD population. Patients with AD often develop psychosocial distress with high rates of mental disorders, such as depression and anxiety[14–18]. However, relatively little is known about AD and self-perceived stress in adults[19–21]. Stress could aggravate and trigger skin diseases[22]. Likewise, some dermatoses are a source of stress and impair quality of life[19].

Despite their importance, sleep and psychological stress in AD were investigated by a few studies. Moreover, the literature in this field is limited to using simple dichotomous or Likert-type questions when comparing AD and healthy subjects[5,20,21,23]. Other studies on sleep in AD have even referred to single items taken from mood or quality of life questionnaires, neglecting the multidimensionality of sleep[5,6,23]. Therefore, the first aim of our study was to use a set of validated questionnaires to investigate sleep quality, insomnia, depression, anxiety, and perceived stress in AD patients through a case-control study. We hypothesize that more severe sleep disturbances, insomnia, depression, anxiety, and perceived stress may be observed in adults with AD than in the healthy population.

Although the relationship between AD, sleep, and psychological disorders is widely recognized, it is unclear how AD is associated with sleep and mental health problems. Investigations on the association between AD severity and sleep disorders showed conflicting results[5]. In most studies, sleep disturbances and quality appeared to worsen with AD severity; in others, only weak correlations or no significant correlation have been observed[3–5,9]. Similarly, some studies reported that increasing AD severity is associated with higher rates of depression, alexithymia, suicidal ideation, and anxiety[15,16,18,24], but others showed that AD adults were more likely to develop depression and anxiety regardless of atopic eczema severity[14]. In contrast, most studies did not correlate psychological symptoms with AD severity[18]. To our knowledge, few studies have investigated the relationship between AD severity and self-perceived stress[19,20].

Over time, the chronic nature of AD leads patients to face several difficulties that depend not only on the condition severity but especially on the personal perception of the disorder[25]. The perception of the disease is strongly influenced by the individual's experience and interpretation of the disorder[26].

To date, the severity-dependent relationship between AD symptoms and sleep and psychological disturbances has been studied mainly through objective tools widely used in clinical trials. However, the importance of patients' disease perception versus objective measures should be considered in clinical and research settings[25,26].

In this regard, the second objective of our study was to investigate the severity-dependent relationship between AD symptoms and sleep quality, insomnia, depression, anxiety, and perceived stress by differentiating clinical-oriented measures from patient-oriented subjective measures of the disease.

Materials and Methods

Participants and procedures

We conducted a descriptive, cross-sectional, case-control, observational study. AD patients were recruited from the AD outpatient clinics at the Dermatology Departments of San Salvatore Hospital (University of L'Aquila, Italy) from July 2020 to December 2021. Inclusion criteria for AD patients were as follows: (i) Adult patients affected by AD according to Hanifin's and Rajka's diagnostic criteria; (ii) Patients who voluntarily signed informed consent on the study objectives; (iii) Patients able to complete the questionnaires through a digital medium. Exclusion criteria consisted of (i) patients affected by other cutaneous and systemic disorders, (ii) patients with a previous diagnosis of a psychiatric disorder or psychological symptoms, and (iii) patients being treated with systemic drugs that interfere with sleep, excluding agents for the treatment of AD. The control group comprised healthy individuals without skin diseases and a prior diagnosis of psychiatric and psychological conditions, recruited both in outpatient Dermatology Departments and among family

members of AD patients. Control participants were matched to each AD patient for age (± 1 year) and sex, as these two demographic factors are associated with different sleep and psychological characteristics[27–30].

The AD group underwent a clinical evaluation in which AD characteristics were collected by experienced dermatologists using the Eczema Area and Severity Index[31] (EASI), a reliable and sensitive tool for assessing the physical signs of AD/eczema. The total EASI score ranges from 0 to 72, with the highest score indicating more severe atopic dermatitis symptoms.

Subsequently, AD participants were invited to complete an online survey via Google Forms collecting information on age, sex, self-perceived atopic eczema severity, sleep quality and insomnia severity symptoms using the Patient-Oriented Eczema Measure[32] (POEM), the Pittsburgh Sleep Quality Index[33] (PSQI) and the Insomnia Severity Index[34] (ISI), respectively.

The (POEM) is a validated, patient-oriented assessment measure for monitoring the severity of atopic eczema. A higher score suggests more severe AD symptoms (range 0–28). The PSQI is a 19-item questionnaire widely used to evaluate sleep quality. A higher total score (range 0–21) indicates more severe sleep problems. The ISI is a 7-item clinical tool to assess insomnia severity (range 0–28). A higher score indicates more severe insomnia symptoms. We also assessed depressive symptoms, anxiety, and perceived stress through a set of validated questionnaires: the Beck Depression Inventory-second edition[35] (BDI-II), the Generalized Anxiety Disorder-7[36] (GAD-7), and the 10-item Perceived Stress Scale[37] (PSS-10), respectively. The BDI-II is a 21-item questionnaire used in clinical practice to evaluate depressive symptoms (range, 0–63). A higher score denotes greater severity of depressive symptoms. The GAD-7 is a validated 7-item questionnaire for screening symptoms of generalized anxiety and assessing its severity in clinical practice and research. A higher total score (range 0–21) reflects more severe anxiety. The PSS-10 is a 10-item questionnaire evaluating thoughts and feelings related to stressful events. A higher total score (range 0–40) indicates more significant perceived stress.

Likewise, the control group completed an online survey in which sleep quality, insomnia, depression, anxiety, and perceived stress were examined using the same validated questionnaires.

The study was approved by the Institutional Review Board of the University of L'Aquila (protocol number 35/2020). Online informed consent was obtained from all participants, who consented to the publication of the questionnaire results for scientific purposes.

Statistical analysis

Statistical analyses were performed using SPSS v.22 (IBM Corp., Armonk, NY, USA). To investigate differences in sleep quality, insomnia, and psychological symptoms between AD and healthy adults, the questionnaire scores (PSQI, ISI, BDI-II, GAD-7, PSS-10) of the two groups (Atopic Dermatitis, Control) were compared using the independent samples t-Test. Cohen's d was computed to provide an effect size estimate of the comparisons between groups.

We estimated the influence of objective and subjective severity of AD on sleep quality and insomnia by performing several univariable linear regression analyses, with EASI and POEM scores as independent variables and PSQI and ISI scores as dependent variables.

Similarly, we performed univariable linear regression analyses to test if objective (EASI) and self-perceived (POEM) severity of AD (independent variables) significantly predicted depression (BDI-II), anxiety (GAD-7), and self-perceived stress (PSS-10; dependent variables). The level of significance was set at $p < 0.05$, and all analyses were two-tailed.

Results

A total of 114 subjects were recruited: a group of 57 AD adult patients (mean age ± std. dev., 34.28 years ± 13.07; 27 males; range, 18–67 years) with a mean disease duration of 23.46 ± 12.12 and a control group of 57 healthy adults (34.39 years ± 13.09; 27 males; 18–67 years) without skin diseases.

Clinical patterns concerning AD onset and course, clinical phenotype, current AD treatments, comorbidities, and clinical-oriented (EASI) and patient-oriented (POEM) severity of AD are shown in Table 1.

Please, insert Table 1 about here

Sleep variables

The two groups significantly differed in sleep quality (PSQI: t_{112}=3.16, p=0.002, Cohen's d=0.59) and insomnia severity (ISI: t_{112}=2.83, p=0.006, Cohen's d=0.53; Figure 1). The AD group reported poorer sleep quality (PSQI: mean ± std. dev., 7.58 ± 3.90) and more severe insomnia symptoms (ISI: 8.39 ± 5.81) than the healthy subjects (PSQI: 5.42 ± 3.37; ISI: 5.51 ± 5.04).

Please, insert Figure 1 about here

Psychological variables

The analyses showed significant differences between the two groups in the severity of depressive symptoms (BDI-II: t_{112}=2.52, p=0.013, Cohen's d=0.47) and perceived stress (PSS-10: t_{112}=2.00, p=0.048, Cohen's d=0.37). The AD group reported more severe depressive symptoms (BDI-II: 10.77 ± 8.41) and higher levels of perceived stress (PSS-10: 17.68 6.53) compared to healthy controls (BDI-II: 6.97 ± 7.73; PSS-10: 15 ± 6.96) (Figure 2). The measure of anxiety (GAD-7) did not differ between AD (7.05 ± 4.58) and control participants (6.23 ± 5.28; t_{112}=0.89, p=0.38, Cohen's d=0.17).

Please, insert Figure 2 about here

Regression analyses

Regression analyses indicated that objective (EASI) and subjective (POEM) severity of AD similarly predicted sleep quality (PSQI: R^2=0.26, $F_{1,54}$=18.64, p<0.001; R^2=0.24, $F_{1,55}$=16.92, p<0.001, respectively) (Figures 3A–B). As shown in Figure 3C–D, the subjective AD severity largely predicted insomnia symptoms (R^2=0.31, $F_{1,55}$=24.27, p<0.001) than the objective measure (ISI: R^2=0.19, $F_{1,54}$=12.26, p<0.001). Therefore, more severe AD was associated with worse sleep quality and more insomnia symptoms.

Please, insert Figure 3 about here

As shown in Figures 4A–B, the self-perceived severity of AD (POEM) significantly predicted depressive symptoms (BDI-II; R^2=0.20, $F_{1,55}$=13.52, p< 0.001). However, the relationship between objective severity of atopic eczema (EASI) and depression was not significant (BDI-II; R^2=0.05, $F_{1,54}$=2.84, p=0.098). Finally, objective (EASI) and subjective (POEM) measures of AD severity comparably predicted anxiety symptoms (Figures 4C–D; GAD-7: R^2=0.15, $F_{1,54}$=9.21, p=0.004; R^2=0.17, $F_{1,55}$=11.37, p=0.001) and self-perceived stress (Figure 4E–F; PSS-10: R^2=0.10, $F_{1,54}$=5.74, p=0.02; R^2=0.07, $F_{1,54}$=4.05, p=0.049).

Please, insert Figure 4 about here

Discussion

We demonstrated significant differences in sleep and mental health measures between adults with AD and healthy controls. Using validated questionnaires, the AD group reported poorer sleep quality and more severe insomnia symptoms than the control participants. Our results align with recent studies that showed lower sleep quality, higher sleep disturbances, and a greater risk of insomnia in adult AD patients[5,38].

AD patients also presented more severe depressive symptoms than controls. On the other hand, we did not observe a significant difference in anxiety between the two groups. The current literature on the mental health of the AD population seems consistent in showing high rates of depression and anxiety in adults with AD compared to the general population[18,39]. However, previous studies have found conflicting results regarding whether AD is associated with increased mental health disorders[15].

Our results also showed higher levels of perceived stress in the AD group compared with controls. Psychological stress has been identified as a major aggravating factor in AD[22]. Similarly, itching, discomfort,

disfigurement, perceived social stigmatization, isolation, poor quality of life, and sleep disturbances lead the AD population to experience more psychological distress[2,40–42]. However, comparative studies between AD and healthy adults have not been reported.

The present study also showed that objective and subjective severity of AD significantly predicted sleep quality and insomnia. More severe AD was associated with worse sleep quality and greater insomnia symptoms. Several recent studies also reported that sleep disturbances seem to worsen with the severity of AD[8,9,23,43]. Moreover, our results highlighted that, although objective and subjective disease severity similarly predict sleep quality, patient-oriented subjective severity of AD appeared to contribute more to the manifestation of insomnia symptoms in AD adults.

AD patients may experience a significant amount of itching, pain, and discomfort, which can lead to sleep disturbances[6]. Although objective measures of AD provide a quantitative assessment of the disorder, the subjective severity of AD may be a more complete and accurate predictor of insomnia, taking into account the physical and psychological factors of the condition.

To the same extent, objective and subjective severity of AD also predicted anxiety symptoms and self-perceived stress. On the other hand, the self-perceived severity of AD, but not the objective measure, significantly predicted depressive symptoms. Therefore, anxiety and stress symptoms of AD patients increased with increasing objective and subjective severity of the disease. However, depressive symptoms exhibited by AD adults were exclusively related to personal perception of disease severity.

A recent study highlighted higher levels of self-perceived stress in patients with severe AD [19], similar to our findings. Two recent meta-analyses showed a significant positive association between AD and anxiety and depression[16,18]. Silverberg et al.[15] found that patients with moderate and severe AD had significantly worse mental health than those with mild AD. The relation between the clinical severity of AD and psychological well-being is central to clinician behaviour. When treating patients with moderate-to-severe AD, dermatologists should be vigilant and screen and refer to a specialist for psychiatric symptoms.

Recently, the absence of a causal role of AD in the development of depressive and anxiety disorders has been proposed[44], supporting the existence of an indirect link between AD and psychological measures driven by other concomitant conditions. In this regard, recent studies suggested that sleep disturbances might predispose AD patients to experience psychological symptoms[45,46].

Although the present study aligns with the recent literature, our results suggest a different impact of objective and subjective AD severity on the global disease burden. In clinical practice, there is a wide discrepancy between patient-oriented subjective evaluation and clinician-oriented measurement[47]. This could be partially explained by physicians' underestimation of the intensity of symptoms. Moreover, the severity of AD partially depends on the personal perception that individuals attribute to the disorder[25]. Our results underline the importance of using patient-oriented severity tools alongside objective indexes in clinical and research practice.

Overall, AD appears to strongly affect the physical and mental well-being of patients, with a considerable impact on sleep and psychological health. However, the pathogenesis of sleep and psychological disorders in AD patients is complex and not fully understood[4,14]. Currently, there is a need for a consensus guiding the evaluation and management of sleep and psychological disorders in AD patients. In detail, most dermatological investigations do not focus on evaluating sleep disorders, limiting the management and treatment of these disturbances. Polysomnography and actigraphy are objective and valid but impractical in dermatological studies[5]. However, the use of self-administered validated questionnaires could easily guarantee the evaluation of sleep quality in AD patients[5], also offering the possibility to follow the time course of the disturbance. On the psychological side, there are no specific tools designed for the psychological assessment of AD patients in the clinical setting[48]. In addition to an overall analysis of the patient's quality of life, physicians and researchers should also pay more attention to the specific psychological symptoms exhibited by AD patients, such as depression, anxiety, and psychological stress, which could exacerbate the severity of the skin condition, triggering a vicious circle from which it is challenging to get out[16,18].

Our study has limitations. Our findings were obtained in a small clinical sample undergoing different pharmacological treatments. The assessment of insomnia, depression/anxiety symptoms, and stress using self-reported tools might have produced a selection bias by including only individuals able to complete questionnaires via a digital medium. However, in our study, the use of electronic questionnaires at home was well accepted by patients, reduced the risk of non-completion in waiting or dedicated rooms, and minimized the risk of incomplete filling or erroneous completion.

In conclusion, the present study showed poor sleep quality and high levels of insomnia, depression, and perceived stress in AD patients, highlighting a worse health context for individuals with greater disease severity. The disease burden in AD is multifaceted and difficult to estimate as in addition to the severity of the condition as represented by clinical signs, poorer sleep quality, severe insomnia conditions, the coexistence of underdiagnosed anxiety/depression symptoms, and impaired stress responses are disease-specific symptoms that contribute to the broad impact of the disease on patients' life. Overall, our results suggest the importance of adopting a multidisciplinary approach to the management and treatment of patients with AD, ensuring an adequate screening for sleep and psychological disorders, with particular attention to personal perception of disease severity.

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Table 1. Clinical characteristics of AD patients.

Abbreviations: AD, Atopic Dermatitis; SD, Standard Deviation; EASI, Eczema Area and Severity Index; POEM, Patient-Oriented Eczema Measure.

		AD patients
		N (%)
Clinical Disease pattern	Early onset AD	41 (71.9)
	Adult onset AD	16 (28.1)
	Persistent pattern	43 (75.4)
	Relapsing pattern	14 (24.6)
Phenotype	Classical flexural AD	39 (68.4)
	Prurigo nodularis-like AD	7 (12.3)
	Head/neck AD	4 (7.0)
	Nummular type AD	3 (5.3)
	Erythrodermic AD	2 (3.5)
	Chronic hand eczema	2 (3.5)
Current Treatment	Dupilumab	28 (49.1)
	Antihistamines	10 (17.5)
	Topical treatment	10 (17.5)
	Cyclosporine	5 (8.7)
	Upadacitinib	2 (3.5)
	Methotrexate	2 (3.5)
	Atopic comorbidities (asthma, rhinitis, conjunctivitis)	17 (29.8)
	Thyroiditis	4 (7.0)
	Alopecia	3 (5.3)
Comorbidities	Hypertension	2 (3.5)
	Inflammatory bowel disease	2 (3.5)
	Metabolic syndrome, migraine, previous stroke, previous thyroid carcinoma, and coeliac disease	1 (1.7)
		Mean ± SD
Objective and Subjective severity of AD	Eczema Area and Severity Index (EASI)	9.11 ± 8.10
	Patient-Oriented Eczema Measure (POEM)	12.33 ± 8.68

Figure 1. Comparisons of sleep quality (PSQI) and severity of insomnia symptoms (ISI) between Atopic Dermatitis (grey) and Control (white) groups. Center lines show the medians; box limits indicate the 25th and 75th percentiles; whiskers extend to the 5th and 95th percentiles; dots represent outliers; crosses represent sample means. Significant differences are indicated with asterisks (** $p < 0.01$).

Abbreviations: PSQI, Pittsburgh Sleep Quality Index; ISI, Insomnia Severity Index.

Figure 2. Comparisons of depressive symptoms (BDI-II), anxiety (GAD-7), and perceived stress (PSS-10) between Atopic Dermatitis (grey) and Control (white) groups. Center lines show the medians; box limits indicate the 25^{th} and 75^{th}percentiles; whiskers extend to the 5th and 95th percentiles; dots represent outliers; crosses represent sample means. Significant differences are indicated with asterisks (* $p < 0.05$).

Abbreviations: BDI-II, Beck Depression Inventory-second edition; GAD-7, Generalized Anxiety Disorder-7; PSS-10, Perceived Stress Scale-10; N.S., not significant.

Figure 3. Scatter plots and the corresponding regression lines for the relationships between severity of atopic eczema measures (EASI and POEM; independent variables) and sleep questionnaire scores (PSQI and ISI; dependent variables). Significant differences are indicated with asterisks (*** $p < 0.001$).

Abbreviations: EASI, Eczema Area and Severity Index; POEM, Patient-Oriented Eczema Measure; PSQI, Pittsburgh Sleep Quality Index; ISI, Insomnia Severity Index.

Figure 4. Scatter plots and the corresponding regression lines for the relationships between severity of AD measures (EASI and POEM; independent variables) and psychological status questionnaire scores (BDI-II, GAD-7, and PSS-10; dependent variables). Significant differences are indicated with asterisks (*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$).

Abbreviations: EASI, Eczema Area and Severity Index; POEM, Patient-Oriented Eczema Measure; BDI-II, Beck Depression Inventory-second edition; GAD-7, Generalized Anxiety Disorder-7; PSS-10, Perceived Stress Scale-10; N.S., not significant.

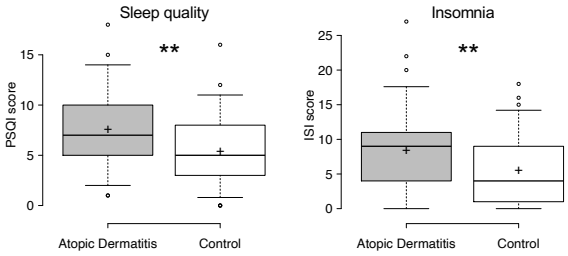

Figure 1_Esposito & Amicucci et al.

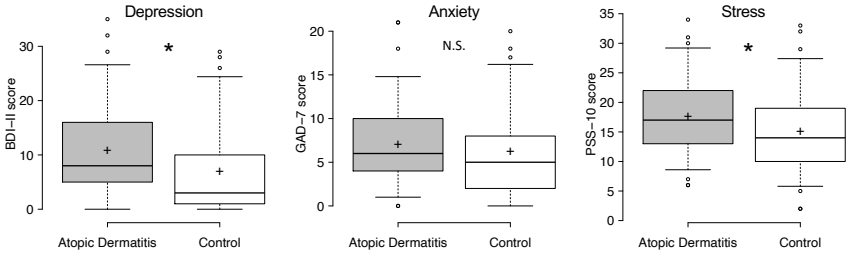

Figure 2_Esposito & Amicucci et al.