

Association Between Serum Cortisol Levels, Stress Physiology, Pathological Changes, and Flare Frequency in Chronic Acne severity

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ABSTRACT

Background: Chronic acne is a common inflammatory skin disease which can be due to hormonal, physiological, psychological and pathological factors. A rise in serum cortisol levels, from stress, can alter sebaceous gland activity, inflammation, and acne flare frequency. The correlation of serum cortisol levels with stress physiology, pathological changes and chronic acne severity still needs to be further assessed clinically.

Objective: To determine the association between serum cortisol levels, stress physiology, pathological changes, and flare frequency with chronic acne severity.

Methods: The study was descriptive cross-sectional study which was done at Mardan Medical Complex, Mardan from January 2023 to June 2023. A total of 75 patients with chronic acne was included. A structured proforma was completed for demographic data, duration of acne, family history, severity of acne, type of lesions, scarring, post-inflammatory hyperpigmentation, sleep disturbance, perceived stress level, and monthly frequency of flares. The acne was graded as mild, moderate or severe with clinical examination. Venous blood was drawn to measure cortisol in the morning. Data were analysed by employing SPSS. For quantitative variables, mean and standard deviation were used and for qualitative variables, frequency and percentage were used. Where appropriate, the following statistical analysis techniques were used: chi-square test, ANOVA, correlation analysis, and logistic regression. The p value was calculated and a value of < 0.05 was deemed statistically significant.

Results: The mean age of the participants was 22.8 ± 4.9 years. Among 75 patients, 29 (38.7%) were males and 46 (61.3%) were females. Mild acne was observed in 21 (28.0%) patients, moderate acne in 34 (45.3%), and severe acne in 20 (26.7%). The mean serum cortisol level increased with acne severity, from 14.8 ± 3.7 $\mu\text{g/dL}$ in mild acne to 19.3 ± 5.1 $\mu\text{g/dL}$ in moderate acne and 25.1 ± 5.8 $\mu\text{g/dL}$ in severe acne ($p < 0.001$). High perceived stress and frequent flare episodes were significantly more common among patients with severe acne. Serum cortisol level showed a positive correlation with acne severity score ($r = 0.61$, $p < 0.001$) and monthly flare frequency ($r = 0.54$, $p < 0.001$). Raised cortisol, high perceived stress, and frequent flares were significant predictors of moderate-to-severe acne.

Conclusion: Higher serum cortisol levels, increased perceived stress, disturbed sleep, and frequent flare episodes were associated with greater chronic acne severity. Patients with severe acne showed more pathological changes, including scarring, post-inflammatory hyperpigmentation, and nodulocystic lesions. Assessment of stress physiology and flare frequency may be useful in the routine clinical evaluation of patients with chronic acne.

Keywords: Acne vulgaris, serum cortisol, stress physiology, chronic acne, acne severity, flare frequency, pathological changes

INTRODUCTION

Acne vulgaris is an inflammatory disorder of pilosebaceous unit, and is often encountered in adolescents and young adults. Acne is sometimes regarded as a cosmetic issue, but it may actually cause significant physical, psychological and social suffering. It can appear as comedones, papules, pustules, nodules, cysts, post-inflammatory hyperpigmentation and permanent scarring and may last for months or years. Acne severity is individual to patient and can be affected by many interacting factors such as sebum production, follicular hyperkeratinization, bacterial colonization, inflammation, hormonal influences, and lifestyle factors¹⁻³.

Stress is a factor that has been increasingly acknowledged in exacerbating inflammatory skin conditions, such as acne. Stress (psychological or physiological) stimulates the hypothalamus-pituitary-adrenal axis, leading to greater release of corticotropin-releasing hormone, adrenocorticotropic hormone and cortisol. Cortisol is a key hormone in the body that is released during stress and is essential for maintaining balance in the body, including regulating its metabolism, immune system and inflammatory responses. If the stress is prolonged, elevated cortisol levels can disrupt the healthy balance of skin cells, leading to heightened inflammation, overactive sebaceous glands, weakened barrier function, and delayed healing. Such mechanisms may contribute to the occurrence of acne episodes and exacerbation of lesions⁴⁻⁶.

The skin is not only a site of action for hormones, but also it has local neuroendocrine and immune activity. Stress can

trigger hormonal changes that may cause sebaceous glands to become active, which can lead to more sebum and inflammation. For patients suffering from acne, stress has been shown to exacerbate the condition by contributing to higher levels of inflammatory mediators, changes in immune function and behaviors that can worsen acne, such as poor sleep, irregular skin care routines, dietary changes, and failure to follow-ups with treatment. Many patients have reported that acne outbreaks happen during times of examinations, emotional stress, poor sleep and work-related stress. Thus there may be a link between the severity of acne and the stress physiology of the system and/or local skin pathology⁷⁻¹⁰.

Biological marker for stress response is commonly used is serum cortisol. Cortisol, a hormone with diurnal rhythm, is measured in the morning when the cortisol level can be a good estimate of the endocrine activity related to stress when measured under a standard condition. Although a raised cortisol may not be a direct trigger of acne in every patient, it may make the disease worse in patients who are predisposed to acne by triggering inflammation, sebaceous activity, and flare ups. The evaluation of serum cortisol may help determine the relationship between stress physiology and the clinical severity and pathophysiology of chronic acne in acne patients¹¹.

Pathological alterations in chronic acne include persistent inflammatory lesions, nodulocystic acne, scarring and post-inflammatory hyperpigmentation. The changes are more likely to happen if acne lasts longer and when inflammatory flares of acne are more frequent. Flares can be recurrent and may cause more damage to the tissue and make the disease more difficult to

Received on 28-10-2023

Accepted on 25-12-2023

manage. Flare frequency is an important clinical variable as it represents the activity and recurrence pattern of acne over time. More frequent follow-up is needed in patients who have frequent flares, need early anti-inflammatory therapy, and should consider evaluation of other modifiable triggers including stress and sleep disturbance¹².

The relationship between stress and acne is found in clinical practice, but is less often examined in routine clinical practice by measuring serum cortisol. There are very few studies available on the joint association of cortisol, stress physiology, pathological changes, flare frequency and acne severity at a local level. This relationship might aid the clinician in treating acne with a broader perspective, particularly when encountering chronic or recurrent disease.

The present study was conducted to determine the association between serum cortisol levels, stress physiology, pathological skin changes, and flare frequency with chronic acne severity among patients attending Mardan Medical Complex, Mardan. By assessing both clinical and physiological variables, this study aimed to highlight the role of stress-related factors in the progression and recurrence of chronic acne.

METHODOLOGY

This study was conducted at Mardan Medical Complex, Mardan, from January 2023 to June 2023. A descriptive cross-sectional study design was used to evaluate the association between serum cortisol levels, stress physiology, pathological changes, flare frequency, and severity of chronic acne. A total of 75 patients diagnosed with chronic acne were included in the study. Patients were recruited from the dermatology outpatient department after fulfilling the eligibility criteria. Chronic acne was defined as acne persisting for three months or more, with recurrent inflammatory or non-inflammatory lesions.

Patients aged 15-35 years, both males and females, were included who had acne vulgaris diagnosed clinically. Patients on systemic steroids, hormonal therapy, isotretinoin, oral contraceptive pills or other medications that may alter serum cortisol levels for the past three months were not included. Patients were also excluded for the presence of known endocrine disorders (Cushing syndrome, Addison disease, thyroid dysfunction, polycystic ovarian syndrome with active hormones, chronic systemic illness, acute infection or lactation). The following criteria were used to minimize confounding factors that might affect the concentration of cortisol, activity of acne or inflammatory status.

Demographic and clinical details were collected with an informed consent form, which was completed on a structured proforma. The variables that were collected were age, gender, duration of acne, family history of acne, involvement of acne lesions, type of lesions, acne scarring, post acne hyperpigmentation, disturbance of sleep and perceived stress level, and the number of acne flares occurred monthly. The severity of acne was evaluated using clinical examination and acne lesions count, and was classified into mild, moderate, and severe acne. Mild acne consisted of primarily comedones with few inflammatory papules, moderate acne consisted of multiple papules and pustules, and severe acne consisted of extensive inflammatory lesions, nodules, cysts or visible scarring.

Patients were asked to report on their perceived stress in the last month, sleep disturbance, stress due to the examination and/or stress due to work, and increase in acne in the past months when stressed. Stress level was classified as low, moderate or high based on patient response and stress related symptoms. The size and frequency of the flares were measured in terms of the number of exacerbations of acne per month. Flares were also classified as "rare", "occasionally" or "frequently". Rare flares were considered as 1 or fewer episodes per month, occasional flares were 2-3 episodes per month, and frequent flares, more than 3 episodes per month.

Blood samples were drawn from all participants from the veins for the measurement of serum cortisol. Blood samples were

ideally taken in the morning (between 08:00 and 10:00 h) to minimise the impact of the diurnal variation. Venous blood (about 3-5 mL) was drawn aseptically into a plain tube. Clotting and centrifugation were done to obtain serum. Serum cortisol levels were determined by a standard laboratory-based immunoassay procedure, following the protocol of the hospital laboratory. The cortisol levels were measured in micrograms per deciliter ($\mu\text{g}/\text{dL}$) and have been analyzed as a continuous variable as well as a categorical variable based on the laboratory reference range (normal or raised cortisol level).

The clinical evaluation of pathological changes associated with chronic acne was done. These include inflammatory papules, pustules, nodulocystic lesions, scarring, post-inflammatory hyperpigmentation and seborrhea. Scars and nodules/cysts were regarded as a marker for more advanced pathological skin involvement. To assess if there were any physiological changes related to a flare due to greater serum cortisol level, stress category, and flare frequency, the relationships were analyzed between these changes and the pattern of chronic acne.

Data was entered and analyzed in the SPSS software. The quantitative variables (age, duration of acne, serum cortisol level, and flare frequency) were given as mean \pm standard deviation. Qualitative variables like gender, severity of acne, type of stress, raised cortisol level, sleep disturbance, acne type and acne scarring were shown as frequencies and percentages. One-way ANOVA was used to compare the mean serum cortisol levels between the mild, moderate and severe acne groups. To test association between categorical variables (stress level, raised cortisol status, frequency of flares, acne severity) the chi-square test was performed. Correlation analysis was used to assess the relationship between serum cortisol level, rating of stress, acne severity and acne flare frequency. Logistic regression analysis was performed to determine the predictors for moderate-to-severe acne. The p value was < 0.05 considered as statistically significant.

RESULTS

The study comprised of 75 patients with chronic acne. The mean age of the patients was 22.8 ± 4.9 years, and most of the patients were between 18 and 25 years. Out of 75 patients, 29 (38.7%) were males and 46 (61.3%) were females. The mean time for acne was 3.1 ± 1.4 years. Thirty-one (41.3%) had a positive family history, while 44 (58.7%) did not have a family history of acne.

Regarding acne severity, 21 (28.0%) patients had mild acne, 34 (45.3%) had moderate acne, and 20 (26.7%) had severe acne. The most common clinical presentation was papulopustular lesions in 39 (52.0%) patients, followed by comedonal acne in 22 (29.3%) patients, and nodulocystic lesions in 14 (18.7%) patients. 28 (37.3%) patients had acne scarring and 36 (48.0%) patients had post inflammatory hyperpigmentation.

The serum cortisol level of the individuals in the study was $19.6 \pm 6.3 \mu\text{g}/\text{dL}$. In 33 (44.0%) of the patients raised cortisol levels were seen. Acne severity was associated with the mean level of cortisol. Patients with mild acne had a mean cortisol level of $14.8 \pm 3.7 \mu\text{g}/\text{dL}$, those with moderate acne had $19.3 \pm 5.1 \mu\text{g}/\text{dL}$, while patients with severe acne had the highest mean cortisol level of $25.1 \pm 5.8 \mu\text{g}/\text{dL}$. This difference was statistically significant ($p < 0.001$).

The perception of stress was measured by stress categories related to stress physiology. Overall, 18 (24.0%) patients had low stress, 32 (42.7%) had moderate stress, and 25 (33.3%) had high stress. Patients with severe acne were more likely to have high stress. In severe acne patients 12 (60.0%) had high stress, while 3 (14.3%) patients with mild acne had high stress. There was a statistically significant correlation between level of stress and severity of acne ($p = 0.002$).

Forty-three (57.3%) patients reported sleep disturbance. The mean serum cortisol concentration was found to be significantly higher in the patient group with disturbed sleep than in the group with normal sleep, $22.1 \pm 5.9 \mu\text{g}/\text{dL}$ vs $16.2 \pm 4.7 \mu\text{g}/\text{dL}$, $p < 0.001$.

Furthermore, patients with sleep disturbance, high stress were more likely to experience frequent acne flares.

The mean flare rate was 3.2±1.5 episodes/month. 29 (38.7%) patients reported frequent flares (more than three episodes a month). In patients with severe acne, 13 (65.0%) of them had frequent flares while 4 (19.0%) patients with mild acne had frequent flares. The association between the frequency of flare and the severity of acne was statistically significant (p = 0.001).

Pathological changes were more common in moderate and severe acne patients. A total of 12 (60.0%) of the patients with severe acne had acne scarring, 13 (38.2%) of patients with moderate acne had acne scarring and 3 (14.3%) of patients with mild acne had acne scarring. Likewise, patients who experienced severe acne had more nodulocystic lesions. From these findings it can be inferred that the more of such changes in the skin were visible the more likely it was that there had been chronic inflammatory activity or repeated acne flares.

The serum cortisol level was correlated with acne severity score significantly (r = 0.61, p < 0.001). There was also a positive correlation between serum cortisol level and monthly flare frequency (r = 0.54, p < 0.001). The flare frequency had a moderate positive correlation with perceived stress score (r = 0.49; p = 0.003).

Table 1: Demographic characteristics of study participants

Variable	Frequency / Mean	Percentage
Total sample size	75	100%
Mean age	22.8 ± 4.9 years	—
Age 15–20 years	26	34.7%
Age 21–25 years	33	44.0%
Age >25 years	16	21.3%
Male	29	38.7%
Female	46	61.3%
Positive family history	31	41.3%
Mean duration of acne	3.1 ± 1.4 years	—

Table 2: Clinical pattern and severity of acne

Clinical variable	Frequency	Percentage
Mild acne	21	28.0%
Moderate acne	34	45.3%
Severe acne	20	26.7%
Comedonal lesions	22	29.3%
Papulopustular lesions	39	52.0%
Nodulocystic lesions	14	18.7%
Acne scarring present	28	37.3%
Post-inflammatory hyperpigmentation	36	48.0%

Table 3: Association of serum cortisol level with acne severity

Acne severity	Number of patients	Mean serum cortisol level µg/dL	Raised cortisol n (%)	p-value
Mild	21	14.8 ± 3.7	4 (19.0%)	
Moderate	34	19.3 ± 5.1	15 (44.1%)	<0.001
Severe	20	25.1 ± 5.8	14 (70.0%)	

Table 4: Association of perceived stress level with acne severity

Stress level	Mild acne n (%)	Moderate acne n (%)	Severe acne n (%)	Total
Low stress	10 (47.6%)	7 (20.6%)	1 (5.0%)	18
Moderate stress	8 (38.1%)	18 (52.9%)	6 (30.0%)	32
High stress	3 (14.3%)	9 (26.5%)	12 (60.0%)	25
Total	21	34	20	75

p-value = 0.002

Table 5: Flare frequency according to acne severity

Flare frequency	Mild acne n (%)	Moderate acne n (%)	Severe acne n (%)	Total
Rare flares	9 (42.9%)	5 (14.7%)	1 (5.0%)	15
Occasional flares	8 (38.1%)	18 (52.9%)	6 (30.0%)	32
Frequent flares	4 (19.0%)	11 (32.4%)	13 (65.0%)	28
Total	21	34	20	75

p-value = 0.001

Table 6. Correlation of cortisol and stress markers with acne outcomes

Variables correlated	Correlation coefficient	p-value
Serum cortisol level and acne severity score	r = 0.61	<0.001
Serum cortisol level and flare frequency	r = 0.54	<0.001
Stress score and acne severity score	r = 0.52	0.001
Stress score and flare frequency	r = 0.49	0.003

Table 7: Predictors of moderate-to-severe acne

Predictor	Odds ratio	95% confidence interval	p-value
Raised serum cortisol	3.42	1.31–8.91	0.012
High perceived stress	2.86	1.08–7.59	0.034
Sleep disturbance	2.21	0.89–5.46	0.087
Frequent flares	3.08	1.16–8.18	0.024
Positive family history	1.74	0.68–4.42	0.245

Mean Serum Cortisol Levels According to Acne Severity

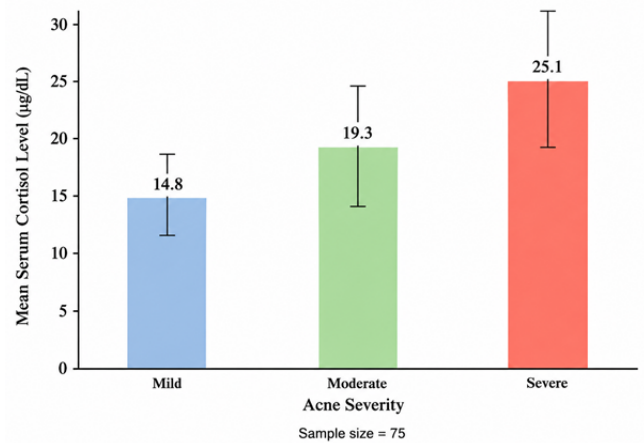


Figure 1. Mean serum cortisol levels according to acne severity: The bar graph shows a progressive rise in mean serum cortisol level from mild acne (14.8 ± 3.7 µg/dL) to moderate acne (19.3 ± 5.1 µg/dL) and severe acne (25.1 ± 5.8 µg/dL) among 75 patients. This indicates that higher cortisol levels were associated with increasing chronic acne severity

For logistic regression analysis, elevated serum cortisol, high perceived stress, and a high rate of flares per month were predictive factors of moderate-to-severe acne. Patients with increased serum cortisol levels were more likely to have moderate to severe acne than those with normal cortisol levels (OR 3.42, 95% CI 1.31–8.91, p = 0.012). A higher perceived stress level was also significantly associated with more severe acne (OR = 2.86, 95% CI: 1.08–7.59, p = 0.034).

Overall, there was an association of higher serum cortisol, greater perceived stress, poor sleep and more frequent flare episodes with greater chronic acne severity. Patients suffering from severe acne had elevated cortisol levels, increased incidence of acne flares, and increased incidence of pathological changes in the skin including scarring and nodulocystic lesions.

DISCUSSION

The present study evaluated the association between serum cortisol levels, stress physiology, pathological skin changes, flare frequency, and chronic acne severity among 75 patients attending Mardan Medical Complex, Mardan. The findings showed that moderate acne was the most common presentation, followed by mild and severe acne. A clear rise in mean serum cortisol level was observed across increasing acne severity groups. Patients with severe acne had the highest mean cortisol level, while patients with mild acne had the lowest level. This pattern suggests that activation of stress-related hormonal pathways may contribute to worsening acne severity and recurrent flare activity^{13,14}.

The connection between stress and acne is biologically logical because psychological and physiological stress can trigger the hypothalamic-pituitary-adrenal axis, which results in the release of more cortisol. Cortisol can affect the function of the sebaceous glands, inflammatory reactions and regulation of the skin barrier. It has also been reported in the literature that stress related HPA-axis activity can influence the activity of the sebaceous glands and can worsen acne lesions. In this study, elevated serum cortisol occurred more often in patients with severe acne, suggesting that cortisol levels may not only be used as a measure of acute stress but also as a measure of a state of the body that is linked to the inflammatory activity of acne¹⁵⁻¹⁷.

In this study, perceived stress was significantly related to the severity of acne. Patients with severe acne reported high stress while low stress was more common in mild acne patients. This is in line with previous clinical studies that reported that an increase in stress scores correlates with greater acne severity. There are several ways stress can aggravate acne, such as the increase in inflammatory signaling, immune response, sebum production, disruption of sleep, and failure to maintain proper skin care or treatment. Acne is not only a local skin problem but also a problem of the systemic and psychophysiological influences as well¹⁸.

Another significant result of the current study is the frequency of flares. Severely affected acne patients had more than mild acne patients regarding monthly flares. There was also a positive correlation between the serum cortisol level and the frequency of flares. This means that those who had higher cortisol levels had a greater risk of having multiple acne flares. Recurrent flares may keep inflammation going for longer, make lesions worse and increase the likelihood of scarring and pigmentation after the flare. The findings have stressed the need to routinely ask for the flare patterns and stress periods, sleep patterns, and lifestyle triggers in acne patients¹⁹.

The pathological skin changes were higher in patients with moderate and severe acne. Patients with more severe acne were more likely to have scarring, post-inflammatory hyperpigmentation and nodulocystic lesions. This could be due to the ongoing inflammation and the repeated flare ups, resulting in a higher tissue damage and slower healing. This process can be further exacerbated by stress-related biological changes, which can affect the regulation of the immune system and inflammatory mediators. Recent reviews also indicate that chronic stress may play a role in exacerbating inflammatory dermatological diseases such as acne by interfering with the maintenance of the normal state of the skin and inflammatory control²⁰.

In the present study, it was also determined that sleep disturbance occurred in chronic acne patients and that the mean level of serum cortisol was high. Poor sleep can exacerbate the activity of the stress response system and cause hormonal imbalance, inflammation and poor skin recovery. During clinical examination, patients with chronic acne frequently complain of aggravation of acne during the stress of the examination, emotional stress, sleep deprivation or irregular daily routine. In acne patients with persistent or treatment resistant acne, evaluation of sleep and stress may be useful.

Raised serum cortisol, high perceived stress and frequent acne flares were all significantly associated with moderate to severe acne as determined by logistic regression analysis. These results indicate that stress physiology and level of flares could be a significant factor in the progression of chronic acne. Acne is, however, a multifactorial disease, and cortisol should not only be considered as the sole driver of severity of the disease. Other factors, including genetic susceptibility, androgen activity, sensitivity of the sebaceous glands, diet, skin care practices, bacterial colonization and inflammatory tendencies, can also play a role in the disease process²¹.

There are certain limitations of this study. The number of patients was not very large and the research was carried out in one centre, hence the results may not be generalizable. This was measured in a single serum sample of cortisol, but cortisol

concentrations can fluctuate throughout the day, and may be influenced by acute stress, sleep, dietary status, and medications. It was measured clinically and a standardized stress scale would yield better evidence in future studies. Even with these drawbacks, the findings of this study offer some local evidence that serum cortisol, perceived stress, sleep disturbance, and flare frequency are related to the severity of chronic acne.

CONCLUSION

This study concluded that higher serum cortisol levels, increased perceived stress, disturbed sleep, and frequent acne flares were significantly associated with greater chronic acne severity. Patients with severe acne showed higher mean cortisol levels, more frequent flare episodes, and more pathological skin changes such as scarring, post-inflammatory hyperpigmentation, and nodulocystic lesions. These findings suggest that stress physiology may play an important role in the clinical course of chronic acne.

Assessment of stress, sleep pattern, and flare frequency should be included in the routine evaluation of patients with persistent acne. Along with standard dermatological treatment, stress reduction, sleep improvement, lifestyle counseling, and early management of inflammatory lesions may help reduce flare frequency and prevent long-term complications such as scarring. Further multicenter studies with larger sample sizes and repeated cortisol measurements are recommended to confirm these findings.

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This article may be cited as: Sarwar Z., Farukh U., Shah S. J., Shabir S., Wazir R. J., Samad A., Association Between Serum Cortisol Levels, Stress Physiology, Pathological Changes, and Flare Frequency in Chronic Acne severity. Pak J Med Health Sci, 2023;17(12):879-883