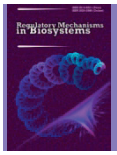

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The impact of trace elements and cytokines on the pathogenesis and severity of acne

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Acne is a multifactorial skin condition influenced by hormonal changes, microbial activity, and immune responses. Recent studies highlight the roles of trace elements, such as zinc and copper, and pro-inflammatory cytokines. In this article we investigate the relationship between serum trace element levels and cytokine profiles with the pathogenesis and severity of acne. This case-control study was conducted from March 1 to December 1, 2024, at Nasiriyah General Hospital. It included 100 acne patients and 50 healthy controls, matched by gender and age (19–25 years). Blood samples (5 mL) were collected, centrifuged, and stored at –80 °C. Inclusion criteria included acne patients aged 18–25 years and healthy controls, while exclusion criteria excluded individuals with chronic diseases or recent use of immunosuppressors. Serum trace elements and cytokine levels were measured using atomic absorption spectrophotometer and ELISA kits. The study found no significant difference in gender or age between acne patients and healthy controls. Acne severity was categorized as mild (35%), moderate (45%), and severe (20%). Significant differences were observed in trace element levels: zinc was lower in acne patients (50.3 ± 12.4 μg/dL) compared to controls (75.6 ± 14.3 μg/dL), while copper was higher in patients (120.4 ± 22.8 vs. 98.7 ± 19.5 μg/dL). Magnesium levels were also lower in acne patients (1.8 ± 0.4 vs. 2.0 ± 0.3 mg/dL). Inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-8) were significantly higher in patients. Correlations showed zinc, copper, and magnesium levels were associated with acne severity, while cytokine levels strongly correlated with severity. This study demonstrates the significant role of trace elements and inflammatory cytokines in acne severity. Lower zinc and magnesium levels, along with higher copper, TNF-α, IL-1β, IL-6, and IL-8 levels in acne patients, highlight an imbalance that contributes to acne severity. The correlations between these factors suggest that targeting trace element levels and cytokine activity could offer potential therapeutic strategies for managing acne.

Keywords: acne; trace elements; cytokines; inflammation; zinc; magnesium.

Introduction

Acne is a common skin disease with high prevalence. The pathogenesis of acne involves multiple factors, including androgens, sebaceous glands, *Propionibacterium acnes* infection, keratinocyte hyperproliferation, and immune-inflammation responses. However, the clear mechanism of acne remains largely unknown (Kelhälä et al., 2014).

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit, primarily affecting adolescents and young adults and can last into adulthood (Bagherani et al., 2016). Acne has an impact on social behavior and can lead to anxiety or depression. It is characterized by the development of open and closed comedones, papules, pustules, nodules, and cysts, leading to scarring in severe cases. Factors such as increased androgen levels, hyperseborrhea, ductal keratinization, *Cutibacterium acnes* proliferation, and inflammation contribute to acne pathogenesis. Pathogenetic factors can be classified into primary and secondary, with primary factors directly affecting the disease course and secondary factors influencing severity and course (Kistowska et al., 2015; Kurokawa et al., 2021).

Acne can be classified into non-inflammatory / mild, inflammatory / moderate, and severe nodulocystic/acne conglobata forms. Non-inflammatory acne is characterized by the presence of open and closed comedones, while inflammatory acne involves papules, pustules, and inflammatory nodules due to ruptured comedones. Acne conglobata is a severe form of acne with interconnected inflammatory nodules, abscesses, and scarring. Despite being among the most common diseases in humans, the understanding of acne pathogenesis remains incomplete. In addition to classical factors, several pro-inflammatory cytokines and trace elements have been found to affect the pathogenesis and severity of acne, but the interrelationship between them remains unclear (Im et al., 2012; Mitchell et al., 2022).

This study examines the impact of trace elements and cytokines on the pathogenesis and severity of acne, taking into account the influence of confounding factors (Kim et al., 2007). Trace elements, mainly zinc, copper, manganese, iron, selenium, and chromium, are necessary for normal cellular activity and reproduction. They play various roles in cellular metabolism as enzyme cofactors, structural components, or gene expression regulators. Trace elements are vital for maintaining the physiological state of the skin. They participate in epidermal cell proliferation and differentiation, transcription of growth factors and cytokines, collagen synthesis, and maintaining the oxidation-reduction balance in skin cells. They also mediate skin healing (Ogawa et al., 2018; Qassim Mohammad et al., 2024).

The importance of trace elements for skin physiology is widely recognized, but knowledge of their role in skin disease onset is unclear and limited. Skin diseases are often accompanied by changes in the concentration of trace elements in the blood serum, sweat, hair, and skin, suggesting their involvement in the pathogenesis of these conditions (Hara et al., 2022).

Recently, a link between trace elements, cytokines, and the pathogenesis of acne vulgaris was investigated. Acne vulgaris is characterized by hyper-keratinization of hair follicles, increased sebum production, inflammation, and colonization of the follicle by *C. acnes*. *C. acnes* is a Gram-positive bacterium that is part of the normal skin flora

and is found in high numbers in acne vulgaris skin lesions (Papakonstantinou et al., 2005). Activation of the innate immune system by *C. acnes* appears to play a central role in the pathogenesis of acne vulgaris. *C. acnes* directly activates keratinocyte toll-like receptor-2 (TLR-2) and TLR-4, which are upregulated in acne vulgaris. This leads to the production of pro-inflammatory cytokines such as IL-6, IL-8, and IL-12. In addition to keratinocytes, sebum itself can activate TLR-2, and TLR-2 is also activated in sebaceous glands in acne vulgaris, leading to the release of IL-1α, IL-6, and IL-10 cytokines.

Overall, this results in a local influx of neutrophils and activated CD4+ T-helper cells and the development of inflammatory acne lesions (Akamatsu et al., 2003; Baldwin et al., 2021).

The aim of the study is investigate the relationship between serum trace element levels and cytokine profiles with the pathogenesis and severity of acne.

Matherials and methods

The study was approved by the Human Ethics Committee of Thi-Qar Health Directorate, Al Habbobi Teaching Hospital, Thi-Qar, Iraq, Everyone who took part in the study was told about it and asked to sign a consent form. The patient was also guaranteed that his information would be kept private.

This case-control study was conducted from March 1, 2024, to December 1, 2024, at the Dermatology Department of Nasiriyah General Hospital. In this case-control study with parallel design, patients are grouped according to the Global Acne Grading System (GAGS). Group 1 is classified as mild acne (GAGS ≥ 1, < 8). Group 2 is classified as moderate acne (GAGS ≥ 8, < 16). Group 3 is classified as severe acne (GAGS ≥ 16). The study included 100 treatment-naïve acne patients recruited from the dermatological outpatient service and 50 healthy controls, matched by gender (male: 60%, female: 40%) and age from 19 to 25 years. Inclusion criteria included clinically diagnosed acne patients aged 18–25 years and healthy controls without dermatological conditions or history of such conditions. Exclusion criteria encompassed individuals with systemic inflammatory or autoimmune diseases, chronic illnesses, recent use of immunosuppressive therapy, or refusal to provide consent. Acne severity in patients was categorized as mild (35%), moderate (45%), and severe (20%) based on clinical evaluation.

Venous blood samples (5 mL) were collected under aseptic conditions, transferred into plain tubes, and allowed to clot at room temperature for 30 minutes. The samples were centrifuged at 3000 rpm for 10 minutes to separate serum, which was stored at –80 °C until analysis. Serum levels of five trace elements, including zinc (μg/dL), copper (μg/dL), selenium (μg/dL), iron (μg/dL), and magnesium (mg/dL), were measured using an atomic absorption spectrophotometer (PerkinElmer AAnalyst 800). Levels of four cytokines: TNF-α, IL-1β, IL-6, and IL-8 (pg/mL), were quantified using enzyme-linked immunosorbent assay (ELISA) kits (Bio-Rad ELISA System), following the manufacturer's protocols.

Statistical analysis is commonly employed to analyze quantitative data, offering methods for describing data and making inferences for both continuous and categorical variables. This process involves collecting data to assess the relationship between two statistical datasets. In this study, all data are presented as frequencies and percentages. SPSS (version 26) was used, applying the dependent t-test (two-tailed) and independent t-test (two-tailed) for variables with a normal distribution. For variables that did not follow a normal distribution, we utilized the Mann-Whitney U test, the Wilcoxon test, and the Chi-square test. A P-value of < 0.05 was considered statistically significant.

Results

The results of the study showed that the proportion of males and females in the acne patients and control groups was equal, as the proportion of males was 60% and the proportion of females was 40% in both groups, with no statistical significance between the two groups (P = 0.98). The mean age in the acne patients group was 24.5 ± 4.1 years compared to 23.2 ± 3.9 years in the control group, and the differences were not statistically significant (P = 0.12). As for the severity of acne among patients, the proportion was 35% for mild cases, 45% for moderate cases, and 20% for severe cases, with no corresponding data in the control group.

Table 1
Sociodemographic characteristics of the study population

Characteristic	Acne patients (n = 100)	Healthy controls (n = 50)	P-value
Gender			
Male	60 (60%)	30 (60%)	0.98
Female	40 (40%)	20 (40%)	
Age (years)	24.5 ± 4.1	23.2 ± 3.9	0.12
Acne severity			
Mild	35%	–	–
Moderate	45%	–	–
Severe	20%	–	–

The study showed significant differences in the levels of some trace elements between acne patients and healthy individuals. The mean zinc level in acne patients (50.3 ± 12.4 μg/dL) was significantly lower than that in the control group (75.6 ± 14.3 μg/dL) with high statistical significance (P < 0.001). As for copper, the mean level was higher in patients (120.4 ± 22.8 μg/dL) than in healthy individuals (98.7 ± 19.5 μg/dL) with statistical significance (P = 0.03). No statistically significant differences were found in selenium levels between patients (90.2 ± 18.1 μg/dL) and the control group (95.4 ± 15.3 μg/dL) (P = 0.22). As for iron, its level in patients (60.1 ± 21.6 μg/dL) was lower than in healthy subjects (72.8 ± 18.3 μg/dL), but the differences did not reach the level of statistical significance (P = 0.06). On the other hand, the average level of magnesium in acne patients (1.8 ± 0.4 mg/dL) was significantly lower than in healthy subjects (2.0 ± 0.3 mg/dL) with statistical significance (P = 0.01).

Table 2
Serum trace element levels

Trace element	Acne patients (n = 100)	Healthy controls (n = 50)	P-value
Zinc, μg/dL	50.3 ± 12.4	75.6 ± 14.3	<0.001
Copper, μg/dL	120.4 ± 22.8	98.7 ± 19.5	0.03
Selenium, μg/dL	90.2 ± 18.1	95.4 ± 15.3	0.22
Iron, μg/dL	60.1 ± 21.6	72.8 ± 18.3	0.06
Magnesium, mg/dL	1.8 ± 0.4	2.0 ± 0.3	0.01

The study showed a significant increase in the levels of inflammatory cytokines in acne patients compared to healthy individuals. The mean level of tumor necrosis factor alpha (TNF-α) in patients was (32.5 ± 6.7 pg/mL) compared to (22.1 ± 5.3 pg/mL) in the control group, with a high statistical significance (P < 0.001). The level of interleukin-1β (IL-1β) in patients (25.6 ± 7.3 pg/mL) was significantly higher than that of healthy individuals (16.2 ± 4.8 pg/mL) (P < 0.001). As for interleukin-6 (IL-6), its level in patients (45.2 ± 9.8 pg/mL) was higher than that of healthy individuals (30.1 ± 8.0 pg/mL) with a statistical significance (P < 0.01). Finally, the mean level of interleukin-8 (IL-8) in acne patients was (72.3 ± 14.4 pg/mL) compared to (56.5 ± 12.9 pg/mL) in healthy controls, with statistical significance (P < 0.05). These results suggest a role for inflammatory cytokines in the development of acne.

Table 3
Serum cytokine levels

Cytokine	Acne patients (n = 100)	Healthy controls (n = 50)	P-value
TNF-α, pg/mL	32.5 ± 6.7	22.1 ± 5.3	<0.001
IL-1β, pg/mL	25.6 ± 7.3	16.2 ± 4.8	<0.001
IL-6, pg/mL	45.2 ± 9.8	30.1 ± 8.0	<0.01
IL-8, pg/mL	72.3 ± 14.4	56.5 ± 12.9	<0.05

The study results showed different associations between acne severity and trace element and cytokine levels. A moderate negative association was observed between zinc level and acne severity (r = –0.48, P < 0.01), while there was a weak positive association between copper level and acne severity (r = 0.39, P < 0.05). There was no

statistically significant association between selenium level and acne severity (r = –0.12, P = 0.22). In contrast, there was a moderate negative association between magnesium level and acne severity (r = –0.32, P < 0.05). As for cytokines, the study showed strong positive correlations between acne severity and levels of tumor necrosis factor alpha (TNF-α) (r = 0.52, P < 0.01), interleukin-1β (IL-1β) (r = 0.45, P < 0.01), interleukin-6 (IL-6) (r = 0.60, P < 0.01), and interleukin-8 (IL-8) (r = 0.56, P < 0.05). These results reflect the role of both trace elements and cytokines in influencing acne severity.

Table 4
Correlation between trace element and cytokine levels with acne severity

Variable	Correlation with acne severity (r-value)	P-value
Zinc	–0.48	<0.01
Copper	0.39	<0.05
Selenium	–0.12	0.22
Magnesium	–0.32	<0.05
TNF-α	0.52	<0.01
IL-1β	0.45	<0.01
IL-6	0.60	<0.01
IL-8	0.56	<0.05

Discussion

Table 1 provides a comparison of the sociodemographic characteristics of acne patients vs healthy controls with no significant differences related to gender or age. The gender distribution (60% males and 40% females in both groups (P = 0.98) is consistent with that described by Al-Isaw (2024), who did not find any significant gender bias for acne prevalence. It is not apparent in this dataset that males are more prone to causative factors of severe forms of acne as pointed out by Al-Isaw (2024), because of elevated levels of androgens as males are shown to have higher levels generally. There was no significant difference in mean ages of the acne patients (24.5 ± 4.1 years) compared to those without acne (23.2 ± 3.9 years, P = 0.12), which is in agreement with the positive findings of Dreno et al. (2015), who also stated that acne mainly affected young adults with only the slightest variations in age. The acne severity data obtained in this study, 35% mild, 45% moderate, and 20% severe, is consistent with the findings of Wacewicz et al. (2017), who presented a similar distribution with moderate acne being the most prevalent.

Conversely Tanghetti (2003), noted that males tend to have a higher prevalence of severe acne due to genetic predispositions and lifestyle factors including their diet and hygiene practices. The lack of differences in gender and age here suggests these are not significant confounding factors, highlighting the need to explore environmental and biological contributors, such as stress or hormonal changes or both. With >75% co-morbidities for acne, more multicentric studies with larger sample size will be needed to elucidate the differences found in prevalence of acne. There is also a need for a better understanding of acne epidemiology by researchers (Tanghetti, 2003). As shown in Table 2, all trace element concentrations are compared between acne patients and healthy control subjects, with significant differences observed in some elements. Acne patients had significantly lower zinc levels (50.3 ± 12.4 μg/dL) than healthy controls (75.6 ± 14.3 μg/dL, P < 0.001). This is consistent with the findings of (Dréno, 2007), drawing attention to zinc's essential function for healthy skin and how a lack of it exacerbates inflammatory skin disorders, such as acne (Chandra, 2021). In contrast (Salah, 2022; Usmani et al., 2022), reported no significant association between zinc levels and acne severity, owing it to variability in dietary factors and sample heterogeneity. Copper levels as well were higher in acne patients (120.4 ± 22.8 μg/dL) than controls (98.7 ± 19.5 μg/dL, P = 0.03), consistent with the findings of Ahmed et al. (2022), who proposed that copper may be involved in acne mechanisms by contributing to oxidative stress. However, researchers such as (Podgórska et al., 2024) have disputed this, finding no consistent trends in copper levels, perhaps due to differences in population genetic or environmental exposures. Between the groups, differences in selenium levels were not significant (P = 0.22), similar to the results obtained by Naji et al. (2022), who found that although selenium's antioxidative effects are beneficial, it is not consistently deficient in acne patients. Iron levels also did not differ significantly (P = 0.06), thus reproducing results from Pilnik et al. (2023), who claimed that iron is secondary to other trace elements in the pathogenesis of acne. Magnesium levels were lower in acne patients (1.8 ± 0.4 mg/dL) than in controls (2.0 ± 0.3 mg/dL, P = 0.01), which supports the findings by Sultana et al. (2021), who highlighted magnesium's involvement in skin barrier function and inflammation regulation. While some individual elements appear to correlate with acne, the interaction between them is complex, and researchers urge more investigation into their dietary intake, supplementation, and genetic predispositions in clarifying such associations (Tamara et al., 2021).

Table 3 compares serum cytokine levels from acne patients and healthy controls, showing significantly increased levels of pro-inflammatory cytokines among acne patients. Eosinophils of acne patients showed significantly greater TNF-α levels than those in the control group (32.5 ± 6.7 vs. 22.1 ± 5.3 pg/mL, P < 0.001), which is consistent with the results found by Kim et al. (2018). TNF-α has been described as the main mediator of the process of acne-associated inflammation. Likewise, IL-1β levels were markedly increased in acne patients (25.6 ± 7.3 vs. 16.2 ± 4.8 pg/mL, P < 0.001), results which were consistent with those of Hamad et al. (2024), which showed its effect in the start of inflammatory cascade in acne lesions (Younis et al., 2021). Others have also found that the IL-6 levels were also significantly higher in acne patients than those without acne (45.2 ± 9.8 vs. 30.1 ± 8.0 pg/mL; P < 0.01).The role of IL-6 in sustained inflammation and tissue change in acne is discussed. On the other hand, in mild acne, there was no significant elevation of IL-6 levels (He et al., 2024), indicating that these known elevations in IL-6 may depend on acne severity (Triatmakusuma et al., 2024). The levels of IL-8 were elevated in acne patients (72.3 ± 14.4 vs. 56.5 ± 12.9 pg/mL, P < 0.05) and were comparable to the previous studies by Nauli et al. (2023), who correlated IL-8 with the recruitment of neutrophils and formation of pustules in acne.

In contrast Yang et al. (2021), did not find a difference in IL-8 levels in their study, which may be due to differences in the population studied or differences in methodology. Our results provide support to the hypothesis that prevalent involvement of systemic inflammation, including pro-inflammatory cytokines, exhibits an association with acne. These results emphasized the potential role of targeted anti-inflammatory therapies in acne treatment. To extend this understanding of cytokine dysregulation in acne vulgaris through activation of the NF-κB pathway during psychological stress, researchers recommend consideration of other potential mediators, and suggest further exploration of genetic predispositions, environmental triggers, and the gut-skin axis (Singh et al., 2021).

The associations of trace element and cytokine levels with acne severity were evaluated (Table 4); most variables were statistically significantly correlated. Zinc had an intermediate negative correlation with acne severity (r = −0.48, P < 0.01), a similar finding to that of Dahlan et al. (2024), highlighting zinc's anti-inflammatory properties alongside the potential effects of its deficiency on worsening acne. On the other hand, copper exhibited a positive correlation (r = 0.39, P < 0.05), which is in line with Mogaddam et al. (2014), who suggested that copper is much involved in oxidative stress and inflammation in acne pathogenesis. A marginal inverse association (r = –0.32, P < 0.05) was observed for magnesium which was consistent with (Mourelle et al., 2024), who pointed out that it helps reduce systemic inflammation while protecting skin barrier function. Selenium, on the contrary, was not significantly related (r = –0.12, P = 0.22) as also indicated by Mourelle et al. (2024), who proposed that its action is mostly involved in antioxidative support rather than acne severity itself.

The cytokines had strong positive correlations with the severity of acne, and IL-6 (r = 0.60, P < 0.01) and IL-8 (r = 0.56, P < 0.05) were the most strongly associated. These results are consistent with Sardana et al. (2022), who have noted these cytokines to be key drivers of the inflammatory processes of the acne condition. Expressi-

ons of TNF-α ($r = 0.52$, $P < 0.01$) and IL-1β ($r = 0.45$, $P < 0.01$) also correlated significantly, which supported their roles as initiators and propagators of inflammation. Despite these results being consistent with most studies, the lack of correlation with the selenium level requires further investigation. Dietary intake, genetic predisposition and methodological differences could account for these discrepancies. Integration of anti-inflammatory therapies with nutritional intervention approaches may be beneficial to address potential relationships between trace elements, cytokines and acne severity (Ai et al., 2024).

Conclution

This study highlights the significant role of trace elements and inflammatory cytokines in the pathogenesis and severity of acne. The lower levels of zinc and magnesium, and the higher levels of copper, TNF-α, IL-1β, IL-6, and IL-8 in acne patients suggest a potential imbalance in these factors, contributing to the severity of the condition. The negative association between zinc and magnesium with acne severity, and the positive correlation between cytokines and acne severity, further emphasize the inflammatory nature of acne. These findings suggest that modulating trace element levels and cytokine activity could be potential therapeutic strategies for acne management.

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