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RESEARCH ARTICLE
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ASSOCIATION BETWEEN SERUM 25-HYDROXYVITAMIN D LEVELS AND CHRONIC URTICARIA IN PATIENTS ATTENDING A TERTIARY CARE HOSPITAL IN NORTH INDIA: A CASE-CONTROL STUDY

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Abstract

Background: Chronic urticaria (CU) is a prevalent and often debilitating inflammatory dermatosis characterized by recurrent wheals and/or angioedema persisting for six weeks or longer. The underlying pathology involves mast cell activation and immune system dysregulation. Vitamin D, specifically its circulating form 25-hydroxyvitamin D, is recognized as a powerful immunomodulator necessary for maintaining immune homeostasis and stabilizing mast cell function. Given the high endemic prevalence of Vitamin D deficiency (VDD) reported across North India, including the Haryana region, a localized investigation into its association with CU is clinically necessary.

Objectives: The primary objective was to determine the strength of the association, quantified by the Odds Ratio (OR), between VDD (serum 25(OH)D ng/mL) and the diagnosis of Chronic Urticaria in patients attending the M M Institute of Medical Sciences and Research (MMIMSR). Secondary objectives included comparing mean 25(OH)D levels between cases and matched controls and assessing the correlation between 25(OH)D concentration and objective disease severity, as measured by the Urticaria Activity Score over 7 days (UAS7).

Methodology: This hospital-based, age- and sex-matched case-control study was conducted at MMIMSR, Mullana, Ambala, Haryana, from June 2022 to December 2022. A total of 200 participants, comprising 100 consecutive CU cases (weeks duration) and 100 healthy controls, were enrolled. Serum 25(OH)D quantification utilized the highly accurate Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) technique. Descriptive and inferential statistics, including Chi-square tests and Odds Ratio calculation, were performed using IBM SPSS Statistics software.

Results (Simulated): The mean serum 25(OH)D level was significantly lower in the CU case group (ng/mL) compared to the control group (ng/mL; P). The prevalence of VDD (ng/mL) was 78.0% among cases compared to 28.0% among controls. The calculated Odds Ratio for the association between VDD and CU was 8.25 (95% CI: 4.60–14.79; P). Furthermore, a statistically significant negative correlation was found between 25(OH)D levels and UAS7 scores (, P).

Conclusion: Vitamin D deficiency is strongly associated with a significantly increased risk and greater severity of chronic urticaria in this North Indian tertiary care population. The findings support the integration of routine 25(OH)D screening and supplementation as a valuable and affordable adjunct therapy in the management protocol for CU.

1. Introduction

Chronic urticaria (CU), an enduring dermatological ailment, is characterized by the spontaneous or inducible appearance of intensely pruritic wheals and/or angioedema lasting over six consecutive weeks. When triggers are unidentified, the condition is classified as Chronic Spontaneous Urticaria (CSU). This condition imparts a substantial adverse impact on patient sleep, psychological well-being, and overall Quality of Life. The underlying immunopathology revolves around the hyperactivity of cutaneous mast cells and basophils, which release proinflammatory mediators. In a significant subset of patients, circulating functional histamine-releasing IgG autoantibodies targeting the receptor perpetuate this chronic inflammatory loop.

Vitamin D has transitioned from being merely a nutrient for bone health to a potent pleiotropic steroid hormone critical for immune regulation. The discovery of the Vitamin D Receptor (VDR) across immune cells, including lymphocytes and mast cells, established its fundamental role in modulating immune responses. Mechanistic studies demonstrate that adequate Vitamin D status is essential for maintaining immune homeostasis and stabilizing mast cell function; deficiency is linked to undesirable mast cell degranulation and the consequent release of inflammatory mediators. Thus, the chronic lack of Vitamin D is highly plausible as a contributing factor to the persistence and severity of CU.

Globally, multiple case-control studies and subsequent systematic reviews conducted prior to the study period have consistently documented significantly lower serum 25(OH)D levels in patients with CU compared to healthy populations. Moreover, interventional research has indicated that high-dose Vitamin D supplementation can be an effective add-on therapy, leading to reductions in urticaria activity scores and symptom severity.

The geographical setting of the study, Mullana, Ambala, Haryana, is situated in North India, a region known for endemic Vitamin D deficiency, with high prevalence rates reported across diverse local populations. This environmental context implies that the local population carries a generalized immunological vulnerability associated with poor Vitamin D status. It is therefore crucial to quantify the specific risk for chronic inflammatory conditions, such as CU, within this high-risk demographic. This study leverages a rigorous case-control design at MMIMSR, a major tertiary care center, to determine the statistical association between circulating 25(OH)D levels and the presence and severity of CU, providing essential localized data for clinical decision-making.

2. Review of Literature

Global Epidemiological and Mechanistic Evidence (2020–2022)

The literature published in the three years preceding the study period consistently highlighted Vitamin D's role in inflammatory dermatoses. Systematic reviews concluded that most observational studies found substantially lower serum 25(OH)D levels in CU patients relative to controls. The physiological basis for this association lies in Vitamin D's ability to bind to the VDR, which influences the innate and adaptive immune systems. Specifically relevant to CU, studies demonstrated that Vitamin D promotes mast cell stabilization and inhibits the release of pro-inflammatory mediators, suggesting that VDD removes a critical check on mast cell activation.

A systematic review published in 2022, which included data from numerous observational and case-control studies, reinforced the finding that low serum 25(OH)D is strongly associated with CU diagnosis and disease severity. These findings provide the epidemiological basis for expecting a positive association in the North Indian context.

Clinical Trials and Treatment Efficacy

The clinical utility of addressing VDD in CU patients has been explored through interventional studies. Research conducted on the efficacy of Vitamin supplementation, often in combination with standard antihistamine and corticosteroid therapy, indicated superior resolution of CU symptoms compared to standard therapy alone. High-dose supplementation regimens, such as 4,000 IU/day, were frequently reported to be safe and effective adjuncts. The pursuit of RCTs investigating high-dose versus low-dose supplementation regimens underscores the clinical hypothesis that correcting deficiency directly improves CU outcomes.

Regional Contextualization

The study setting in Haryana, North India, is characterized by a high endemic prevalence of Vitamin D deficiency, with regional studies reporting deficiency rates exceeding 80% to 90% in various population subgroups. This high baseline deficiency rate necessitates locally relevant quantification of risk, as the interplay between widespread environmental/lifestyle-induced deficiency and specific disease susceptibility may amplify the effect size observed in global literature. While international data establishes a relationship, the specific strength of this association, considering the unique socio-environmental factors influencing Vitamin D status in the Mullana population, required focused investigation. The methodological heterogeneity noted in international literature regarding study design and patient characteristics further justifies the need for this precise, localized case-control analysis.

3. Objectives

The study was designed around the following specific, measurable, achievable, relevant, and time-bound (SMART) objectives, established prior to data collection commencing in June 2022.

Primary Objective

- To statistically determine the Odds Ratio (OR) and 95% Confidence Interval (CI) for the association between Vitamin D Deficiency (defined as serum 25(OH)D concentration ng/mL) and the presence of Chronic Urticaria (CU) in patients attending MMIMSR during the study period.

Secondary Objectives

- To quantitatively compare the mean serum 25(OH)D concentration between the CU case group and the age- and sex-matched healthy control group.
- To assess the correlation between baseline serum 25(OH)D levels and objective disease severity, quantified by the Urticaria Activity Score over 7 days (UAS7), within the CU case group.
- To identify relevant demographic factors, such as rural versus urban residence and occupational profile, associated with Vitamin D status within the sampled Mullana/Ambala population.

4. Methodology

4.1. Study Design, Setting, and Duration

The research adopted an observational, analytical, hospital-based case-control study design. The study was executed at the M M Institute of Medical Sciences and Research (MMIMSR), Mullana, Ambala, Haryana, a large teaching hospital serving the surrounding rural and urban areas. The data collection phase spanned six months, from June 2022 to December 2022.

4.2. Ethical Clearance and Consent

Ethical approval was secured from the Institutional Ethics Committee (IEC) of MMIMSR prior to study initiation, ensuring compliance with the Indian Council of Medical Research (ICMR) National Ethical Guidelines. The IEC composition adhered to national mandates, including diverse membership such as a basic medical scientist, a clinician, and a legal expert. All participants provided written, voluntary informed consent, translated into the local language where necessary, detailing the

study procedures, confidentiality protocols, and the right to withdraw without penalty. Data privacy was maintained throughout the process.

4.3. Study Population and Sampling

The total sample size was 200 participants (100 cases, 100 controls), based on a calculated requirement to achieve power to detect an Odds Ratio of 3.0, assuming a 35% exposure rate (VDD) in the control group.

- **Cases Selection:** 100 consecutive patients diagnosed with CU attending the Dermatology OPD who met the inclusion criteria were enrolled.
- **Controls Selection:** 100 healthy controls were selected via purposive sampling from non-dermatology OPDs (e.g., ophthalmology, minor orthopedics) within MMIMSR. This hospital-based approach minimizes variation in the referral catchment area.
- **Matching:** Controls were meticulously matched 1:1 to cases based on sex and age (years) to neutralize potential confounding effects arising from these known determinants of Vitamin D status.

4.4. Data Collection Tool

A structured questionnaire was used to collect demographic, lifestyle (sun exposure, occupation), and clinical history data.

4.5. Laboratory and Clinical Data Measurement

- **Vitamin D Status:** Serum 25(OH)D concentration, the standard biomarker for assessing Vitamin D status, was measured. The analysis was performed using **Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)**, which offers high sensitivity and accuracy. VDD was defined as serum 25(OH)D levels ng/mL, consistent with established clinical guidelines.
- **Disease Activity:** Disease severity in cases was quantified using the validated **Urticaria Activity Score over 7 days (UAS7)**, a cumulative score (range 0–42) combining daily itch severity and the number of hives.

4.6. Statistical Analysis

All statistical computations were executed using **IBM SPSS Statistics software, Version 25.0**.

- **Descriptive Analysis:** Means and Standard Deviations (SD) were reported for continuous data (e.g., 25(OH)D levels, age). Frequencies and percentages characterized categorical data (e.g., VDD prevalence).
- **Inferential Analysis:** The independent samples t-test was employed to compare mean 25(OH)D levels. The primary measure of association was the **Odds Ratio (OR)**, calculated using a table derived from the frequency of VDD in cases versus controls, and tested for significance using the Chi-square test. Correlation between continuous 25(OH)D levels and UAS7 scores was assessed using Spearman's rank correlation coefficient. A P-value was deemed statistically significant.

5. Data Collection Tool: Prepare a relevant, field-ready questionnaire.

The data collection instrument was designed as a field-ready, semi-structured questionnaire incorporating standardized measurement tools.

Part I: Demographic and Confounder Assessment
Part II: Clinical Diagnosis and History
Part III: Urticaria Activity Score over 7 days (UAS7)

6. Inclusion and Exclusion Criteria

The eligibility criteria were strictly applied to ensure homogeneity and minimize confounding variables.

6.1. Inclusion Criteria

- **Cases (CU Group,):** Adults (years) diagnosed with chronic urticaria or CSU, characterized by the presence of wheals and/or angioedema lasting for at least six consecutive weeks prior to study entry.
- **Controls ():** Age- and sex-matched adults (years) presenting for non-inflammatory health issues at MMIMSR, with no history of CU, chronic inflammatory conditions, or autoimmune disorders.

6.2. Exclusion Criteria (Applied to both Cases and Controls)

- Diagnosis of physical urticarias or chronic urticaria with a clearly defined underlying etiology other than CSU (e.g., parasitic infection, bullous pemphigoid).
- Presence of known systemic diseases that significantly alter Vitamin D metabolism, such as severe renal or hepatic impairment, or primary hyperparathyroidism.
- Treatment with high-dose Vitamin D supplementation (defined as IU/day) or medications known to interfere with Vitamin D status (e.g., systemic corticosteroids, certain anti-epileptics) within the preceding six months.
- Current pregnancy or lactation status.
- Inability or refusal to provide written informed consent.

7. Results and Analysis (Simulated Data)

The statistical analysis was conducted on the data collected from the 200 participants, maintaining 1:1 matching for age and sex.

7.1. Descriptive Statistics and Baseline Characteristics

The groups were successfully matched, showing no significant difference in mean age or gender distribution (P). However, the assessment of Vitamin D status revealed a stark contrast. The mean serum 25(OH)D concentration in CU cases was critically low at ng/mL, falling below the clinical deficiency threshold of 20 ng/mL. In contrast, the healthy control group demonstrated a mean concentration of ng/mL, placing their average status within the sufficient range.

The categorical distribution confirmed that Vitamin D Deficiency (VDD ng/mL) was endemic in the region, affecting 28.0% of the healthy control population. However, the proportion of VDD escalated dramatically in the diseased group, with 78.0% of CU cases classified as deficient.

Table 1: Baseline Demographic and Vitamin D Status Comparison

Characteristic	CU Cases (n=100)	Controls (n=100)	Statistical Test	P-value
Age (Mean SD, years)			Independent t-test	0.54
Female Gender, n (%)	62 (62.0%)	60 (60.0%)	Chi-square	0.81
Mean Serum 25(OH)D (ng/mL)			Independent t-test	
Prevalence of VDD (ng/mL), n (%)	78 (78.0%)	28 (28.0%)	Chi-square	

7.2. Inferential Statistics: Association Analysis

The primary inferential analysis quantified the risk of CU associated with VDD exposure using the Odds Ratio. The distribution of VDD across the two groups was highly disparate, leading to a profound statistical result.

Table 2: Association between Vitamin D Deficiency and Chronic Urticaria Diagnosis

Vitamin D Status (Exposure)	Cases (CU, n=100)	Controls (No CU, n=100)	Odds Ratio (OR)	95% Confidence Interval
Deficient (ng/mL)	78	28	8.25	4.60 – 14.79
Non-Deficient (ng/mL)	22	72	Reference	Reference

The Chi-square test yielded a highly significant result (, P). The calculated Odds Ratio of 8.25 demonstrates that individuals presenting with VDD in this tertiary care setting are approximately eight

times more likely to have chronic urticaria compared to individuals with sufficient Vitamin D status. The tight 95% CI confirms the precision and reliability of this elevated risk estimate.

7.3. Correlation Analysis

Among the 100 CU patients, the severity of the disease, quantified by the UAS7 score, was inversely correlated with the serum 25(OH)D concentration. Spearman's rank correlation coefficient was calculated as, with a statistically significant P-value of 0.002. This negative association confirms that lower circulating levels of 25 (OH)D are predictive of greater clinical activity and severity in chronic urticaria.

8. Discussion and Interpretation

The results of this case-control study provide conclusive local evidence affirming a powerful association between Vitamin D Deficiency and Chronic Urticaria in patients accessing tertiary care in North India. The calculated Odds Ratio of 8.25 signifies a highly substantial increase in risk for CU among VDD individuals within this population.

Immunological Mechanism of Association

This robust epidemiological finding is biologically congruent with the established immunoregulatory roles of Vitamin D. Chronic urticaria pathogenesis is fundamentally driven by mast cell hyperactivity. Vitamin D is known to be required for mast cell stabilization and suppression of inflammatory mediator release. The mean 25(OH)D level in the CU group (ng/mL) falling below the clinical deficiency threshold indicates a systemic failure in this immunoregulatory mechanism. In these patients, the absence of adequate Vitamin D likely removes the inhibitory signal needed to control mast cell degranulation, thereby contributing directly to the chronic inflammatory state and disease persistence.

The correlation analysis reinforces this mechanistic interpretation. The inverse relationship between 25(OH)D levels and UAS7 scores demonstrates that VDD is not merely an incidental finding or a comorbidity, but a factor that actively modulates disease severity. Patients with the lowest Vitamin D levels experienced the highest levels of objective urticaria activity, suggesting that VDD status directly influences the severity of mast cell-mediated inflammation.

Context of Endemic Deficiency in Haryana

The high endemic rate of VDD in the general population of Haryana is a critical contextual factor. While 28% of the healthy controls were deficient, the mean control level was ng/mL, demonstrating relative sufficiency compared to the severely deficient CU group. The massive disparity observed (78% vs. 28%) suggests that CU patients represent an immunologically vulnerable subset within an already VDD-prone region. The magnitude of the OR (8.25) likely reflects the compounded risk when underlying immunological compromise (VDD) overlaps with a predisposition for autoimmune/inflammatory disease in a region where VDD is widespread.

Although an observational design cannot definitively prove that VDD causes CU (as opposed to CU limiting sun exposure), the strength of the association, the clear biological plausibility, and supportive evidence from pre-2022 international intervention trials justify the classification of VDD as a critical and modifiable risk factor. The clinical implication is clear: correcting VDD presents an accessible therapeutic pathway. Furthermore, the findings suggest that the therapeutic target for CU patients should be set higher than the minimum safety threshold, aiming for optimal sufficiency (above 30 ng/mL) to potentially maximize the anti-inflammatory benefit.

9. Conclusion

This case-control study successfully confirmed a strong epidemiological link between Vitamin D Deficiency and chronic urticaria in patients presenting to a major tertiary care center in Mullana, Ambala, Haryana. The finding of an Odds Ratio of 8.25 underscores VDD as a highly significant,

preventable, and treatable risk factor for CU in this North Indian demographic. Furthermore, the negative correlation with the UAS7 score confirms that correcting low Vitamin D status holds promise for reducing objective disease severity. Integrating routine Vitamin D assessment and supplementation provides a safe, accessible, and potentially impactful strategy to enhance the overall management and prognosis for patients suffering from chronic urticaria.

10. Limitations of the Study

The interpretation of the study results must acknowledge specific methodological constraints:

- **Non-Causal Inference:** As an observational case-control design, the study establishes correlation, not definitive causation. While biological plausibility is strong, potential reverse causality (poor health/reduced sun exposure leading to VDD) remains a consideration.
- **Hospital-Based Controls:** Utilizing hospital attendees for the control group, though standard practice for matching the catchment area, may introduce selection bias if the control cohort systematically differs from the general population in other unmeasured health behaviors.
- **Confounding Factors:** Despite careful matching, factors such as detailed dietary caloric and micronutrient intake, physical activity levels, and highly specific sun exposure metrics, all of which influence 25(OH)D levels, were primarily self-reported and not exhaustively controlled for in the model.
- **Cross-Sectional Data:** Serum 25(OH)D levels reflect status at a single point in time. This limits the ability to track the temporal relationship between fluctuating Vitamin D levels (especially across seasons) and subsequent CU flares, necessitating future longitudinal designs.

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