STUDY

The Response of Skin Disease to Stress

Changes in the Severity of Acne Vulgaris as Affected by Examination Stress

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Background: Although emotional stress has long been suspected to exacerbate acne vulgaris, previous reports addressing its influence on acne severity have been mainly anecdotal.

Objectives: To elucidate the possible relationship between stress and acne exacerbation by evaluating changes in acne severity during nonexamination and examination periods and to assess the possible relationship of these changes in severity with perceived examination stress by using previously validated scales measuring acne severity and perceived stress.

Design: Prospective cohort study.

Setting: General university community.

Participants: A volunteer sample of 22 university students (15 women and 7 men) with a minimum acne vulgaris severity of 0.5 on the photonumeric Leeds acne scale (baseline scores, 0.50-1.75).

Main Outcome Measures: Participants were graded on their acne severity using the Leeds acne scale, and had their subjective stress levels assessed with the Perceived Stress Scale questionnaire during both nonexamination and examination periods.

Results: Subjects had a higher mean grade of acne severity and mean perceived stress score ($P<.01$ for both) during examinations. Using regression analysis and adjusting for the effects of confounding variables, such as changes in sleep hours, sleep quality, diet quality, and number of meals per day, increased acne severity was significantly associated with increased stress levels ($r=0.61$, $P<.01$), while self-assessed change in diet quality was the only other significant association ($P=.02$).

Conclusions: Patients with acne may experience worsening of the disease during examinations. Furthermore, changes in acne severity correlate highly with increasing stress, suggesting that emotional stress from external sources may have a significant influence on acne.

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ACNE VULGARIS is the most common skin disease treated by dermatologists, affecting an estimated 85% of the population at some time in their life.[1] The disease's major complications include physical scarring and psychosocial effects, which may persist long after the active lesions have disappeared.[2-4] For these reasons, much dermatological research has been focused on therapeutic interventions to reduce the incidence and severity of acne. Although it is widely believed that factors such as stress and anxiety may not only be a result of acne but can themselves exacerbate acne, little research has been undertaken to demonstrate this latter relationship.

A recent study[5] conducted on 215 graduating medical students showed that 67% of students believed that stress plays a role in acne exacerbations. Moreover, 74% of patients with acne and their relatives also believed anxiety was an exacerbating factor in their disease.[6] These findings suggest that the perception of stress playing an exacerbating role in acne is not only widespread among patients but may be common in the practicing medical community as well.

Increased numbers of studies[7,8] support the pathogenic link between chronic stress and exacerbation of disease. Research[9-12] shows that stress significantly slows wound healing, increases pain intensity, and slows surgery recovery rates. Evidence[13-17] that psychological stress may influence the course of dermatological disease is also growing, especially in the settings of psoriasis, alopecia areata, and atopic dermatitis.

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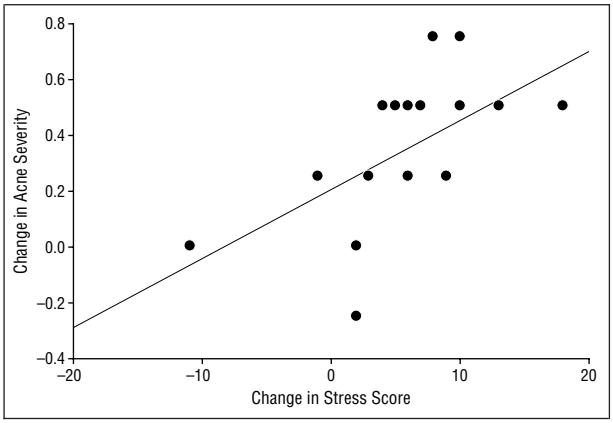

Figure 1. Change in acne severity by change in stress severity. An increase in stress strongly correlated with a progressive increase in acne severity (r=0.61, P<.01).

Clearly, there are some psychological components to the etiology of acne, because treatments such as biofeedback relaxation and cognitive imagery have been shown to be effective.[18] More specifically, patients with acne often complain of breakouts following the experience of frustrating or stressful events,[19,20] and it has been observed that postadolescent patients with acne tend to be intense and ambitious people with high-visibility jobs.[21] Another study[22] linking acne exacerbation with emotional factors reported an increase in acne lesion counts days following an interview during which anger was intentionally provoked.

However, other reports of stress exacerbating acne, as previously outlined, have mainly been anecdotal. Despite widespread patient and physician perception, little research has been undertaken to demonstrate this association in a convincing manner. This study uses established and validated scales of acne severity and perceived stress and the widely accepted model of examination stress to explore the possible interactions between psychological stressors and acne vulgaris.

METHODS

A clinical and questionnaire-based prospective observational cohort study was conducted at the Department of Dermatology, Stanford University School of Medicine. Approval for the study was granted by the university institutional review board. Twenty-two healthy university students (age range, 18-41 years; mean age, 22.25 years) with at least 1 academic examination within the participating academic quarter were recruited for the study by campus advertisements and by recruitment during visits to the general dermatology clinic. The study subjects were roughly representative of the student body in diversity. Twenty-two subjects provided informed consent, 19 (7 men and 12 women) completed the study, and 3 failed to return for the second visit. Of the 19 subjects who completed the study, 7 were white, 6 were Asian, 3 were African American, 1 was Mexican American, 1 was Indian, and 1 was Native American.

All participants were healthy and had an acne severity of at least 0.5 on the photonumeric Leeds acne assessment scale.[23] This scale gives a range of acne vulgaris severity from 0.0 to 10.0, with 0.25-U intervals. Subjects were allowed to use topical or oral acne therapies, excluding isotretinoin, and were also allowed to take oral contraceptives, as long as there was no change in these therapies 8 weeks before enrollment and throughout participation in the study. No subjects were receiving sedatives, antidepressants, or exogenous glucocorticoids.

A single observer (A.C.) graded all subjects' acne severities according to the Leeds technique twice during the study. The first time was approximately 1 month before any examinations (nonexamination period). The second assessment was within a time frame of 3 days before an examination to 7 days after an examination (examination period). All grading was done without knowledge of the subjects' perceived stress scores. However, because the investigator still knew whether it was a nonexamination or an examination period, digital photographs were taken of the subjects from a frontal view, left profile, and right profile, in front of a blue background during the nonexamination and the examination periods. A different investigator (S.Y.C.), blinded to which period the photographs were taken, was then asked to identify in which set of photographs the acne severity seemed improved or worse, or if it remained the same. This investigator, who is a board-certified dermatologist, was not asked to give an absolute Leeds acne score because palpation is an important consideration in the grading, and photographic representation did not allow the kind of detail and clarity required for more refined grading.

On both visits, participants' perceived stress was measured by the Perceived Stress Scale, a 14-item self-questionnaire that measures perceptions of life stress, including how often subjects perceived their life to be uncontrollable, unpredictable, and overwhelming.[24] This scale is widely used in stress research and has demonstrated normative data and reliability, with higher scores indicating increased levels of perceived stress. During each visit, subjects were also asked to estimate how many hours of sleep per night they were experiencing, on average, during the past month; how many meals per day they were eating; and to estimate sleep and diet quality on a scale from 1 to 4 (1, poor; 2, fair; 3, good; and 4, excellent). Statistical analysis using paired t tests, correlation analyses, and regression analyses were completed using Statistical Product and Service Solutions software (SPSS Inc, Chicago, Ill).

RESULTS

By using logistic regression and adjusting for change in sleep hours, change in perceived sleep quality, change in meals per day, and change in perceived diet quality, an increase in stress strongly correlated with a progressive increase in acne severity (r=0.61, β=.59, P<.01) (**Figure 1**). In other words, subjects who had the greatest increases in stress during examination periods also had the greatest exacerbations in acne severity. There were 5 students who reported similar stress levels at both visits, with a perceived stress score either the same or within 3 points. In these subjects, acne severity either remained the same during both periods or varied only by 0.25 in either direction.

Photographic grading by a separate investigator, who was blinded as to which period the pictures were taken, agreed with that of the primary grader in 16 of 19 subjects. One subject was graded as unchanged, instead of worse; another was graded worse, instead of better; and another was graded improved, instead of worse.

Figure 2 shows the differences in subjects' acne severity between nonexamination and examination periods. A paired t test comparing acne severity showed a higher mean Leeds acne score of 1.33 during examination periods (P<.01), which is increased from a mean

score of 0.97 during nonexamination periods. The mean change in acne scores was 0.36, and this increase is significant (SEM, .06), because the minimum clinically detectable difference according to the Leeds technique is 0.25. This also seems to be a reasonable range of impact given that prescription acne therapies typically improve Leeds acne scores by 1.0 to 1.2.[25,26] Not surprisingly, students perceived significantly more stress during examinations when compared with the beginning of the academic quarter, when there were no examinations ($P<.01$). Only 2 students reported lower stress levels during the examination period. Although this increase is consistent with the increases noted in other studies conducted on stress experienced in the academic setting, it is notable that the nonexamination and examination period stress scores were considerably higher in this population when compared with the results of other studies using the same model.

Interestingly, results also suggest that worsening perceived diet quality is significantly associated with acne exacerbation, although its influence on acne severity is weaker than that of increasing stress levels ($r=-0.48$, $\beta=-.48$, $P=.02$). Estimated hours of sleep per night had a small and nonsignificant decline during examination periods, from 6.6 to 6.3 hours ($P=.10$). The association between worsened sleep quality and acne exacerbation was close to significant ($P=.06$). Of the other lifestyle factors recorded, none were significantly different between the examination and the nonexamination periods, and none were associated with changes in acne severity.

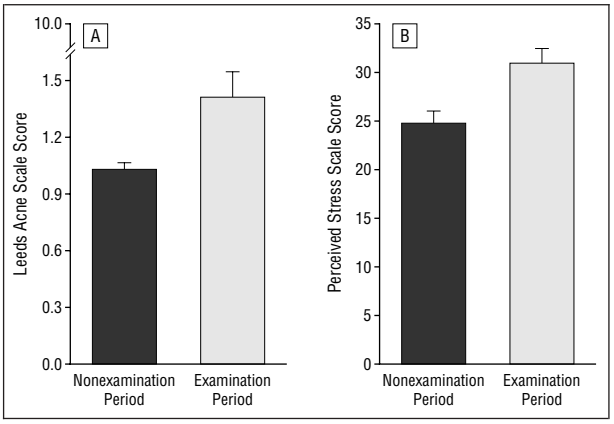

Figure 2. A, Leeds acne scale score. B, Perceived Stress Scale score. Data are given as mean+SEM during nonexamination and examination periods. The difference between the 2 periods was significant ($P<.01$) for A and B.

COMMENT

Acne vulgaris is a common inflammatory condition of the skin affecting more than 80% of teenagers and 25% of adults. One third of adults who have acne admit to feeling embarrassed or self-conscious because of their skin.[27] Despite the prevalence of this condition and considerable research, there is still much unsubstantiated myth surrounding the causes of acne. Specifically, stress is often cited as playing a role in acne flares, even though there is little research to support this claim. Although it is well-known that acne can be a source of significant stress and anxiety,[3,28] scientific evidence outside of anecdotal reports that stress itself may worsen acne has been lacking.

In this study, subjects who demonstrated the greatest increase in perceived stress during examinations also displayed the greatest exacerbation of acne severity in a proportional predictable manner. Although other changes occur in a student's life during examination periods that can potentially confound this study, the association between stress and worsened acne remained significant even after controlling for changes in diet and sleep habits. The calculated correlation coefficient of 0.61 suggests a convincing association, because this is well above the statistically accepted critical coefficient of 0.44 in a study with 20 subjects. More important, the primary investigator (A.C.) did not know the subjects' stress scores at the time of acne grading and, thus, could not predict whether they were more or less stressed.

To assess whether investigator bias may have affected the results of the study, we asked a board-certified dermatologist, blinded to examination period status, to grade randomized clinical photographs of the subjects. There was a discrepancy in grading between the clinical and photographic investigators for only 3 of 19 subjects, suggesting that investigator bias was unlikely a significant factor in affecting study results. Differences in grading may have been due to difficulty in detecting deep or noninflamed lesions on photographs or interrater variability.

It is possible that other factors not controlled for in our study, such as menstrual cycle or hormonal influence, facial hygiene, or picking and squeezing of acne lesions, may have contributed to the worsening of acne during examinations. None of the subjects reported acne flaring with their menstrual cycles. Furthermore, the investigator was trained to differentiate between truly worsened acne and manipulated skin, as picking generally results in acne excoriée, characterized by crusts and excoriations.

As in any study, finding a correlation between 2 variables does not necessarily mean a direct cause-and-effect relationship. It is certainly plausible that the correlation observed is in part due to worsened acne itself causing increased stress, instead of the reverse relationship. However, in a high-achieving population such as university students, subjects tended to report becoming less concerned with their appearance during examinations. Thus, it is more likely that increasing stress exacerbates acne instead of the reverse relationship.

Surprisingly, self-perceived worsening of diet quality was also associated with increased acne severity in this study. However, perceived diet quality was recorded in this study, not a quantifiable measure of the subjects' diets in terms of calories and grams of fat. Furthermore, the scale used to measure diet quality was not a previously validated tool like the Perceived Stress Scale or the Leeds acne scale. These results should, therefore, be interpreted with caution because the hypothesis that diet is an important factor in acne has been largely refuted in previous reports.[29,30]

Various mechanisms have been proposed for why stress may potentially aggravate acne vulgaris. Some investigators[31,32] believe that increased glucocorticoids and adrenal androgens, both hormones known to worsen acne

and possibly induce sebaceous hyperplasia, are released during periods of emotional stress. And corticotropin-releasing hormone, the body's coordinator in the stress response, was found to increase sebaceous lipogenesis and up-regulate sebocyte conversion of androgen precursors to testosterone.[33] There is also research[34,35] suggesting that stress-induced release of neuroactive substances within the epidermis can activate inflammatory processes in the skin. Recently, substance P, a neuropeptide elicited from peripheral nerves by stress, was shown to stimulate the proliferation of sebaceous glands and to up-regulate lipid synthesis in sebaceous cells.[36] Last, psychological stress, including examination stress, can slow wound healing by up to 40%,[37] which could be a factor in slowing the repair of acne lesions.

Just how significant a role stress plays in the pathogenic process of acne vulgaris is yet to be determined. The participants in this study are university students who may be under more stress than the general population. Men were also underrepresented in this study, making up only 37% of the participants. Furthermore, because the subjects studied had acne severities at the lower end of the Leeds acne scale, it is unclear whether the impact of stress will prove to be minimized with more severe forms of disease. On the other hand, the examination stress model studied herein may actually understate the true effects of stress on acne, because emotional conflicts, such as relationships and identity, may have an even greater impact on disease than external stressors like examinations.

Ultimately, the relationship between stress and acne is clinically relevant and worth exploration because possible behavioral interventions may become viable options for patients, as may therapeutic approaches that can be adjusted during times of known stressors.

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