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RESEARCH ARTICLE

Association of clinical features and systemic immune-inflammation index with psychological distress in acne vulgaris

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ABSTRACT

Objective: Activation of the inflammatory response system may cause depressive symptoms and psychological distress. Therefore, it is important to emphasize the link between the proinflammatory state, psychological distress, and clinical features in acne vulgaris (AV), a chronic inflammatory disease. We aimed to examine psychological distress and systemic inflammatory markers (systemic immune-inflammation index (SII) and systemic inflammation response index (SIRI)) and their relationship with illness-related factors in AV patients to address this potential link.

Method: This study recruited 129 patients with AV without any psychiatric disorder and 60 healthy subjects matched with the patient group regarding age and gender. All participants' current depressive, anxiety, and stress levels were assessed with the Depression Anxiety Stress Scale-21 (DASS-21). The severity of acne of the patients was evaluated with Global Acne Scoring System (GASS). SII [neutrophils × platelets/lymphocytes] and SIRI [neutrophils × monocytes/lymphocytes] were calculated through routine blood screenings during the current admission.

Results: DASS-21 Anxiety was significantly higher in the patient group than in controls ($t=2.544$; $p<0.05$), while DASS-21 Depression and Stress, SII, and SIRI did not differ between the groups ($p>0.05$). Duration of illness was positively correlated with DASS-21 Stress ($r=0.30$, $p<0.001$). A multivariate regression model using duration of illness, GASS score, SII, and SIRI revealed that only duration of illness predicted DASS-21 Stress ($\beta=0.31$, $p<0.05$).

Conclusion: Independent of systemic proinflammatory status, psychological distress is associated with the duration of illness in AV patients. Clinicians should be more attentive in monitoring psychological distress in AV patients, particularly those with prolonged illness duration, and be more willing to seek help from a specialist psychiatrist to increase the quality of life of patients with AV.

Keywords: Acne vulgaris, biomarkers, psychological distress, systemic inflammation

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INTRODUCTION

Acne vulgaris (AV) is a common disorder of the pilosebaceous unit. It is considered a chronic inflammatory disease of the pilosebaceous unit resulting from androgen-induced increased sebum production, altered keratinization, inflammation, and colonization of Propionibacterium acnes in hair follicles in different parts of the body such as the face, neck, chest, and back (1,2). Although acne often occurs in adolescence, it often persists into adulthood, with 26% of women and 12% of men reporting acne in their forties (3).

AV and numerous dermatological diseases have been associated with psychiatric disorders (4). It has been reported that psychological stress affecting epidermal permeability may precipitate inflammatory dermatological diseases such as AV (5). Moreover, even if there is no accompanying psychiatric comorbidity, it may impair interpersonal communication by disrupting the skin integrity of the lesions. As a result, the effects that may impair social functioning negatively affect the quality of life (6). In addition, treatments given for dermatological diseases may cause psychiatric symptoms (5).

AV is an inflammatory dermatosis that often affects the face (7). The face is usually the highlight when communicating with a person, and acne on the face can negatively affect the other party's perception (8). Skin lesions resulting from acne have psychosocial effects that cannot be ignored (9). It has been reported that patients with acne experience decreased self-esteem, weakened self-image, social isolation, and limitations in participation in daily activities (10). Patients with AV have a high risk of adversely affecting their quality of life, such as people with diseases such as epilepsy and asthma, so the psychological impact may be much more profound. Moreover, patients with acne are more prone to depression and suicidal ideation (9). As a part of the psychological effect, increased anxiety, anger, and frustration are observed in patients with AV (11). In addition, previous studies have reported increased depression and anxiety in patients with AV (12–15). Due to AV's adverse mental health effects, the success of patients in this period when they take a step in their professional, social, and academic life can be seriously affected.

The interplay between systemic inflammation and the local immune response was recognized as a hallmark of AV. One of the key mechanisms involved in the development of acne includes the induction of inflammation and dysfunction of innate and adaptive immunity (16). Systemic immune-inflammation index (SII) and systemic inflammation response index (SIRI), novel integrated indicators based on peripheral neutrophil, monocyte, lymphocyte, and platelet counts, have been considered reliable tools for increased systemic inflammatory status and prognosis in many patient populations, including malignancies and inflammatory diseases (17–19). On the other hand, a considerable body of evidence suggests that inflammatory response system activation and administration of proinflammatory cytokines may induce depressive symptoms and psychological distress through modulation of the central and peripheral serotonergic system in animals and humans (20,21). Taken together, it appears a requisite to highlight the association between proinflammatory status, psychological distress, and clinical features of AV. Therefore, this study aimed to examine depressive, anxiety, and stress levels along with SII and SIRI in AV patients. We hypothesized that clinical features of AV, as well as the increased systemic proinflammatory status, may be linked to the psychological distress that patients with AV experience.

METHODS

Study Design and Selection of Participants

This cross-sectional study consisted of patients with AV who were admitted to the dermatology outpatient unit in Istanbul Bagcilar Training and Research Hospital between August 2021 and December 2021. During data collection, 183 patients with AV between 18 and 35 years of age were initially identified and enrolled in the study. Patients with at least one mental disorder were excluded (n=20). The presence of a psychiatric diagnosis was established independently by two senior psychiatrists. It was based on the Structured Clinical Interview for DSM-5 Disorders-Clinician Version (SCID-5-CV), which is used to evaluate whether the DSM-5 diagnostic criteria of psychiatric disorders are met (22,23), along with an assessment of personal medical records. The remaining exclusion criteria were as follows: having any dermatological disease other than AV (n=3), previously acquired cutaneous/aesthetic trauma or scars (n=8), illiteracy or uncooperativeness to psychometric instruments or the interview (n=2), pregnancy or lactation (n=3),

using immunosuppressive agents (n=3), presence of a medical comorbidity (e.g., liver or kidney failure, neurological and infectious diseases, endocrine disorders including thyroid dysfunction, and metabolic disorders) (n=5), obesity or being underweight (body mass index (BMI) > 29.9 kg/m^2 or <18.5 kg/m^2, respectively) (n=2), heavy smoking (>20 cigarettes per day) (n=3), and major pathology in laboratory results (n=5). After applying the exclusion criteria, the final patient sample comprised 129 subjects (98 females and 31 males). A senior dermatologist confirmed the AV diagnosis. The patients were recruited independently of the clinical types of lesions. All patients were under AV treatment for at least 4 weeks.

The control group consisted of age- and gender-matched healthy controls (n=60, 47 females and 13 males) who were admitted to our psychiatry outpatient units for purposes of pre-employment health check-ups or employee medical examinations and were matched by smoking and BMI status. Control subjects did not have any mental disorders, including alcohol or substance use disorders that were diagnosed in the past or currently. They were confirmed with the administration of SCID-5-CV. All participants were physically in normal health, and routine recent blood tests were performed. The local Ethics Committee approved the study [IRB: 09.07.2021-21/516], which was conducted according to the Helsinki Declaration. Written informed consent was obtained from all participants.

Procedure

According to the hospital protocol, complete blood count (CBC) screening is performed through routine blood sampling upon admission to the outpatient unit using a standard venipuncture technique from antecubital veins. After collecting background information, including age and duration of illness, current depression, anxiety, and psychological stress levels were assessed for all participants with the Turkish version of the Depression Anxiety Stress Scale-21 (DASS-21). For the patient group, a senior dermatologist determined the grading of the acne lesions with the Global Acne Scoring System (GASS). Sample analysis was performed with the Sysmex XT1800i. All individuals' white blood cell, neutrophil, monocyte, lymphocyte, and platelet counts were recorded. SII was calculated as [neutrophils × platelets/lymphocytes] (17), and SIRI was calculated as [neutrophils × monocytes/lymphocytes] (19).

Grading of Acne Lesions Determined by GASS

According to this system, six different acne regions have different coefficients (two for the forehead and each of the cheeks, one for the chin and nose, and three for the chest and upper back). The severity of the acne is scored between 0 and 4 for each region. After the individual region points were multiplied by their coefficients, the scores of the six regions were added to obtain a "global score." Total of the score may range from 0 to 44. From the score, severity of acne is determined (0=no exist, 1–18=mild, 19–30=moderate, 31–38=severe, and >39=very severe) (24).

Depression Anxiety Stress Scales-21 (DASS-21)

DASS-21 is a 21-item self-report questionnaire designed to measure the severity of depression, anxiety, and stress symptoms (25). Each item of the DASS-21 corresponds to one of the three subscales (depression, anxiety, and stress), with 7 items per subscale. DASS-21 was adapted into Turkish by Yildirim et al. (26). Among the current sample, the DASS-21 and subscales evidenced a Cronbach's alpha of 0.93 for DASS-21, 0.86 for depression, 0.78 for anxiety, and 0.83 for stress. The scale is a 4-point Likert from 0 (never) to 3 (almost always) and evaluates symptoms from last week.

Statistical Analysis

Statistical analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS) for Mac OS, Version 23.0 software (IBM Corp.). After the descriptive data analysis, including background and clinical information, CBC values, and DASS-21 scores, we used either the Chi-squared test to compare qualitative data or Student's t-test to compare continuous variables between groups' assessments. The association between continuous clinical data, SII, SIRI, and DASS-21 scores was examined with Pearson's correlation test in the patient group. Multivariate linear regression analysis with the forwarding method was used to determine the effects of duration of illness, GASS score, SII, and SIRI on DASS-21 Stress scores in AV patients. The significance level was accepted as $p<0.05$.

RESULTS

Descriptive and comparative characteristics of the study sample are presented in Table 1. Of the total participants, 76% (n=98) of the patients and 78.3% (n=47) of the healthy controls were females. The mean age was 23.97±6.37 years for the patient group

Table 1: Descriptive and comparative characteristics of the study sample

	Patients (n=129) Mean±SD/n (%)	Controls (n=60) Mean±SD/n (%)	Test statistics, p
Age	23.97±6.37	24.1±5.43	t=-1.290; p=0.592
Gender			χ^2=0.128; p=0.720
Female	98 (76)	47 (78.3)	
Male	31 (24)	13 (21.7)	
Education (>11 years)	67 (51.9)	55 (91.7)	χ^2=28.247; p<0.001
Smoking	22 (17.1)	18 (30)	χ^2=4.113; p=0.150
WBC ($\times 10^9$ L)	7.24±1.87	7.14±1.52	t=0.387; p=0.700
Neutrophil ($\times 10^9$ L)	4.28±1.49	4.32±1.17	t=-0.221; p=0.825
Lymphocyte ($\times 10^9$ L)	2.25±0.71	2.22±0.60	t=0.262; p=0.793
Platelet ($\times 10^9$ L)	264.21±60.88	261.37±46.67	t=0.320; p=0.749
SII	573.19±440.14	542.23±213.92	t=0.517; p=0.606
SIRI	1.14±1.55	1.02±0.78	t=0.576; p=0.565
DASS-21 depression	5.02±3.83	4.23±3.31	t=1.362; p=0.175
DASS-21 anxiety	5.81±4.32	4.42±3.04	t=2.544; p=0.012
DASS-21 stress	5.2±4.14	4.1±3.45	t=1.914; p=0.058
Duration of illness (years)	5.29±4.48		
GASS	26.33±6.58		

SD: Standard deviation; WBC: White blood cells; SII: Systemic immune-inflammation index (neutrophil × platelet-to-lymphocyte ratio); SIRI: Systemic inflammation response index (neutrophil × monocyte-to-lymphocyte ratio); DASS-21: Depression Anxiety and Stress Scale-21; GASS: Global Acne Scoring System. Statistical significance set at 0.05 (bold values).

and 24.1±5.43 years for controls. Age and gender were not significantly different between the groups (p>0.05). Education level was significantly lower in the patient group (χ^2=28.247, p<0.001). There was no difference between the patient and control groups in terms of white blood cell (t=0.387, p=0.700), neutrophil (t=-0.221, p=0.825), lymphocyte (t=0.262, p=0.793), platelet (t=0.320, p=0.749) counts, SII (t=0.517, p=0.606), and SIRI (t=0.576, p=0.565). There was no significant difference between the patient and control groups in DASS-21 Depression (t=1.362, p=0.175) and DASS-21 Stress (t=1.914, p=0.058). DASS-21 Anxiety was significantly different from the control group in the patient group (t=2.544, p=0.012). The mean duration of illness was 5.29±4.48 years, and the GASS score was 26.33±6.58 in patients with AV.

We further evaluated the correlation between duration of illness, GASS score, DASS-21 Depression, Anxiety, and Stress scores as well as SII and SIRI among the patients. Duration of illness was positively correlated with DASS-21 Stress (r=0.30, p<0.001). DASS-21 Stress was positively correlated with DASS-21 Anxiety (r=0.78, p<0.05) and DASS-21 Depression (r=0.82, p<0.05). SII was positively correlated with SIRI (r=0.56, p<0.001). Other correlations were not statistically significant (r=-0.14 to 0.21) (Table 2).

Multivariate linear regression analysis was performed using clinical variables and systemic inflammatory markers as independent variables to evaluate factors that could have an effect on the DASS-21 Stress score (Table 3). The model was significant (χ^2(4.300)=88.125, p=0.044), and only the duration of illness (β=0.31, p<0.05) was significantly associated with DASS-21 Stress.

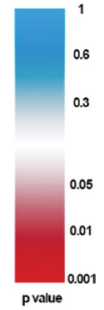
DISCUSSION

In this study, we categorized psychological distress according to depression, anxiety, and stress subscales of DASS-21. We compared the relationship between psychological distress, systemic inflammatory state, and some of the clinical characteristics of AV between patients and controls and within the patient group. According to our findings, duration of illness was associated with psychological distress among a sample of AV patients, independent of peripheral proinflammatory status. Moreover, anxiety symptoms are higher in AV patients than in healthy subjects.

Previous studies have indicated that psychiatric symptoms, including depression, anxiety, and even suicidality, are associated with AV in both adult and adolescent populations (25,27). Furthermore, a

Table 2: Correlations between clinical features, inflammatory markers, and DASS-21 scores in patients with acne vulgaris

r	1	2	3	4	5	6	7
1. Duration of illness (years)	1						
2. GASS	-0.14	1					
3. SII	0.06	0.10	1				
4. SIRI	0.03	0.02	0.56	1			
5. DASS-21 depression	0.02	0.21	-0.04	0.07	1		
6. DASS-21 anxiety	0.14	0.12	-0.05	0.07	0.79	1	
7. DASS-21 stress	0.30	0.14	-0.09	0.06	0.82	0.78	1



r: Pearson's correlation coefficient; SII: Systemic immune-inflammation index; SIRI: Systemic inflammation response index; DASS-21: Depression Anxiety and Stress Scale-21; GASS: Global Acne Scoring System.

Table 3: Multivariate linear regression analysis of clinical features and inflammatory markers for DASS-21 Stress score in patients with acne vulgaris

	Unstandardized coefficients		Standardized coefficients			
	B	SE	β	t	σ	[95% CI]
DASS-21 stress*						
Duration of illness (years)	0.306	0.148	0.305	2.074	**0.044**	[0.008–0.604]
Constant	4.709	1.092		4.312	**0.000**	[2.506–6.913]

*: Results from linear regression (forward), model summary; $\chi^2(4.300)=88.125$, p=0.044, adjusted R^2 of 0.071, covariates excluded by the model: smoking, Global Acne Scoring System, systemic immune-inflammation index, systemic inflammation response index. P<0.05 statistically significant (bold values). Multivariate linear regression analyses of covariates (duration of illness, Global Acne Scoring System score, systemic immune-inflammation index and systemic inflammation response index) for DASS-21 depression and DASS-21 Anxiety scores did not produce statistically significant models.

significant relationship was found between acne severity and emotional/behavioral symptoms (28). Despite anxiety symptom scores being higher in the patient group than in healthy subjects in our study, acne symptom severity was not associated with depressive, anxiety, and stress levels among patients. Such a negative association may be related to excluding patients with psychiatric diagnoses such as anxiety and depressive disorders. Indeed, there are conflicting results on whether depression, anxiety, and psychological distress are associated with the severity of AV. A number of studies reported that social anxiety and depressive symptoms have not been associated with acne severity (29,30).

AV is a chronic inflammatory disease. In addition, stress due to the psychological burden caused by the disease can trigger various reactions in the immune system and may lead to an increased proinflammatory status (31). The functions of the hypothalamic–pituitary–adrenal (HPA) and inflammatory status have a reciprocal relationship (32). The HPA axis is one of the body's neuroendocrine networks that respond to psychological stress. Psychological distress may be associated with an impaired balance between inflammation and HPA axis (33). In the skin, a peripheral HPA axis similar to the central axis exists. Glucocorticoids are key effector molecules of the HPA axis and are essential for cutaneous homeostasis (34). Theoretically, a weakened antioxidant defense system and altered immune system functions may interplay to increase the risk of psychological sequelae in AV (35). However, we could not confirm such a relationship according to our findings. Such a negative association may be partially due to the fact that the local inflammation is more prominent than the systemic inflammation in AV. The immunochemical pathways underlying the initiation and spread of inflammation in acne are complex and unclear. Local inflammation occurs in and around the acne lesion (36). A local inflammation around the lesion may not have caused changes in systemic inflammatory markers. Although increased systemic inflammation is associated with psychological distress and depressive-like behavior in both animals and humans (37,38), we could not detect any relationship between inflammation markers and anxiety, depression, and stress. This may be related to the discrepancy between central and peripheral inflammation and the complex interplay between psychological distress between inflammation, which may be influenced by many factors such as coping strategies.

There was a significant relationship between the duration of AV disease and DASS-21 Stress, independent of the systemic proinflammatory status. The DASS-21 Stress score has been associated with difficulty in relaxation, irritability, and agitation. In fact, difficulty in relaxation, irritability, and agitation are common psychiatric symptoms in the young population. In addition, youth irritability was a specific predictor of depressive and anxiety disorders after 20 years (39). Therefore, it may be expected that stress increases in individuals due to the appearance of the disease at a young age and the negative experiences experienced during the disease. In addition, congruently, the duration of illness has been associated with the levels of psychological distress in patients with AV (30).

The limitations of the study include a cross-sectional single-center design as well as an inequality in the female-to-male ratio. Being more educated than the control group of patients may have affected the perceived stress and psychiatric symptoms. The exclusion of individuals with psychiatric disorders may have contributed to the lack of significant differences between groups. The DASS-21 is a self-report instrument and may not be sufficient to evaluate depressive, anxiety, and stress symptoms comprehensively. The number of control subjects was relatively smaller than the study group. Although we excluded many confounders, such as obesity or being underweight and heavy smoking, other factors might have affected inflammatory markers.

Our results suggest that psychological distress is associated with the duration of illness in a sample of patients with AV. Anxiety levels may be increased in patients compared to healthy subjects. Although we have found that systemic inflammation was not related to the severity of AV and psychiatric symptoms, future large-scale follow-up studies are warranted to demonstrate the clinical significance of SII and SIRI as novel peripheral inflammatory markers in AV patients. Because SII and SIRI are two new and promising indices of systemic inflammation recommended for predicting poor outcomes in diseases, we may implicate that the faster and more effective the treatment of AV, the lower the risk of psychological distress, psychiatric comorbidity, and the response time to treatment. We believe that medical interventions taking psychiatric conditions into account will significantly increase the quality of life of patients with AV. Therefore, clinicians should be more attentive in monitoring psychological distress in AV patients, particularly with long illness duration, and be more willing to seek help from a specialist psychiatrist.

Contribution Categories		Author Initials
Category 1	Concept/Design	M.N.N., H.G., B.T., E.S., H.B.
	Data acquisition	H.G., B.T.
	Data analysis/Interpretation	Y.H.B.
Category 2	Drafting manuscript	M.N.N., H.G., Y.H.B.
	Critical revision of manuscript	Y.H.B.
Category 3	Final approval and accountability	M.N.N., H.G., B.T., Y.H.B., E.S., H.B.
Other	Supervision	Y.H.B.

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