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Evaluation of Serum Zinc, Copper, and Hematological Parameters (Hemoglobin, Total Leukocyte Count, Neutrophil-to-Lymphocyte Ratio) in Acne Vulgaris: A Case-Control Study

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Abstract

Serum zinc and copper concentrations along with hematological markers—hemoglobin, total leukocyte count (TLC), and neutrophil-to-lymphocyte ratio (NLR)—were investigated to assess their associations with acne vulgaris in a case-control design. Treatment-naïve individuals with moderate to severe acne were compared to age- and sex-matched controls without dermatologic disease. Serum zinc was significantly lower and copper significantly higher among acne cases ($p < 0.01$). Hemoglobin levels were modestly lower ($p = 0.04$), TLC was elevated ($p = 0.02$), and NLR was significantly higher in the acne group ($p < 0.001$). Logistic regression indicated that low zinc (< 70 µg/dL), high copper (> 120 µg/dL), and NLR > 2.0 were independently associated with acne (ORs 3.2, 2.8, 4.5 respectively; all $p < 0.05$). These findings suggest systemic micronutrient imbalance and subclinical inflammation in acne pathogenesis. Serum zinc and copper levels combined with NLR may serve as accessible biomarkers for disease severity and guide nutritional or anti-inflammatory interventions. Keywords: acne vulgaris, zinc, copper, neutrophil-to-lymphocyte ratio.

Introduction

Acne vulgaris remains one of the most common inflammatory dermatoses affecting adolescents and young adults worldwide. Characterized by follicular hyperkeratinization, sebaceous overactivity, microbial colonization, and inflammation, acne pathophysiology is multifactorial. Emerging evidence implicates systemic micronutrient disturbances and low-grade inflammatory responses in disease expression and severity, supplementing traditional models that focus on intrafollicular pathobiology.1-3

Trace elements—particularly zinc and copper—play critical roles in skin homeostasis, immune modulation, and antioxidant defense. Zinc possesses anti-inflammatory, antibacterial, and anti-sebum properties and is integral to keratinocyte maturation. Comparatively, copper is a cofactor in enzymatic antioxidant systems but in excess may exacerbate oxidative stress. An imbalance in these trace elements has been proposed to disturb cutaneous physiology, potentially contributing to acne initiation and propagation.4-6

Recent case-control studies have reported lower serum zinc levels in acne patients relative to controls, with levels inversely correlated to severity. For instance, one 2023 study noted significantly decreased zinc in moderate-to-severe acne, aligning with earlier supplementation trials demonstrating clinical improvement. Meanwhile, elevated copper levels—or increased copper-to-zinc ratio—have been associated with greater oxidative stress and inflammatory burden in acne, though data remain variable.7-10

Beyond micronutrients, hematological markers such as neutrophil-to-lymphocyte ratio (NLR) have emerged as inexpensive indicators of systemic inflammation across dermatologic conditions. Elevated NLR has been recorded in patients with eruptive and inflammatory acne, suggesting that neutrophilic activation contributes to ambulatory inflammation. Total leukocyte count (TLC) and hemoglobin may also reflect broader systemic milieu, though these parameters have been less systematically evaluated in acne cohorts.

Integration of electrolyte and hematologic data may thus enrich understanding of acne as a systemic disorder, not merely cutaneous. Identifying consistent biomarker patterns could facilitate

early detection of inflammatory or nutritional contributors and support individualized therapeutic plans, including trace element supplementation or anti-inflammatory strategies.

However, most existing studies are limited by small samples, variable inclusion criteria, and inconsistent control matching. A well-powered case-control study is needed to clarify the independent relationships among serum zinc, copper, hemoglobin, TLC, and NLR in acne vulgaris. Such evidence may inform both pathophysiologic models and practical management considerations, including laboratory-guided nutritional interventions.

Accordingly, the present study aimed to evaluate serum zinc and copper levels along with hemoglobin, TLC, and NLR in young adults with moderate to severe acne compared to matched healthy controls. It was hypothesized that acne cases would exhibit lower zinc, higher copper, higher NLR, and altered hematologic markers, with the magnitude of alteration correlating with acne severity. Moreover, the study explored whether these markers independently predicted acne presence. The findings are intended to enhance clinician's capacity to address systemic aspects of acne through accessible laboratory measures.

Methodology

A prospective case-control study enrolled treatment-naïve individuals aged 16–30 years presenting at Niazi Medical College, Sargodha with moderate to severe acne vulgaris, defined by an established global acne grading scale (GAGS >18), alongside age- and sex-matched healthy controls without dermatologic disease or recent systemic illness. Exclusion criteria included prior systemic acne treatment within 3 months, use of trace element supplementation, chronic inflammatory or hematologic disorders, pregnancy, or any medication likely to affect micronutrient levels. Sample size determination using Epi Info software targeted detection of a 15 µg/dL difference in serum zinc between groups (SD 30), power 0.8, alpha 0.05, requiring 90 per group; allowing for 10 percent attrition, 100 participants were recruited per arm. Following verbal informed consent, venous blood samples were drawn after overnight fasting. Serum zinc and copper were quantified by atomic absorption spectrophotometry, hemoglobin by automated hematology analyzer, TLC and differential counts similarly derived, NLR calculated by dividing neutrophil count by lymphocyte count. Data analyses included group comparisons via Student's t-

tests for continuous variables or Mann-Whitney U where appropriate, and chi-square for categorical comparisons. Logistic regression modeled independent associations of biomarker thresholds with acne presence (adjusted for age, sex, BMI), reporting odds ratios and 95 percent confidence intervals. Correlation analyses assessed relationships between serum markers and acne severity. Statistical significance was set at $p < 0.05$.

Results

Table 1. Baseline characteristics and biomarker levels

Parameter	Acne Cases (n = 100)	Controls (n = 100)	p-value
Age, years	21.8 ± 3.4	22.1 ± 3.2	0.48
Male sex, n (%)	48 (48%)	47 (47%)	0.88
BMI, kg/m²	23.6 ± 2.8	23.3 ± 2.7	0.36
Serum zinc, µg/dL	68.2 ± 15.7	81.4 ± 18.2	<0.001
Serum copper, µg/dL	126.5 ± 22.3	114.8 ± 19.7	<0.001
Hemoglobin, g/dL	13.2 ± 1.4	13.6 ± 1.3	0.04
TLC, ×10³/µL	7.8 ± 1.9	7.2 ± 1.5	0.02
NLR	2.1 ± 0.7	1.5 ± 0.5	<0.001

Table 1 shows that despite comparable demographic characteristics, acne patients had significantly lower serum zinc, higher copper, higher TLC and NLR, and slightly lower hemoglobin.

Table 2. Logistic regression of biomarker thresholds and acne risk

Biomarker threshold	Adjusted OR (95% CI)	p-value
Zinc < 70 µg/dL	3.2 (1.8–5.6)	<0.001
Copper > 120 µg/dL	2.8 (1.6–5.0)	0.001
NLR > 2.0	4.5 (2.5–8.2)	<0.001

Table 2 demonstrates that low zinc, high copper, and elevated NLR were independently associated with increased odds of acne after adjusting for age, sex, and BMI.

Table 3. Correlations between biomarkers and acne severity (GAGS)

Biomarker	Pearson r	p-value
Zinc (µg/dL)	−0.33	<0.001
Copper (µg/dL)	0.29	0.002
NLR	0.36	<0.001
Hemoglobin	−0.12	0.22

Table 3 indicates moderate inverse correlation between zinc and acne severity, and direct correlation between copper, NLR and severity; hemoglobin did not correlate significantly.

Discussion

This case-control study affirmatively documents that individuals with moderate to severe acne vulgaris exhibit a distinct profile of micronutrient imbalance and hematological activation: significantly reduced serum zinc, elevated copper, decreased hemoglobin, elevated TLC, and higher NLR. The associations persisted after adjustment for demographic covariates, supporting the hypothesis of systemic contributors to acne pathogenesis.11-13

Lower serum zinc in acne patients aligns with several studies from the past five years. A 2022 cohort reported negative correlation of zinc levels with acne severity, reinforcing the element's role in immune regulation and follicular keratinization. Zinc's antimicrobial and anti-

inflammatory effects may be essential in controlling Propionibacterium colonization and sebaceous activity, with deficiency fostering persistence of inflammatory lesions.14-16

Elevated copper, and particularly an increased copper-to-zinc ratio, has been linked to oxidative stress and inflammation in acne. Recent publications indicate that copper augments oxidative pathways and can impair antioxidant defenses when in excess. The independent association of high copper with acne risk (OR 2.8) underscores the potential pathophysiological relevance of trace element imbalance.18-20

Hematologic indices reveal a pro-inflammatory systemic milieu. Elevated TLC and particularly NLR in acne cases reflect neutrophil predominance, consistent with neutrophil-mediated inflammation in lesion formation. A 2023 study corroborated elevated NLR in hidradenitis but similar trends in acne suggest broader applicability of this marker as surrogate for systemic inflammation in acne patients.

The modest reduction in hemoglobin among acne patients, though statistically significant, did not correlate with severity. This may reflect mild nutritional influence or chronic low-grade inflammation, but clinical relevance appears limited. Nevertheless, hemoglobin remains readily available and could be monitored if nutritional status is a concern.

Correlation analyses reinforce the clinical utility of these markers. Lower zinc correlated with higher acne severity, while higher copper and NLR correlated positively. These relationships suggest that biochemical evaluation may provide ordinal information on disease prognosis or treatment response, supporting an integrated assessment model.

Taken together, the combination of low zinc, high copper, and elevated NLR presents a plausible biomarker triad reflecting immune-nutritional imbalance in acne. Considering that zinc supplementation has shown efficacy in randomized trials for inflammatory acne, these findings provide mechanistic support for targeted micronutrient therapy, especially in resource-limited settings where laboratory data can inform personalized treatment.

Limitations include cross-sectional design, single-center recruitment, and lack of longitudinal intervention data. While associations are strong, causality cannot be inferred. Nutritional intake

and other confounders were not deeply assessed; future studies should incorporate dietary assessment and evaluate the effect of zinc supplementation or anti-inflammatory interventions on these biomarkers and clinical outcomes.

Future research directions include randomized supplementation trials targeting patients with documented low zinc, exploring whether normalization of trace elements reduces NLR and improves clinical outcomes. Additional investigation into the copper-to-zinc ratio as a composite marker may refine risk stratification and guide therapeutic approaches.

Conclusion

Acne vulgaris is associated with a systemic profile of low serum zinc, elevated copper, and increased inflammatory marker NLR, independent of hemoglobin. These accessible biomarkers may inform personalized nutritional and anti-inflammatory strategies in acne management. Longitudinal interventional studies are warranted to evaluate whether correcting trace element imbalance translates into improved clinical outcomes.

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