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Serum Zinc, Copper, and Copper–Zinc Ratio in Psoriasis: Association with Disease Severity

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ABSTRACT:

Background: *Psoriasis is a chronic immune-mediated inflammatory skin disorder in which oxidative stress and immune dysregulation play key pathogenic roles. Trace elements such as zinc and copper are essential for antioxidant defense and immune function, and their imbalance—often expressed as the copper–zinc (Cu/Zn) ratio—has been implicated in various inflammatory conditions. However, evidence regarding their association with psoriasis severity remains inconclusive.*

Aim: *To evaluate serum zinc, copper, and Cu/Zn ratio in patients with psoriasis and to assess their association with disease severity as measured by the Psoriasis Area and Severity Index (PASI).*

Materials and Methods: *This hospital-based cross-sectional observational study included 50 adult patients with clinically diagnosed psoriasis attending a tertiary care teaching hospital in South Gujarat, India. Disease severity was assessed using PASI scoring. Fasting serum zinc and copper levels were measured using atomic absorption spectrophotometry, and the Cu/Zn ratio was calculated. Data normality was assessed using the Shapiro–Wilk test, and non-parametric statistical methods were applied. Associations between PASI score and biochemical parameters were analyzed using Spearman's rank correlation coefficient.*

Results: *The mean PASI score was 8.38 ± 6.63, indicating predominantly mild to moderate disease severity. Serum zinc, copper, and Cu/Zn ratio showed considerable inter-individual variability. Serum copper levels differed significantly across PASI-defined severity groups ($p = 0.030$), whereas serum zinc levels and Cu/Zn ratio did not show significant variation. Correlation analysis demonstrated no association between PASI score and serum zinc ($r_s = +0.03$), while weak negative correlations were observed between PASI score and serum copper ($r_s = -0.31$) and Cu/Zn ratio ($r_s = -0.21$).*

Conclusion: *The study highlights altered trace-element homeostasis in psoriasis, with serum copper levels showing significant variation across disease severity categories. However, serum zinc levels and Cu/Zn ratio did not demonstrate a significant correlation with PASI score, suggesting limited utility as markers of disease severity. Further large-scale longitudinal studies incorporating dietary assessment and inflammatory biomarkers are needed to better elucidate the role of trace elements in psoriasis.*

KEYWORDS:

Psoriasis; Zinc; Copper; Copper–zinc ratio; Oxidative stress; Psoriasis Area and Severity Index (PASI)

1. Introduction

Psoriasis is a chronic, immune-mediated inflammatory skin disorder affecting approximately 2–3% of the global population. It is characterized by well-demarcated erythematous plaques covered with silvery scales, with disease severity ranging from limited cutaneous involvement to extensive body surface area involvement [1,2]. The pathogenesis of psoriasis involves a complex interplay between genetic predisposition, environmental triggers, and immune dysregulation, particularly mediated through pro-inflammatory cytokines

such as tumor necrosis factor-α (TNF-α) and interleukins, including IL-11, IL-23, and IL-22.[3–6].

Increasing evidence suggests that oxidative stress plays a significant role in the initiation and perpetuation of psoriatic inflammation. Enhanced production of reactive oxygen species, coupled with an impaired antioxidant defense system, contributes to keratinocyte hyperproliferation and sustained inflammatory responses in psoriasis [7,8]. Micronutrients with antioxidant properties, especially trace elements such as zinc and copper, are therefore of particular interest in understanding disease pathophysiology and potential prognostic relevance [9].

Zinc and copper are essential trace elements that function as cofactors for numerous enzymes involved in immune regulation, antioxidant defense, and cellular proliferation. Zinc is crucial for DNA synthesis, wound healing, and immune modulation, while copper plays an important role in connective tissue formation, melanin synthesis, and redox reactions [10–14]. However, excess copper can participate in free radical generation via redox cycling, leading to oxidative tissue damage and amplification of inflammatory pathways [12].

Zinc and copper exhibit a well-recognized antagonistic relationship, and their balance is often better reflected by the copper–zinc (Cu/Zn) ratio rather than absolute serum concentrations alone. The Cu/Zn ratio has been proposed as a sensitive marker of systemic oxidative stress and inflammation and has been shown to correlate with disease severity in various inflammatory and malignant conditions [15–18].

Several studies have reported altered serum zinc and copper levels in patients with psoriasis, though findings remain inconsistent, and their relationship with disease severity is not clearly established [15–17]. Variations in study design, population characteristics, nutritional status, and analytical methods may partly explain these discrepancies. Given the chronic inflammatory nature of psoriasis and the biological relevance of these trace elements, evaluating their levels in relation to disease severity may provide further insight into their role in disease progression and potential therapeutic implications.

In this context, the present study was undertaken to assess serum zinc, copper, and Cu/Zn ratio in patients with psoriasis and to evaluate their association with disease severity as measured by the Psoriasis Area and Severity Index (PASI).

2. Aim and Objectives

Aim

To assess the association between serum zinc, copper, copper–zinc ratio, and disease severity in patients with psoriasis.

Objectives

1. To measure serum zinc and copper levels and calculate the Cu/Zn ratio in psoriasis patients.
2. To evaluate the relationship between these trace elements and disease severity using the PASI score.

3. MATERIALS AND METHODS

This hospital-based cross-sectional observational study was carried out in the Department of Biochemistry in collaboration with the Department of Dermatology at a tertiary care teaching hospital in South Gujarat, India, after obtaining approval from the Institutional Ethics Committee. The study was conducted during the approved postgraduate study period. Clinically diagnosed cases of psoriasis attending the dermatology outpatient department were enrolled after obtaining informed written consent.

A total of 50 patients aged 18 years and above were included in the study. Diagnosis of psoriasis was made by a qualified dermatologist based on characteristic clinical features. Patients with other systemic inflammatory or autoimmune disorders, hepatic or renal diseases, metabolic illnesses, pregnant or lactating women, and those receiving mineral or antioxidant supplementation within the preceding three months were excluded to avoid confounding effects on trace element levels.

A detailed clinical evaluation was performed for each patient. Assessment of disease severity was carried out using the Psoriasis Area and Severity Index (PASI), which was evaluated by a dermatologist trained in PASI scoring to minimize inter-observer variability. PASI scoring was based on the assessment of erythema, induration, and desquamation over four body regions—head, upper limbs, trunk, and lower limbs—with

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appropriate weighting according to the extent of body surface area involvement.

After an overnight fast, 5 mL of venous blood was collected from each participant under strict aseptic precautions. The blood samples were allowed to clot and centrifuged to obtain serum, which was stored at -20°C until biochemical analysis. Serum zinc and copper concentrations were estimated using Atomic Absorption Spectrophotometry (AAS) with an iCE 3500 Atomic Absorption Spectrophotometer employing flame atomization, following standard operating procedures and manufacturer's guidelines. Calibration was performed using standard reference solutions, and internal quality control measures were maintained throughout the analysis to ensure accuracy and reproducibility of results.

The copper–zinc (Cu/Zn) ratio was calculated by dividing the serum copper concentration by the serum zinc concentration for each subject. Collected data were entered into Microsoft Excel and analyzed using appropriate statistical software. The normality of continuous variables was assessed using the Shapiro–Wilk test. Since most variables showed non-normal distribution, non-parametric statistical tests were applied. Continuous variables were expressed as mean ± standard deviation for descriptive purposes and median with interquartile range. Comparisons across different severity groups were performed using appropriate non-parametric tests, and correlations between PASI score and biochemical parameters were assessed using Spearman's rank correlation coefficient. A p-value less than 0.05 was considered statistically significant.

4. RESULTS

Table 1. Baseline Characteristics of Psoriasis Patients (n = 50)

Variable	Mean ± SD	Median (IQR)	Range
Age (years)	41.4 ± 10.1	40.5 (33–47)	25–70
PASI score	8.38 ± 6.63	4.0 (3.0–14.7)	1.1–21.2
Zinc (µg/dl)	211.1 ± 65.1	193.4 (170.4–242.1)	109.3–398.3
Copper (µg/dl)	124.2 ± 45.9	116.5 (92.0–145.1)	54.9–294.4
Cu/Zn ratio	0.65 ± 0.35	0.56 (0.43–0.78)	0.24–2.10

Table 1 summarizes the baseline demographic, clinical, and biochemical characteristics of the study population. The patients exhibited a wide age range with predominantly mild to moderate disease severity, as reflected by the median PASI score. Serum zinc and copper levels showed considerable inter-individual variability, as indicated by broad ranges and interquartile distributions. The Cu/Zn ratio likewise demonstrated substantial variation among patients, suggesting heterogeneity in trace-element balance within the study population.

Table 2. Normality Testing of Study Variables (Shapiro–Wilk Test)

Variable	p value	Distribution
PASI score	<0.001	Non-normal
Zinc (µg/dl)	0.001	Non-normal
Copper (µg/dl)	0.002	Non-normal
Cu/Zn ratio	<0.001	Non-normal

As shown in Table 2, the Shapiro–Wilk test demonstrated that PASI score, serum zinc, serum copper, and the Cu/Zn ratio all significantly deviated from a normal distribution ($p < 0.05$). This indicates that the assumptions of normality required for parametric statistical tests were not met for these variables. Consequently, non-parametric statistical methods were applied for group comparisons and correlation analyses in the present study to ensure the validity and robustness of the statistical inferences.

Table 3. Comparison of Biochemical Parameters Across the Severity of Psoriasis

Parameter	Test	H value	p value
PASI score	Kruskal–Wallis	37.21	<0.001
Zinc (µg/dl)	Kruskal–Wallis	2.51	0.285
Copper (µg/dl)	Kruskal–Wallis	7.00	0.030
Cu/Zn ratio	Kruskal–Wallis	3.38	0.185

Interpretation:

PASI scores increased significantly with increasing severity of psoriasis. Serum copper levels also

differed significantly across severity groups, whereas zinc levels and Cu/Zn ratio showed no statistically significant variation across PASI-defined severity categories.

Figure 1. Scatter Plot with Regression Line Showing the Correlation Between PASI Score and Serum Zinc (µg/dl)

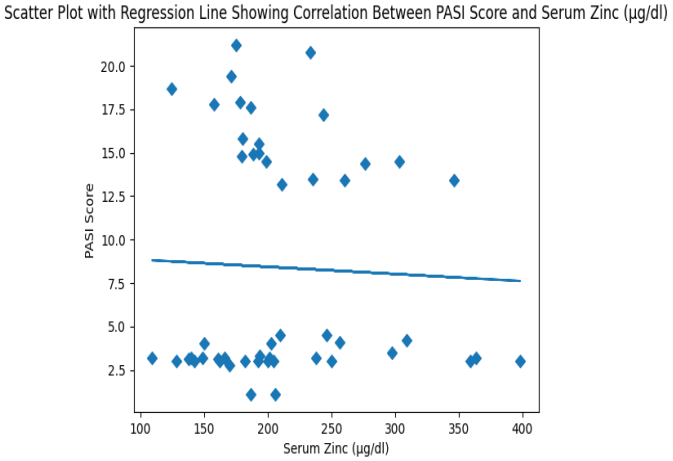

Figure 1 shows the regression line is nearly flat with a very slight negative slope, confirming no meaningful association between PASI score and serum zinc levels.

Figure 2: Scatter Plot with Regression Line Showing the Correlation Between PASI Score and Serum Copper (µg/dl)

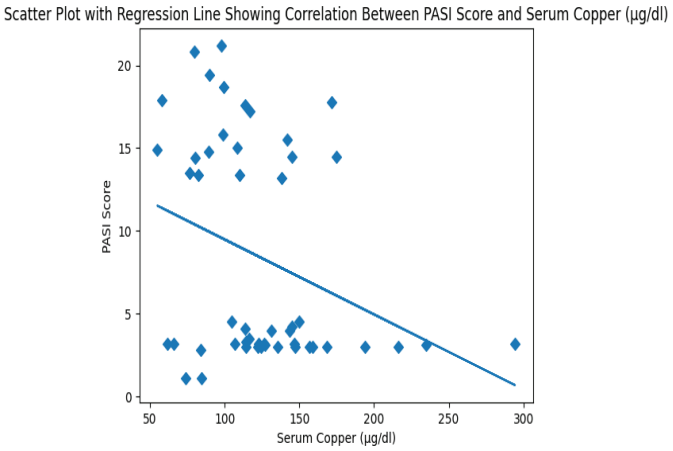

Figure 2: The regression line demonstrates a downward slope, indicating a weak negative relationship between PASI score and serum copper levels.

Figure 3: Scatter Plot with Regression Line Showing the Correlation Between PASI Score and Cu/Zn Ratio

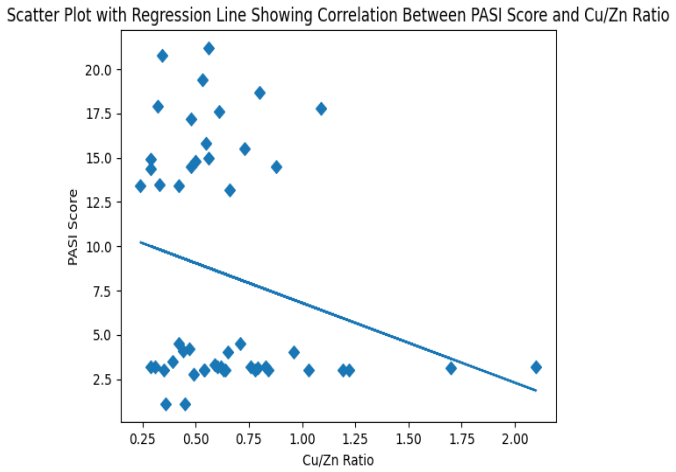

Figure 3 shows a negative slope is observed, suggesting a weak inverse relationship between PASI score and Cu/Zn ratio.

Table 4. Correlation of PASI Score with Biochemical Parameters (Spearman's Rank)

Variables	r_s	Strength
PASI vs Zinc	+0.03	No correlation
PASI vs Copper	-0.31	Weak negative
PASI vs Cu/Zn ratio	-0.21	Weak negative

5. Discussion

Psoriasis is a chronic immune-mediated inflammatory disorder characterized by keratinocyte hyperproliferation and systemic immune activation, processes that may influence trace-element homeostasis. Copper and zinc play essential roles in antioxidant defense, immune modulation, and epidermal differentiation, and disturbances in their metabolism have been increasingly explored in psoriasis. The biological relevance of zinc and copper in psoriasis can be better understood in the context of the psoriatic inflammatory cycle. Psoriasis is characterized by activation of dendritic cells and T helper (Th1 and Th17) lymphocytes, leading to increased production of pro-inflammatory cytokines such as **TNF-α, IL-17, IL-22, and IL-23**, which stimulate keratinocyte proliferation and sustain cutaneous inflammation. This inflammatory cascade generates increased levels of **reactive oxygen species (ROS)**, contributing to oxidative stress within the epidermis.[17]

Trace elements play critical modulatory roles in this process. **Zinc** functions as a cofactor for numerous antioxidant enzymes, including **superoxide dismutase**, and contributes to

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stabilization of cell membranes, regulation of keratinocyte proliferation, and modulation of immune responses. Zinc deficiency may therefore impair antioxidant defense mechanisms and promote inflammatory signaling pathways. **Copper**, on the other hand, participates in redox reactions and serves as a cofactor for enzymes involved in oxidative metabolism and connective tissue formation. While physiologic copper supports antioxidant activity through copper-dependent enzymes, excess copper may also contribute to **free radical generation via redox cycling**, thereby amplifying oxidative damage in inflammatory conditions.[18-22]

The balance between these two trace elements is reflected in the **copper–zinc ratio**, which has been proposed as an indicator of systemic inflammation and oxidative stress. Alterations in this ratio may therefore influence the inflammatory microenvironment in psoriasis by modifying the balance between oxidative injury and antioxidant defense mechanisms.[23]

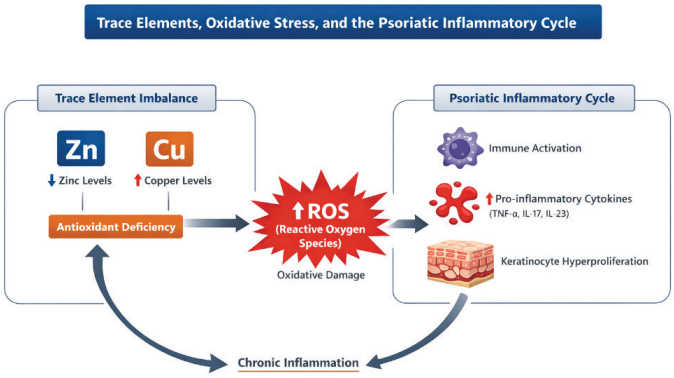

Figure 4: a simple schematic figure showing the "Trace Elements–Oxidative Stress–Psoriasis Inflammatory Cycle

In the present study, serum copper levels demonstrated a statistically significant difference across psoriasis severity groups, whereas serum zinc levels and the Cu/Zn ratio did not show significant variation with disease severity. Correlation analysis revealed no meaningful association between PASI score and serum zinc levels, while serum copper and Cu/Zn ratio showed weak negative correlations with PASI score. These weak correlations did not reach clinical or statistical significance, suggesting limited utility as severity markers.

Several Indian studies have reported significantly decreased serum zinc levels and elevated serum copper levels in psoriasis patients compared with healthy controls. Sheikh et al.[24] observed markedly reduced zinc and increased copper levels, along with altered serum protein fractions, suggesting chronic inflammation and enhanced epidermal turnover as contributory mechanisms. Basavaraj et al.[25] also reported elevated copper levels in both mild and severe psoriasis, supporting the concept of copper behaving as an acute-phase reactant through increased ceruloplasmin synthesis during inflammation. In contrast, Rao et al.[26] reported significantly reduced zinc, copper, and selenium levels, indicating a possible generalized micronutrient deficiency state influenced by dietary or regional factors.

International studies have similarly demonstrated heterogeneous findings. Ala et al.[27] reported elevated copper levels without significant zinc deficiency in Iranian patients, while Tasaki et al. [28] highlighted increased serum copper and the diagnostic relevance of the Cu/Zn ratio in inflammatory skin diseases, including psoriasis. Compared with these studies, the present findings show that although serum copper levels differ across severity categories, neither zinc levels nor the Cu/Zn ratio reliably correlates with PASI score. The weak inverse relationship observed between PASI score and serum copper contrasts with earlier reports of rising copper levels with increasing severity and may reflect differences in disease chronicity, treatment exposure, inflammatory burden, or adaptive metabolic responses. The weak inverse relationship observed between PASI score and serum copper levels in the present study contrasts with several earlier reports in which copper levels increased with greater disease activity. Copper is widely recognized as an acute-phase reactant, largely due to increased hepatic synthesis of ceruloplasmin during systemic inflammation. Elevated copper levels in psoriasis have therefore often been interpreted as reflecting enhanced inflammatory activity and oxidative stress. However, several factors may explain the inverse trend observed in the present study.

First, the majority of patients in our cohort had **mild to moderate disease severity**, with relatively low PASI scores. In such patients, the systemic inflammatory burden may be insufficient to produce a consistent rise in copper levels. Second, copper metabolism may undergo **adaptive metabolic regulation during chronic inflammation**, where prolonged inflammatory exposure leads to redistribution of trace elements between plasma, liver, and tissues. In chronic inflammatory states, copper may be

increasingly utilized by antioxidant enzymes such as **superoxide dismutase and ceruloplasmin**, potentially resulting in lower circulating levels despite ongoing oxidative stress.[20,21,23]

Third, **nutritional status and dietary micronutrient intake** can significantly influence serum copper concentrations. Regional variations in diet, particularly in populations with variable micronutrient intake, may partly explain discrepancies between studies conducted in different geographic settings. Fourth, **treatment exposure and disease chronicity** may modify trace-element dynamics. Patients receiving topical therapies or having long-standing disease may exhibit metabolic adjustments that alter circulating copper levels independently of current disease severity.[21,23]

Another possible explanation is that serum copper levels alone may not accurately reflect **functional copper activity within inflammatory pathways**, as copper is largely protein-bound in circulation and participates in multiple enzymatic processes within tissues rather than remaining freely available in serum. Consequently, the **Cu/Zn ratio or intracellular trace-element balance** may better represent oxidative stress status than absolute serum copper levels.[29]

The absence of a significant association between zinc levels and disease severity suggests that zinc imbalance, when present, may represent a background metabolic alteration rather than a dynamic marker of psoriasis activity. Moreover, serum zinc levels may not accurately reflect intracellular zinc distribution or tissue utilization, which may be altered during chronic inflammatory states.[18]

Overall, the findings of the present study support the presence of trace-element imbalance in psoriasis while demonstrating that serum zinc levels and the Cu/Zn ratio may have limited utility as markers of disease severity. The variability of findings across studies underscores the influence of nutritional status, inflammatory burden, methodological differences, and population characteristics. Future large-scale longitudinal studies incorporating dietary assessment, inflammatory biomarkers, and treatment variables are warranted to further clarify the role of trace elements in the pathophysiology and clinical monitoring of psoriasis.

Strengths of the Study

- The study employed **standardized severity assessment using PASI scoring**, allowing objective stratification of disease severity.
- Appropriate **non-parametric statistical methods** were used in view of the non-normal distribution of biochemical variables.
- The evaluation of **both individual trace elements and the Cu/Zn ratio** provides a more comprehensive understanding of trace-element balance in psoriasis.
- The findings contribute **region-specific data**, adding to the limited Indian literature on trace elements and psoriasis severity.

Limitations of the Study

- The **cross-sectional design** precludes causal inference between trace-element alterations and disease severity.
- The **sample size**, though adequate for exploratory analysis, may limit the detection of subtle associations.
- **Dietary intake, supplementation status, and inflammatory markers** were not assessed, which may influence serum trace-element levels.
- Serum measurements may not accurately reflect **intracellular or tissue trace-element status**, potentially underestimating their biological relevance.
- Treatment history and disease duration were not fully accounted for, which could have influenced biochemical parameters.

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