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ORIGINAL CONTRIBUTION

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Lesional and circulating levels of interleukin-17 and 25-hydroxycholecalciferol in active acne vulgaris: Correlation to disease severity

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Summary

Objectives: The immunological aspects of inflammatory acne are still incompletely understood, so this study aimed to investigate the possible role of IL-17 and 25 hydroxycholecalciferol (25(OH)D3) in the disease pathogenesis and progression.

Materials and Methods: Across-sectional study has been conducted on 135 patients with active acne vulgaris of various severities and 150 matched controls. ELISA assays of serum and tissue levels of IL-17 and 25(OH)D3, also immunohistochemical and Western blotting demonstration of the expression patterns of lesional IL-17 in comparison with control group, were performed.

Results: The mean serum levels of IL-17 were 544.2 pg/mL ± 477.4 SD and 42.2 pg/mL ± 8.1 SD for acne patients and controls, respectively, with significantly higher levels among the patient group ($P < 0.05$). Higher IL-17 expression levels in active acne lesions when compared with its level in healthy skin of the controls. The mean serum levels of 25(OH)D3 among patients and controls were 33.3 ng/mL ± 9.7 SD and 51.7 ng/mL ± 2.7 SD, respectively, with significantly lower levels among the patient group ($P < 0.05$). There were significantly negative correlations between IL-17 and 25(OH)D3 levels ($P < 0.001$ for both).

Conclusions: Deficiency of vitamin D3 accompanied with higher IL-17 in an inverse pattern may have a possible role in active acne vulgaris.

KEYWORDS

25(OH)D3, acne, ELISA, IL-17, immunohistochemistry, Western blot

1 | INTRODUCTION

Acne vulgaris is one of the commonest dermatological disorders by which millions of people are affected worldwide. An important pathological hallmark is the immune-mediated inflammatory response caused by Propionibacterium acnes (*P.* acnes), the implicated microorganism in acne.[1] CD4+T helper cells' (Th-17) dysregulation induces various inflammatory disorders including acne and linked to many bacterial resistances, via its signature cytokine, IL-17.[2–4]

25-hydroxyvitamin D3 (25(OH)D3, calcidiol), the major circulating form of vitamin D3, plays an important role in the formation of skin barrier via regulating the long chain glycosylceramides processing.[5–7] Also, 25(OH)D3 has a role in skin innate immunity through induction of Toll-like receptor 2 (TLR2) and its coreceptor cluster of

differentiation 14 (CD14),[5–7] resulting in activated cathelicidin induced death of the invasive microorganisms.[7,8] It is demonstrated that vitamin D and its binding receptor highly expressed in sebaceous glands,[9] and as well-known that, sebum overproduction, altered lipid composition and oxidative stress of the skin surface lipids are among the most important pathological consequences contributing to acne development,[3] Vitamin D has been also reported in vitro that it cause dose-dependent modification in the proliferation, regulation of cell cycle and lipid content of the sebaceous glands.[10]

Based on the literature, this study was undertaken to investigate the immune-inflammatory interplay mechanism of 25(OH)D3 and IL-17 in the pathogenesis of active acne vulgaris and also to assess the correlation between both biomarkers to each other on one side and to the disease severity on the other side.

2 | MATERIALS AND METHODS

2.1 | Study population

This case-control, hospital-based study has been conducted on 135 patients with active acne vulgaris of various severities, selected from those attending the Dermatology outpatient clinics-Sohag University Hospital-Upper Egypt. Acne severity was graded, using the Global Acne Grading Scale (GAGS). This grading scale assesses the acne severity through combing the type of acne lesions (papules, pustules, comedones and nodules) and their anatomic sites (forehead, cheeks, nose, chin and back). The GAGS score ranges from 0 (no acne), 1-18 (mild acne), 19-30 (moderate acne), 31-38 (severe acne) to ≥39 (very severe acne).[11] Acne patients who are pregnant or lactating females, cigarette smoking or have any systemic disease, or received any topical or systemic treatment including steroids or calcium or vitamin D supplementation for the last 3 months, were excluded from the study. In addition to 150 healthy volunteers, age, body mass index, and sex matched constituted the control group. Prior to initiation of the study, every included subject was informed about the aim of the study and a written consent was obtained. The study period was from April 1st, 2016 to March 31st, 2017.

2.2 | Laboratory workup

2.2.1 | Blood samples

Five milliliters venous blood was drawn from every included subject, using gel separator tubes, centrifuged at 822 *g* for 15 minutes, and the separated sera were divided into aliquots using 1-ml cryotubes and stored at −200°C till the time of the biochemical analysis of serum IL-17 and 25(OH)D3, using commercially available ELISA assay kits supplied by Chongqing Biospes Co., Ltd, Chongqing, China (Catalog No. BEK1123 for IL-17 and BYEK1472 for 25(OH)D3). The measurements were taken using ELISA multiskan EX micro-plate-photometer (STAT FAX-2100; Thermo Scientific, Palm City, FL, USA). According to the level of 25-OHD, vitamin D deficiency was defined as a 25-OHD level of ≤20 ng/mL and vitamin D insufficiency as 21-29 ng/mL, and normal level as ≥30 ng/mL.[12]

2.2.2 | Lesional skin biopsies

Following local anesthesia using lidocaine 2%, skin punch biopsies were taken from the acne lesions of the included patients and healthy skin of the control group, divided into two parts:

1. The first part of the biopsy was homogenized using lysis buffer (Tris-HCl), pH 7.4 in ice-cold. The buffer contains 1% protease inhibitor cocktail (Cell Signaling Technology, Inc, Danvers, MA, USA). The homogenization process was performed using Potter-Elvehjem rotor-stator homogenizer (glass/teflon homogenizer), and then, homogenates were stored frozen at −80°C for later biochemical and molecular assays in the form of:
   - **a** ELISA determination of tissue 25(OH)D3 and IL-17 levels, using the previously mentioned ELISA assay kits, in the supernatants obtained after centrifugation of the homogenates at 822 *g* for 20 minutes.
   - **b** Western blotting assessment of lesional IL-17 expression[13]: Denaturation of the proteins in each corresponding sample was achieved at 95°C for 5 minutes in 2× Laemmli buffer. Subsequently, 5% 2-mercaptoethanol was added. SDS-PAGE electrophoresis was performed by loading 50 µg protein per lane at 75 volts through 18% resolving gel, followed using a 125 volts within 2-hour duration, then transferred into a PVDF membrane, where T-77 ECL semidry transfer unit was used for 2-hour duration (Amersham BioSciences UK Ltd., Santa Cruz, CA, USA). Then the PVDF membrane was incubated, for immunoblotting, in TBS buffer containing 0.1% Tween and 5% skimmed milk for 1 hour at 4°C, followed by overnight incubation at 4°C with rabbit anti-IL-17 polyclonal antibody (supplied by Biospes Co., Ltd.) at a dilution of 1:500. After being washed three times with TBST buffer, incubation of each membrane for 1 hour at room temperature with an alkaline phosphatase-conjugated goat anti-mouse secondary antibody (supplied by Novus Biologicals, LLC, Littleton, CO, USA) was carried out at a dilution of 1:5000. A commercially available BCIP/NBT substrate detection kit (supplied by Genemed Biotechnologies, Inc, South San Francisco, CA, USA) was used for detection of membrane-bound antibody after being washed five times in TBST. Equivalent protein loading for each lane was confirmed by stripping and reblotting each membrane at 4°C against mouse monoclonal anti–β-actin antibody (supplied by Santa Cruz Biotechnology, Inc, Santa Cruz, CA, USA) at a dilution of 1:5000. Repeated analysis was performed to assure reproducibility of results.
2. The second part of the biopsy was washed with saline and fixed in 10% formaldehyde for histopathological examination. Specimens were dehydrated in ascending grades of alcohol, cleared in three changes in methyl benzoate, impregnated and embedded in paraplast, sectioned at 5 µm using Leica microtome (Nussloch,

Germany), and stained with Harris hematoxylin and eosin according to Drury and Wallington.[14] Some paraffin sections were picked upon positive slides for the immunohistochemical study, which was done using the anti-IL17 antibody (human Polyclonal Anti-IL-17 supplied by Chongqing Biospes Co., Ltd, with catalog No. YPA1374), according to our protocol prescribed in a previously published work.[15]

2.3 | Statistical analysis

Data were analyzed using SPSS computer program version 22.0 (Armonk, NY, USA). Quantitative data were expressed as means ± standard deviation. The data were tested for normality using Shapiro-Wilk test. The nonparametric Mann-Whitney test and Kruskal-Wallis test were used for data which not normally distributed. Independent samples *t* test was used for normally distributed data. Spearman's correlation was used for testing of correlation between different quantitative variables. Chi-square test was used for comparison between qualitative variables. A 5% level was chosen as a level of significance in all statistical tests used in the study.

3 | RESULTS

3.1 | Baseline characteristics of the included patients

This study has been conducted on 135 patients with active acne (54 males and 81 females) with their mean age 21.04 ± 2.8 SD years old and 150 controls (78 males and 72 female) with their mean age 23.1 ± 4.6 SD years old, with nonsignificant differences between the two groups indicating age and sex matching. Also, there was nonsignificant difference as regards the body mass index (BMI) between the two groups (24.5 ± 4.8 and 25.7 ± 6.1, respectively). According to the acne severity using the (GAGS), the included patients were divided into three subgroups: mild acne (n = 45), moderate acne (n = 45), and severe acne (n = 45).

3.2 | Serum and tissue levels of IL-17 among the studied groups

The mean serum levels of IL-17 (pg/mL), using ELISA assays, among patients and controls were 544.2 ± 477.4 SD and 42.2 ± 8.1 SD, respectively, with significantly higher levels among the patient group. There were significant increasing IL-17 serum levels with increasing acne severity (Table 1). The mean lesional homogenate levels of IL-17 (pg/mg tissue protein), using ELISA assays, among patients and controls were 0.8 ± 0.7 SD and 0.16 ± 0.02 SD, respectively, with significantly higher levels among the patient group. There were significant increasing IL-17 lesional homogenate levels with increasing acne severity (0.23 ± 0.08, 0.44 ± 0.08 and 1.7 ± 0.28) in patients with mild, moderate, and severe acne, respectively (Table 1). There were higher IL-17 lesional expression levels among patients with moderate and severe acne vs mild acne and the controls when using Western blotting (Figure 1). Also, there was immune positivity of the membrane of epidermal degenerative cells to anti-IL17 antibody, which was directly related to the acne severity with appearance of immune-reactive lymphocytes to anti-IL17 antibody in the dermis that increased with increased acne severity (Figure 2).

3.3 | Serum and tissue levels of 25(OH)D3 among the studied groups

The mean serum levels of 25(OH)D3 (ng/mL), using ELISA assays, among patients and controls were 33.3 ± 9.7 SD and 51.7 ± 2.7 SD, respectively, with significantly lower levels among the patient group and with increasing acne severity (Table 1). There was higher frequency of 25(OH)D3 insufficiency and deficiency among patients with severe acne (22% and 11%, respectively), while those with mild and moderate acne revealed normal 25(OH)D3 status (66%) according to the reference range, although they had significantly lower levels when compared with the controls.The mean lesional homogenate levels of 25(OH)D3 (ng/mg tissue protein), using ELISA assays, among patients and controls were 0.09 ± 0.1 SD and 0.12 ± 0.05 SD, respectively, with significantly lower levels among the patient group. There were significant decreasing 25(OH)D3 lesional homogenate levels with increased acne severity (Table 1).

3.4 | Correlations between IL-17 and 25(OH)D3 with each other

There were significantly negative correlations between serum and tissue levels of IL-17 vs serum and tissue levels of 25(OH)D3 ($r = -0.918$, -0.724, respectively, $P < 0.001$ for both; Figures 3 and 4).

TABLE 1 Comparison of the mean ± SD of the serum and tissue IL17 and 25(OH)D3 levels between the studied groups

Measured biomarkers	Patients, Mean ± SD (n = 135)				Controls, Mean ± SD (n = 150)	*P*-value
	Total (n = 135)	Mild (n = 45)	Moderate (n = 45)	Severe (n = 45)		
Serum IL17 (pg/mL)	544.2 ± 477.4	95.2 ± 25.4	357.9 ± 125.7	1179.5 ± 120.4	42.2 ± 8.1	0.000*
Tissue IL17 (pg/mg tissue proteins)	0.8 ± 0.7	0.23 ± 0.08	0.44 ± 0.08	1.7 ± 0.28	0.16 ± 0.02	0.000*
Serum 25(OH)D3 (ng/mL)	33.3 ± 9.7	43.6 ± 2.2	35.5 ± 2.2	20.9 ± 1.5	51.7 ± 2.7	0.000*
Tissue 25(OH)D3 (ng/mg tissue proteins)	0.09 ± 0.1	0.08 ± 0.009	0.16 ± 0.22	0.02 ± 0.007	0.12 ± 0.05	0.000*

*Statistically significant ($P < 0.05$).

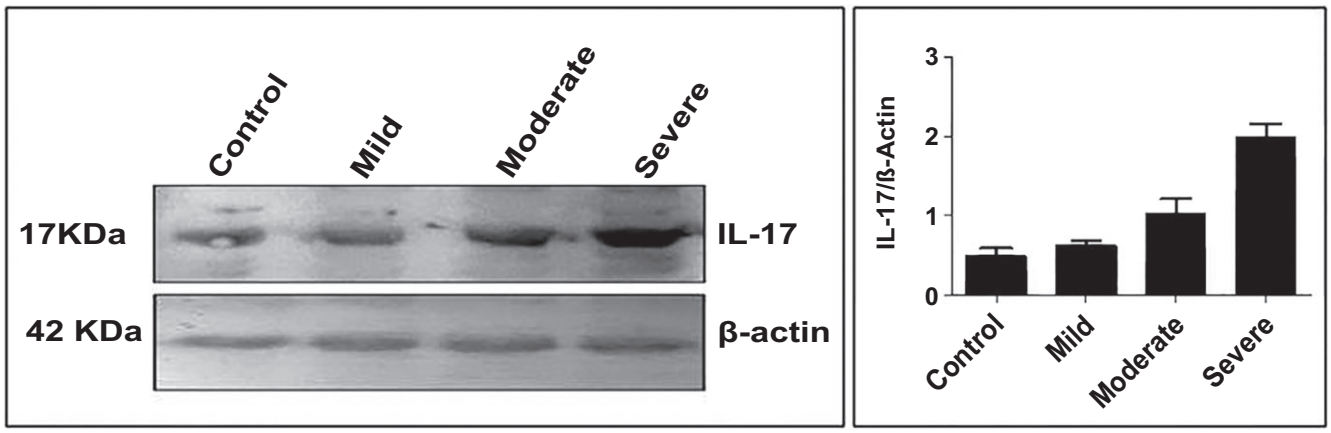

FIGURE 1 Lesional IL-17 expression in patients with active acne and the control group using Western blotting technique, showing higher expression levels of IL-17 in moderate and severe acne when compared with mild acne and the controls

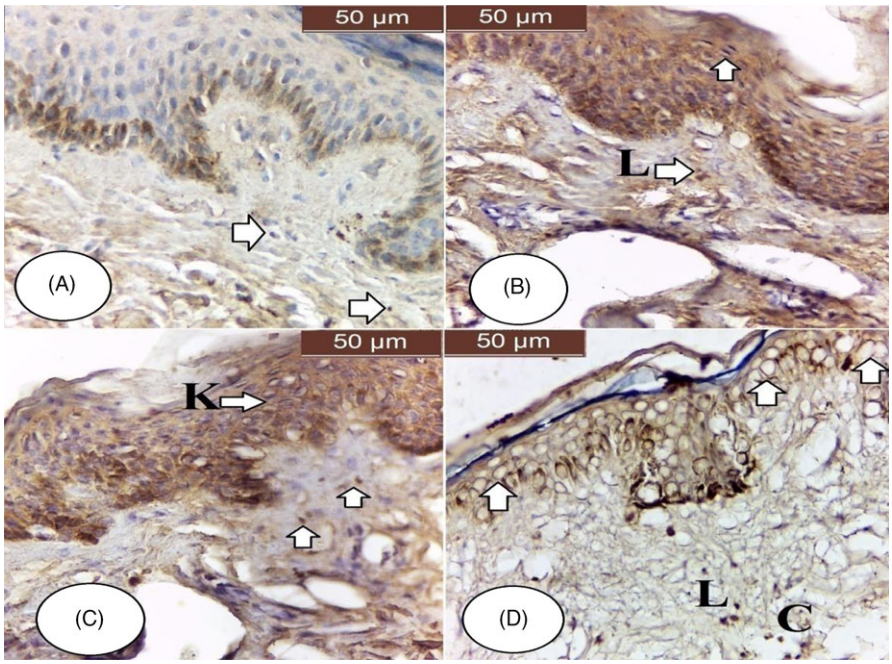

FIGURE 2 Immunohistochemical assessment of lesional IL-17 expression in patients with active acne and the control group: A (control), No obvious immune positivity is detected. Small lymphocytes (arrows) in the dermis are immune negative. B (mild acne), Few keratinocytes appear to have a thin well delineated immune-positive membrane (arrow). Immune-positive lymphocytes (L) are observed in the dermis. C (moderate acne), Some keratinocytes appear to have a thin well delineated immune-positive membrane (K). Immune-positive lymphocytes (arrows) are observed in the dermis. D (severe acne), shows that almost all keratinocytes have a dark brown immune-positive membrane. Many immune-positive lymphocytes (L) are scattered in the dermis mainly around and inside a blood capillary (C)

4 | DISCUSSION

Although acne lesions are one of the commonest inflammatory lesions in the skin, the immunological aspects for such disease are still incompletely understood.[16] The present study demonstrates significant increase in the serum and tissue levels of IL-17 levels in acne patients when compared with the healthy controls, supporting the involvement of IL-17 in the inflammatory pathway of acne vulgaris. These results were in agreement with Agak et al,[1] Kelhala et al,[17] and Kistowska et al.[18]

A few in vitro studies, could be traced in the literature, demonstrate the presence of vitamin D and its receptor in human sebocytes and report vitamin D-induced modulation of lipids and cytokine production, suggesting the functional role theory of vitamin D deficiency in development of acne.[1,19,20] The findings of the present study demonstrate a significant decrease in the serum and tissue levels of 25(OH)D3 levels in acne patients when compared with the healthy controls and with increased acne severity. This could supports vitamin D3 effects on keratinocytes and sebocytes proliferation and differentiation; thus, vitamin D3-deficient state could results in comedogenesis and enhanced sebum production with the resultant *P. acnes* growth which promotes inflammatory process through stimulation of Toll-like receptor.[21] Zouboulis et al[22] reported significantly lower serum vitamin D3 levels among acne patients especially the younger ones having the hyperseborrheic status, supporting the in vitro sebocytic lipogenesis-induced vitamin D deficiency. Our findings were in accordance with Yildizgoren and Togral.[23] Our results were in disagreement with Lim et al[24] and Toossi et al,[25] both studies reported a nonsignificant difference between acne patients and control group as both had vitamin D deficiency as a prevalent condition in their population; however,

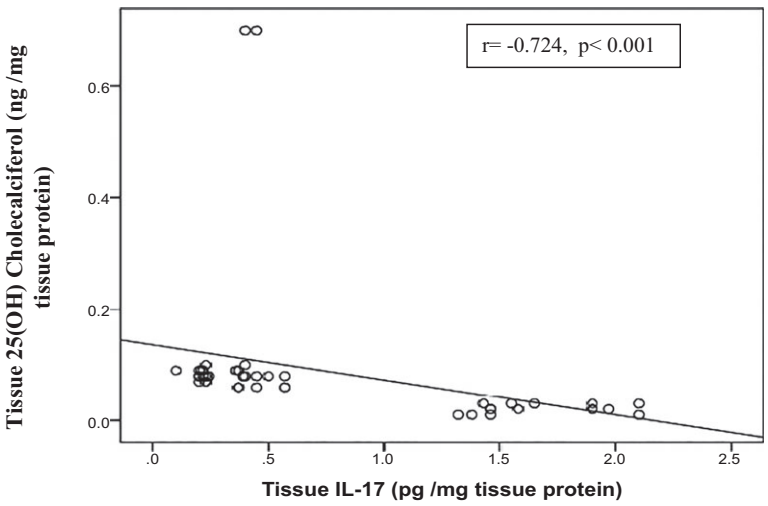

FIGURE 3 Correlation between the tissue IL17 levels and tissue 25(OH) cholecalciferol levels among active acne group

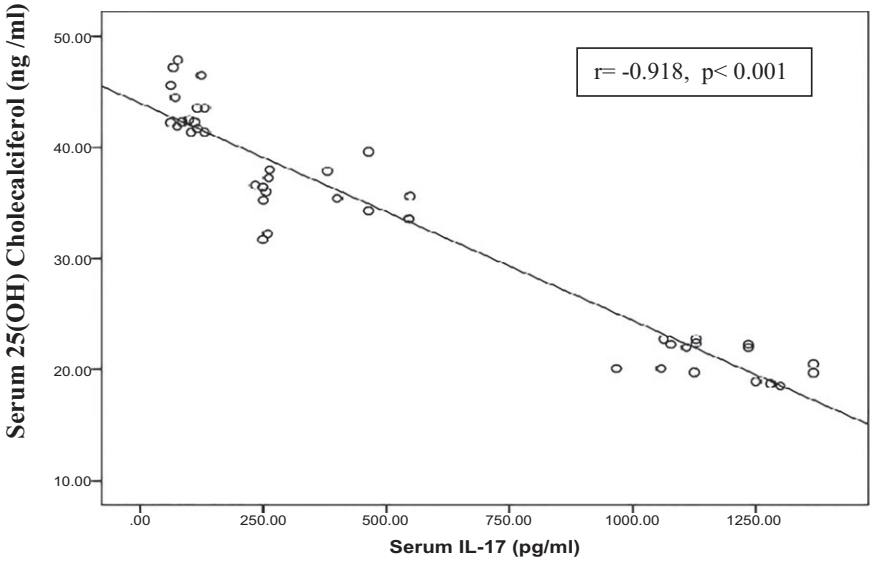

FIGURE 4 Correlation between serum IL17 levels and serum 25(OH) cholecalciferol levels among active acne group

they reported higher frequency of 25(OH)D3 deficiency state among acne patients vs the control group.

To the best of our knowledge, no previous study could be traced in the literature regarding assessment of IL-17 in the lesional tissue of active acne vulgaris using Western blot or immunohistochemical method as we perform in the current study, which confirms the presence of significant increase in the lesional IL-17 expression levels with increasing the severity degree of active acne.

Shedding some light into the molecular aspects of the immunomodulatory effect of active vitamin D3, it is reported that active vitamin D3 inhibits generation of Th17 through decreasing the expression of retinoic acid receptor α (RARα), which is important for differentiation of Th17.[1,26–30] It is reported that vitamin D3 suppresses IL-17-secreting T cells (Th17) through direct transcriptional IL-17 gene expression suppression.[31] It is also recorded that *P. acnes*-induced Th17 differentiation could be inhibited by vitamin D3.[1] This could explain the significant negative correlations found in the present study between the serum and tissue IL17 levels vs serum and tissue vitamin D levels, respectively, among the included patients with active acne. Also, these negative correlations showed in the current study were in line with Lee et al[20] who reported decreased expression of IL-17 in vitamin D-treated cultured sebocytes. However, Shahin et al[32] have been reported the negative correlation between IL-17 and vitamin D3 among patients with systemic lupus erythematosus, but no literature reports could be found regarding this correlation among active acne patients.

5 | CONCLUSIONS

The present study confirms the involvement of IL-17 pathway in inflammatory acne lesions with occurrence of a negative mechanistic interplay with vitamin D3 levels. This opens the way for future

promising studies investigating the possible use of vitamin D3 either topically or systematically alone or combined with anti-IL-17 drugs for active acne cure, especially the severe form.

CONFLICT OF INTEREST

None.

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