The role of calcitonin gene-related peptide in the pathogenesis of acne vulgaris

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Background
Acne vulgaris (AV) is a persistent inflammatory skin condition most commonly affecting teenagers and young adults. AV pathogenesis is a multifactorial process in which inflammation plays a significant role. Calcitonin gene-related peptide (CGRP) is a neuropeptide that participates in inflammation and vasodilation. Emerging evidence suggests that CGRP may contribute to the pathophysiology of inflammatory skin conditions such as AV.
Objective
This study assesses CGRP serum levels in patients with AV and analyses its possible influence on acne severity.
Patients and methods
With the exclusion of patients receiving neurotropic drugs within the past year, patients who were undergoing any form of systemic medical treatment for acne for a minimum of 3 months before the beginning of the study, a case-control study was carried out, including 40 patients with AV and 40 apparently healthy controls matched by age and sex. Serum CGRP levels were estimated using enzyme-linked immunosorbent assay (ELISA) and correlated with acne severity based on standardized clinical grading.
Results
Patients with AV exhibited significantly higher serum CGRP levels than controls ($P<0.001$). Moreover, CGRP levels showed a positive correlation with acne severity.
Conclusion
Elevated CGRP levels in acne patients indicate that CGRP might play a role in the inflammatory processes underlying AV. Targeting CGRP could be explored as a potential therapeutic approach for acne management. Further research is warranted to elucidate the precise mechanisms involved.

Keywords:
acne vulgaris, calcitonin gene-related peptide, neurogenic inflammation, neuropeptide

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Introduction

Acne vulgaris (AV) represents a chronic dermatological condition that impacts more than 9.38% of the global population [1]. AV typically presents with papules, comedones, pustules, nodules, and scars, commonly occurring on the face, back, and chest [2]. Research has revealed that hyperkeratinization of follicular sebaceous ducts, overproduction of secretion, alterations in the composition of sebum, Propionibacterium acne proliferation in hair follicles, and inflammatory processes can contribute to AV [3]. Innate immune responses are triggered by substances that disrupt the pilosebaceous units' normal function. These compounds fall into two categories: (1) exogenous substances that come from the outside world, such as a diversity of microorganisms and their pathogenic byproducts, and (2) neuropeptides (NPs) produced by neuroendocrine cells, and particular lipid mediators from blood and sebum are among host-generated autoantigens. When NPs are recognized by their receptors, they trigger immunological responses. Nevertheless, there is a paucity of research on the roles of immunological responses mediated by NPs in AV [4].

Aim

The current investigation compared the level of serum calcitonin gene-related peptide (CGRP) among AV cases versus healthy control patients to find out the possible correlation with the severity of AV.

Patients and methods

Patients

The study involved 80 participants divided into two groups: group I, which included 40 patients with different severity grades of AV, and group II, which included 40 age-sex-matched apparently normal control patients.

Patients of both sexes with any stage of acne, aged between 15 and 35 years, and under only topical treatment were included in the study.

Patients undergoing any form of systemic treatment for acne for at least three months before the research or neurotropic drugs within the last year, as well as those with tar acne, occupational acne, and other types of acneiform eruptions; any disease affecting the nervous system or psychic condition (anxiety, major depressive, and mood disorders); and pregnant and lactating women were omitted.

All participants in the study underwent the following:

Detailed history including personal details (name, age, sex), the onset, progression, and duration of the disease, any family history of AV, and a record of previous treatments, both systemic and topical.

A comprehensive examination was done to exclude systemic diseases. Local examinations were conducted using the Hayashi scoring system to assess acne severity in patients [5]. Patients were categorized into three groups: group 1, which has mild AV; group 2, which has moderate acne lesions; and group 3, for those with severe and very severe acne lesions, by using Hayashi *et al.*'s [5] acne scoring system, which categorized acne depending on the number of inflammatory lesions on half of the face as 0–5 lesions are considered mild; 6–20 lesions are moderate; 21–50 lesions considered severe; and more than 50 are very severe.

Blood sampling: All participants were venipunctured under aseptic conditions, and a 2 ml peripheral venous blood sample was collected into a serum separator tube. Following clot development, the sample was centrifuged for 15 min at 2000 revolutions per minute (rpm), and the sera were separated and stored at −70°C in labeled sterile cryovials until analysis.

Following manufacturer directions, the enzyme-linked immunosorbent test (ELISA) approach (ELISA kit Catalogue No: DLR-CGRP-Hu and manufacturer: Develop) measured levels of CGRP.

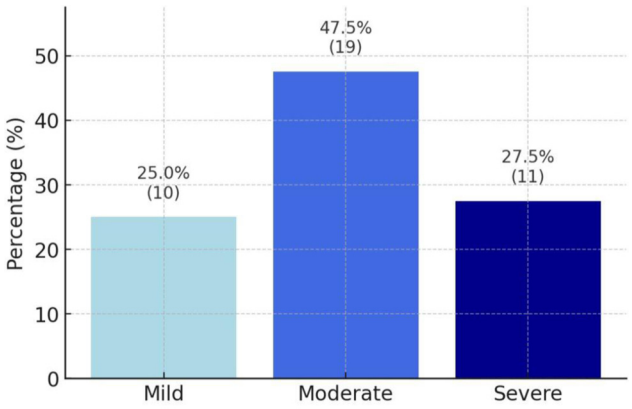
Statistical analysis

The data was updated, coded, tabulated, and subsequently presented on a personal computer utilizing the Statistical Package for Social Science (IBM Corp., 2017, IBM SPSS Statistics for Windows, Version 25.0, Armonk, New York, US: IBM Corporation). The normality of data distribution was tested using the Kolmogorov–Smirnov test. Parametric numerical data is represented by the mean and standard deviation (±SD), whereas nonparametric data is expressed using the median and range. The statistical relevance of the two research groups' variation was evaluated using the Student *t*-test. We utilized the Mann–Whitney *U* test to determine the association between two sets of quantitative variables. To better understand the relationship between several sets of quantitative variables, we employed Kruskal–Wallis's test or analysis of variance (ANOVA). The sensitivity and specificity of the quantitative diagnostic measure in distinguishing between the two groups were evaluated using receiver operating characteristic curve analysis. Fisher's exact and χ^2 tests identify correlations among the qualitative variables. If less than or equal to 0.05 at a 95% confidence interval, the *P* value is believed to be significant.

Results

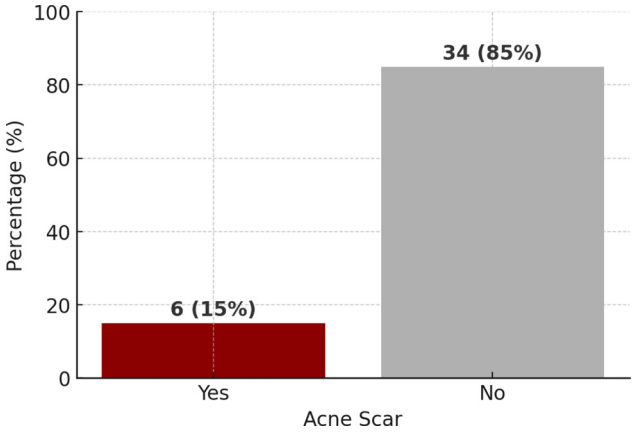
Regarding sociodemographic characteristics, cases of acne compared with the control group in terms of age, sex, marital status, smoking, and occupation showed no statistically significant difference. The severity of acne showed variation in the acne patient group. Most patients had moderate acne (n=19, 47.50%), followed by those who had mild acne (n=10, 25%), and only 11 (27.50%) patients had severe acne (Fig. 1). Acne scarring was observed in 30% of patients (n=12) (Fig. 2). The mean CGRP level in acne patients (728.033±412.212 pg/ml) was significantly higher than that observed in the control group (110.148 ±76.500 pg/ml) (P<0.001) (Table 1). Regarding the association between serum CGRP level and sociodemographic characteristics of the studied groups (age, sex, onset, marital status, premenstrual flare, previous acne treatment, family, and surgical history), no statistically significant difference was found (P>0.05). CGRP levels differed significantly across occupation groups (P<0.05), with 'has no job' having the highest levels. Also, there is a significant correlation between the serum level of CGRP and the severity of acne lesions (P<0.001) (Fig. 3) and the presence of acne scarring (P<0.05) (Fig. 4). At the

Figure 1



Distribution of acne severity.

Figure 2



The presence of acne scars.

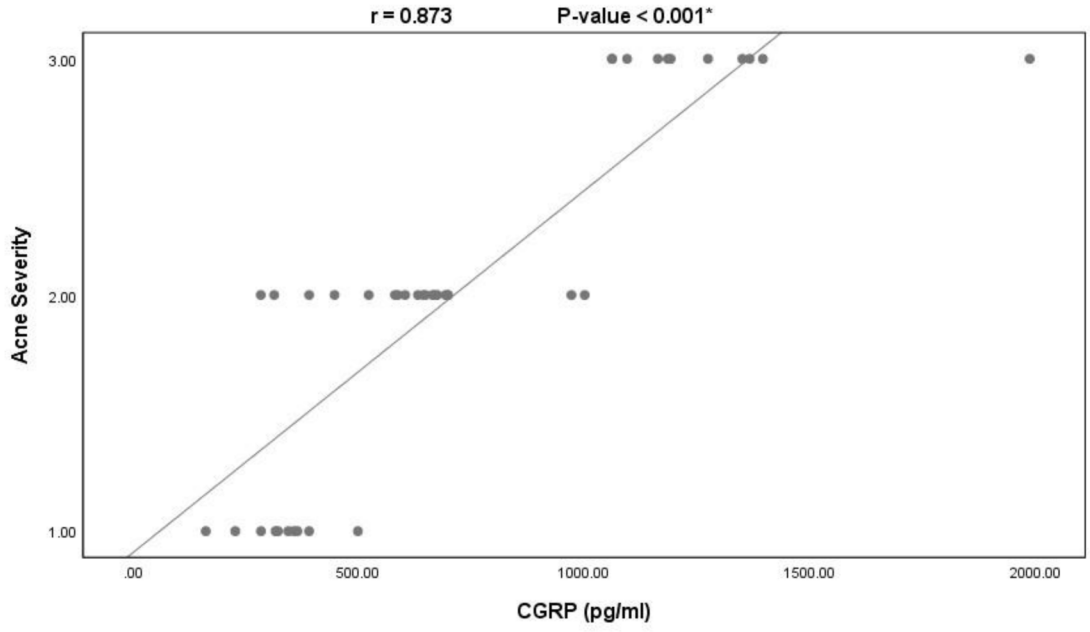
same time, there is a non-significant relation between serum level of CGRP in acne patients with associated diseases (vitiligo, polycystic ovary syndrome, hidradenitis suppurativa, and endometriosis) and BMI (underweight, average, overweight, and obese). Serum CGRP levels showed statistically significant differences depending on the lesion site, as the back and shoulder were elevated more than in the chest ($P<0.001$) (Table 2). Using the receiver operating characteristic curve can significantly determine patients with AV with a high specificity and sensitivity of 100 and 95%, respectively, when the cutoff value was greater than 270.19 pg/ml (Table 3) (Fig. 5).

Table 1 Comparison of serum calcitonin gene-related peptide levels in patient and control groups

	Group		*T*-Test	
CGRP (pg/ml)	Patient	Control	t	*P* value
Range	161.18–1988.03	9.7–270.19	9.321	<0.001*
Mean±SD	728.033±412.212	110.148±76.500		

*P less than 0.001, highly significant.

Figure 3



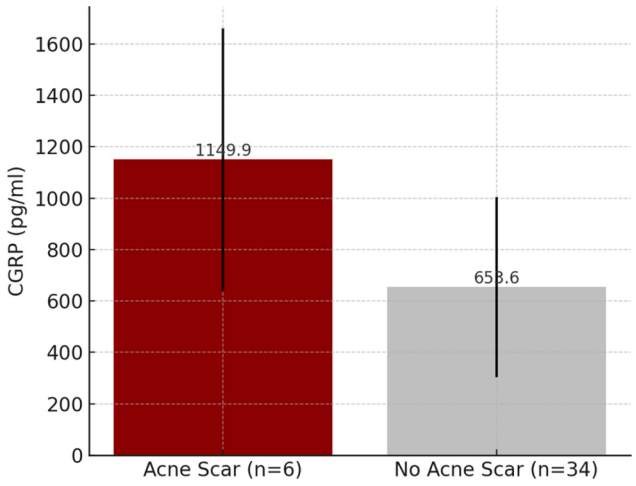
The scatter plot of calcitonin gene-related peptide levels and acne severity demonstrates a strong positive correlation (r=0.873, $P<0.001$).

Table 2 Serum calcitonin gene-related peptide levels in acne patients based on clinical data

	CGRP (pg/ml)		Statistical test	
Patient	n	Mean±SD		*P* value
Site back				
Yes	12	1066.557±423.524	*T*-Test	<0.001*
No	28	582.951±315.593		
Site chest				
Yes	6	925.245±350.788	*T*-Test	0.208
No	34	693.230±416.952		
Site shoulders				
Yes	1	1988.030±0.000	*T*-Test	0.001*
No	39	695.725±362.684		
Acne scar				
Yes	6	1149.915±511.328	ANOVA	0.005*
No	34	653.583±350.894		
Acne severity				
Mild	10	326.185±91.642		
Moderate	19	616.873±182.367	ANOVA	<0.001*
Severe	11	1285.351±261.987		

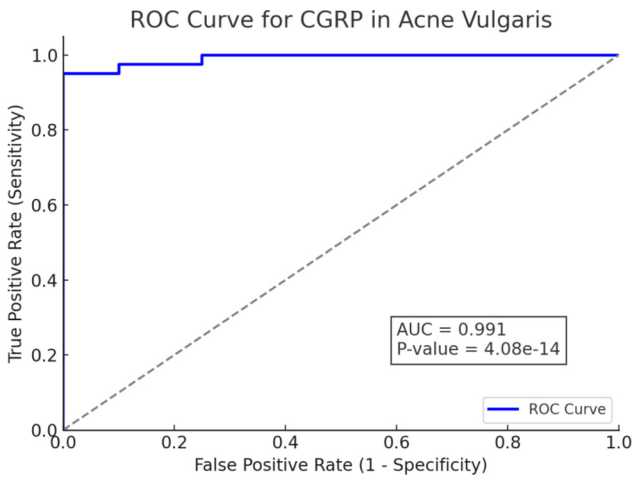
**P* less than 0.001, highly significant.

Figure 4



Comparison of calcitonin gene-related peptide levels in patients with and without acne scars.

Figure 5



Receiver operating characteristic curve for calcitonin gene-related peptide in Acne Vulgaris.

Discussion

Among the most researched NPs are substance P (SP), vasoactive intestinal peptide, CGRP, and α-melanocyte-stimulating hormone (α-MSH). They are generated by nerve cells and distributed mainly by tiny, myelinated A δ fibers (A δ mechanoheat receptors) and unmyelinated afferent neurons (C fibers, such as C-polymodal nociceptors). These NPs play critical roles in modulating various physiological responses, including pain transmission, vasodilation, and immune responses, and are key players in the neurogenic inflammation observed in various conditions, including acne [6,7]; nevertheless, the majority of these can be produced and distributed by cutaneous cells [8]. Designed from the alternate RNA processing of the calcitonin gene, CGRP comprises 37 amino acids. Two variants of CGRP are α-CGRP (CGRP I) and β-CGRP (CGRP II). There are two unique genes in humans [9]. The calcitonin (CALC) I gene provides either calcitonin or α-CGRP through alternative splicing, while a separate CALC II gene yields β-CGRP [10,11]. α-CGRP exhibits greater abundance in certain central and peripheral nervous system areas. β-CGRP is predominantly located in the gastrointestinal tract, enteric nerves, and the pituitary gland [9,12,13]. Secreted by cutaneous sensory nerve fibers, CGRP drives monocyte and leukocyte adherence to endothelial cells. It also initiates the production of proinflammatory cytokines from mast cells, including Interleukin 8 (IL-8) and tumor necrosis factor-α [8].

People who suffer from mental stress or endocrine dyscrasia frequently have worsening AV. This emphasizes the connection between the neuroendocrine system and acne [4]. Connections among neuroendocrine and immunological systems

Table 3 Diagnostic performance of serum levels of calcitonin gene-related peptide in differentiating acne patients from controls

	Receiver operating characteristic curve between the patient and the control					
	Cutoff	Sensitivity	Specificity	Positive predictive value (PPV)	Negative predictive value (NPV)	Accuracy (%)
CGRP (pg/ml)	>270.19	95.00	100.00	100.0	95.2	99.1

were delineated. 'Neuroinflammation,' a mechanism regulated by NPs, plays an essential role in controlling regional immune inflammation, which is at the fundamentals of many skin disorders [8]. Obligate immune cells, including mast cells, Langerhans cells, and macrophages, along with nonobligate immune cells such as sebocytes, melanocytes, endothelial cells, and keratinocytes, have been identified as targets of neuropeptides within the cutaneous immune system [7,14]. However, limited studies have described NPs' direct action on acne's immune response [4]. Toyoda *et al.* [15] reported comparable differences in expression of various NPs within the sebaceous glands in acne-prone versus normal facial skin. Leslei *et al.* [16] investigated how remote inflammation affected the expression of primary sensory neurons of the neuropeptides substance P (SP) and CGRP. They discovered that overexpression of SP and CGRP could result from the synthesis of neurally active inflammatory mediators or neurotrophins in the periphery and could thus represent a potential feedback mechanism wherein inflammation enhances the elements causing neurogenic inflammation.

The present study comprises 40 patients with AV and 40 age-sex-matched apparently normal control patients. In the current investigation, serum CGRP levels were significantly higher in the patient group compared with the control group. In terms of the relationship between CGRP levels and AV severity, serum CGRP levels were significantly greater in severe cases compared with mild and moderate cases. Furthermore, a substantial positive association was found between the CGRP level and acne severity. Additionally, the level of CGRP can indicate acne severity. When the CGRP level is greater than 270.19 pg/ml, we can predict the chance of getting severe acne with 95% sensitivity and 100% specificity. Unlike our investigation, Wienholtz *et al.* [17] showed raised levels of CGRP in plasma in patients with all subtypes of rosacea; they did not find any variation in subtypes or degree of rosacea. Our study provides a novel correlation between serum neuropeptide CGRP and AV pathogenesis. CGRP increases in other diseases, such as migraine. Thang *et al.* [18] found that patients with migraine treated with CGRP inhibitor monoclonal antibodies matched those treated with triptans. CGRP inhibitor monoclonal antibodie exposure was associated with a statistically significant decrease in the rate of acne and rosacea over 1 year. Given that CGRP-mediated neurogenic inflammation may contribute to acne and development, CGRP inhibition could represent a novel treatment modality for these conditions.

Conclusion

The elevated serum CGRP levels observed in acne patients in this study indicate that CGRP may be involved in the inflammatory processes that underlie AV. Targeting CGRP signaling could be explored as a potential therapeutic approach for acne management. Further research is warranted to elucidate the precise mechanisms involved.

Acknowledgments

Declarations

Availability of data and materials: Data and materials will be available after approval for publication of the study and upon request.

Author contribution: Every author participated in drafting the manuscript and its critical review, and they approved the final submission version.

Patient consent for publication: Irrelevant.

Ethical consideration: Before participation, informed consent was acquired from all patients or their parents if they were less than 18 years old. The consent comprised information on the objective of the work, research design, site, time, techniques, and confidentiality. This study followed Good Clinical Practice principles, Declaration of Helsinki provisions, and applicable regulations. It was approved by the Dermatology, Venereology & Andrology Department and the Research Ethics Committee of Benha Faculty of Medicine (Ms 6-8-2024).

Conflicts of interest

There are no conflicts of interest.

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