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Evaluation of Serum Level of Neprilysin in Patients with Acne Vulgaris

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Abstract

Background: Acne vulgaris (AV) is a sebaceous gland condition caused by a wide variety of underlying causes. A major contributor to this illness is the body's abnormal and too abundant production of sebum. Overactive sebaceous glands or increased sensitivity to normal levels of androgen hormones are the root causes of sebum production. Neurocutaneous nerves express the newly discovered zinc-dependent neuropeptide NEP (NEP). Multiple unpleasant stimuli, both internal and external, have been linked to this expression. Allergy contact dermatitis, atopic dermatitis, psoriasis, and atopic vitiligo (AV) all have a common pathogenetic factor: neuropeptides.Aim: to determine how serum NEP levels in acne vulgaris patients relate to overall health and well-being (HRQoL).Subjects and Methods:Fifty patients with acne vulgaris and fifty controls of similar age and gender participated in this case-control study. Between February 2022 and July 2022, they were scouted from the outpatient clinic of the Dermatology, Venereology, and Andrology Department at Benha University Hospitals. The blood NEP concentration was measured using a commercially available, research-use only Enzyme-Linked Immunosorbent Assay (ELISA) kit for human neprilysin. All patients' HRQoL was evaluated with the use of the dermatological life quality index (DLQI).Results: There was no statistically significant difference in age, sex, or body mass index between the patients and the control group. Acne vulgaris patients had a substantially elevated serum NEP level compared to controls. Patients with mild acne had lower serum NEP levels than those with severe acne. Using ROC analysis, we find that NEP may be a predictor of acne vulgaris. There was a link between NEP and HRQoL.Conclusion: Patients with AV had considerably greater serum NEP levels compared to controls. Acne vulgaris patients may experience a decline in quality of life due to this increase. To verify these findings, larger-scale investigations are required.

Keywords: Neprilysin, DLQI and Acne Vulgaris.

1. Introduction

In particular, acne vulgaris (AV) affects more teenagers and young adults than any other chronic skin condition does [1]. Acne is not fatal, but it may cause severe physical and mental complications such as scars, low self-esteem, melancholy, and anxiety [2].

Interactions between hormones, microbes, and the immune system all play a role in AV's complicated pathophysiology. Increased sensitivity of the sebaceous gland to normal amounts of androgen hormones, or an overabundance of these hormones, are the root causes of sebum overproduction [3]. At every point in the development of acne, the inflammatory response is activated. Acne 4 may have a hereditary component as well.

Excessive inflammation of the pilosebaceous units and the surrounding skin is a hallmark of acne vulgaris. Cutibacterium acnes (C.acnes) interacts with keratinocytes, sebocytes, and tissue macrophages to contribute to its development. Bacteria cause 5 because they secrete lipase, hyaluronidase, and proteases and activate immune cells.

When a person has acne, it may have a negative impact on their HRQoL in every area of their lives, including their emotions, relationships, hobbies, and ability to find work.

Cell surface neprilysin (NEP) (94 kDa) is a zinc metalloproteinase that cleaves substrates endoproteolytically just before the 7th hydrophobic amino acid residue. NEP is expressed in the dermis, the keratinocytes, the dermal fibroblasts, and the skin's vascular endothelial cells (ECs) [8].

Neuropeptide mediators are produced by sensory neurons, immune cells, and skin cells in response to either endogenous or external unpleasant stimuli, and neprilysin has been shown to regulate the bioavailability of these mediators [9].

There may be a neurogenic component to the early phases of lesion formation in acne, since changes in the expression of neuropeptides have been discovered during this time period. There is mounting evidence that inflammation plays a role in microcomedogenesis, including an increased production of pro-inflammatory mediators and neuropeptides.

One of the primary pathogenetic facts in several dermatoses, including allergic contact dermatitis, atopic dermatitis, and psoriasis [11], is the presence of neuropeptides.

Therefore, the purpose of this research was to evaluate the serum NEP level and its association with HRQoL in patients with AV.

2. Subjects and Methods

This case-control study was conducted on fifty patients complaining of acne vulgaris and fifty healthy volunteers age and gender matched as a control group. They were recruited from outpatient clinic of Dermatology, Venereology and Andrology Department of Benha University Hospitals, during the period from February 2022 to July 2022.

Ethical approval was obtained from the ethics committee on research involving human subjects of Benha faculty of Medicine(Ms 7.1.2022). Informed consents were obtained from all participants.

Patients with AV more than 6 months duration, older than 18 years, with moderate and severe acne were included in this study.

Participants who receiving chemotherapy, with thyroid disorders, chronic renal, liver diseases or CNS disorder, others dermatological disorders, polycystic ovary syndrome (PCOs), pregnant and lactating women were excluded.

Patients with AV were subjected todetailed history taking, general and local examination. All patients were examined to acne vulgaris severity according to the global acne grading scale (GAGS).Patients' quality of life was evaluated by the DLQI questionnaire. The scoring of each question is as the following: very much=3, a lot =2, a little=1, not at all=0, question unanswered=0, question 7: "prevented work or studying"=3.

The DLQI is calculated by summing the scores of all questions resulting in a maximum of 30 and a minimum of 0. The higher the score, the more the impairment in the quality of life.

Interpretation of DLQI Scores; 0-1 = no effect at all on patient's life, 2-5 = small effect, 6-10 = moderate effect, 11-20 = very large effect, 21-30= extremely large effect [12].

Venous blood samples (5 ml) were taken from patients and control groups to determine the level of serum Neprilysin.A commercial human serum Neprilysin ELISA kit for research use only (Cat #: DZE201124340, HuTai Road, Baoshan District, Shanghai, China). Double antibody sandwich ELISA technique (Enzyme-Linked Immunosorbent Assay) was used to detect serum level of Neprilysin.

Statistical Analysis

The data was managed and analysed using SPSS version 25. (IBM; Armonk, New York; USA). The Kolmogorov-Smirnov test (for cases), the Shapiro-Wilk test (for controls), and direct data visualisation techniques were used to check the normality of the quantitative data (for both). Means and standard deviations were calculated for numerical data in accordance with the assumption of normality. Numbers and percentages were used to summarise the categorical information. The independent t-test was used to compare quantitative data from each research group. Chi-square analysis was used to compare categorical variables. The examined markers were subjected to ROC analysis. For each marker, we determined its area under the curve (AUC) and 95% confidence interval (CI), optimal cut-off point, and diagnostic indices. Pearson's correlation was used to find relationships between variables. We determined the odds ratio and the accompanying 95% confidence interval. There were no one-sided statistical analyses. P values below 0.05 were used to indicate statistical significance.

3. Results

The patients and control groups showed a non-significant difference as regards age, sex and body mass index (BMI) **Table (1)**.

The mean disease duration of the patients was 4.16 ± 2.45 years. Acne severity was assessed by GAGS score with mean equal 27.04 ± 4.33. The percentage of positive family history was 72% and percentage of patients with scars was 60%.

Table (1): General characteristics in patients and control groups.

		Patients (n = 50)	Controls (n = 50)	P
Age (years)	Mean ±SD	21.92±2.88	23.22±4.05	0.07
Sex	Females n (%)	32 (64%)	23 (46%)	0.07
	Males n (%)	18 (34%)	27 (54%)	
Body Mass Index	Mean ±SD	24.75±3.37	24.18±3.59	0.4

*Independent t-test was used for age and BMI. Chi-square test was used for sex
The serum NEP level was significantly higher in patients of AV than the control group (P <0.001) Table (2).

Table (2): Comparison between the study groups regarding Neprilysin.

	Patients		Control		P
	Mean	SD	Mean	SD	
Neprilysin (ng/ml)	1605.54	1817.15	672.42	218.4	<0.001

There was an increase in serum NEP in patients with positive family history of acne compared to those without family history but not statistically significant (P =0.5). There was no significant difference between patients with or without acne scarring regarding NEPlevel (P =0.1). The serum NEPlevel was significantly higher in patients with moderate than severe acne (P = 0.03).

The patients with moderate acne had significantly lower DLQI than those with severe acne. Patients with moderate acne group had higher serum NEP level than patients with severe acne Table (3).

Table (3): Impact of different acne grades on QoL.``

	Moderate	Severe	p value
DLQI	9.7 ± 3.1	7.8 ± 2.1	0.0005
NEP level	1755.43±2058.53	1130.88 ±363.37	0.03

The results shows that the serum Neprilysin level was not statistically correlated with age, age of onset, duration, BMI and GAGS.

The results shows that regarding the univariate logistic regression analysis of various variables for prediction of acne vulgaris, the serum Neprilysin level was a significant predictor of acne vulgaris (P < 0.001).

The results shows that according to the ROC curve analysis, the Neprilysin level cut-off value of 922.5 ng/mL could be predictive of acne vulgaris with 86% sensitivity and 84% specificity (AUC, 0.93 and 95% CI, 0.88-0.98).

4. Discussion

Increased androgens cause abnormal hyperkeratinization of the pilosebaceous duct, leading to comedo formation; increased androgens also cause an increase in sebum production from the enlarged sebaceous gland; bacteria, most commonly C.acnes, colonise and proliferate within the duct; and, finally, an inflammatory response is triggered by the immunological activity of C.acnes 13.

Neprilysin was the first mammalian zinc-activated endopeptidase to be found, placing it in the protease family. NEP can metabolise neurotransmitters, convert endothelin, and break down insulin. It has structural similarities with both the brain enzyme encephalinase and the lymphocyte marker CALLNA11.

The significance of serum NEP in AV patients has not been investigated before. The present study found that serum NEP levels were significantly higher in AV patients compared to the control group (P 0.001).

It's possible that androgens have a role in the development of acne, which might explain this increase. Androgens were shown to increase brain expression of Neprilysin in mature male rats. NEP expression was shown to be elevated by dihydrotestosterone (DHT) over a period of time. DHT has a mediating role in the upregulation of NEP expression and the downregulation of A. In addition, androgen receptor (AR) antagonists may reduce NEP via acting on beta-amyloid protein 14.

All analysed acne patient tissues showed that NEP was substantially expressed in the sebaceous glands. Acne sufferers and controls also differed significantly (P 0.0001) in the ratio of NEP-positive sebaceous acini to total acini. Substance P is secreted endogenously by dermal nerve fibres around sebaceous glands, and this triggers NEP induction in sebaceous cells. This adds to our understanding of how the cutaneous nerve system contributes to the pathophysiology of acne 15 and may have a role in the control of sebaceous gland activity.

Patients with mild acne had a greater serum NEP level than those with severe acne (P = 0.03).

Patients who place a high value on their looks are particularly vulnerable to the psychological effects of the condition, even in its mildest form 16.

Researchers have hypothesised that acne's emotional toll is comparable to that of other chronic conditions like asthma, epilepsy, diabetes, or arthritis.

Although even minor acne may have a major effect on a patient's HRQoL, 17.

Serum levels of NEP were also shown to be elevated in patients with PCOS and other acne-related conditions. Previous research has looked at the correlation between plasma NEP and endocrine metabolic features in PCOS patients. When comparing the PCOS group to the control group, they discovered that the PCOS group had substantially higher plasma NEP levels (P = 0.027). There was no association between plasma NEP levels and body mass index, waist size, or hip size.

Acne is more common in those with hyperandrogenism, which includes conditions like PCOS.

Acne is linked to increasing levels of the hormone dehydroepiandrosterone sulphate (DHEA-S) in premenstrual females, and greater premenstrual DHEA-S levels may be an indicator of more severe acne later in adolescence. In a subgroup of PCOS 20 individuals, elevated DHEA-S is also correlated with clinical acne.

Serum NEP level was not connected with age, onset age, duration, body mass index, or glycemic index in this investigation (P = 0.378, 0.164, 0.890, 0.412, and 0.816).

Our findings are consistent with those of a recent study that looked at how gender and body mass index related to soluble neprilysin (sNEP) and readmissions for HF patients. They discovered that there was no difference in median sNEP across genders (P = 0.377) or body mass index (BMI) (P = 0.560) 21.

Previous research has examined the effects of acne on HRQoL by focusing on the intensity and location of acne lesions. Nearly half of those who reported minor facial and truncal acne also had a negative effect on HRQoL, proving that even moderate acne may be troublesome (6, 22).

When many factors were analysed using univariate logistic regression, serum NEP level emerged as a significant predictor of acne vulgaris (P 0.001). The ROC analysis showed that a NEP cutoff value of 922.5ng/mL was sensitive to diagnose acne vulgaris 86% of the time and specific enough to diagnose it 84% of the time (AUC, 0.93 and 95 percent CI, 0.88-0.98).

The current research has several limitations, including a lack of assaying NEP in acne lesions locally, a limited sample size, and a lack of monitoring changes in serum NEP level in response to various treatment methods. To the best of our knowledge, however, this is the first investigation into the effect of serum NEP levels in acne sufferers.

In conclusion, individuals with acne vulgaris had noticeably elevated serum NEP levels. Acne vulgaris patients may experience a decline in quality of life due to this increase. To verify these findings, larger-scale investigations are required.

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