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Original Article

Biochemistry Section

# Serum 25-Hydroxy Vitamin D Levels in Patients with Polymorphic Light Eruptions: A Case-control Study

K GUNANITHI[1], S BIRUNDHA[2], J RATHI ROOPAVATHY[3]



**Introduction:** Polymorphic Light Eruptions (PMLE) are immune mediated dermal maculopapular eruptions that occurs after sun exposure. Vitamin D deficiency has been gaining attention in many dermatological diseases of varied pathologies. Research studies on vitamin D levels in PMLE are lacking despite it being an immuno modulator.

**Aim:** To estimate the levels of serum 25-OH Vitamin D among patients with PMLE disease and also to compare its level with healthy controls

**Materials and Methods:** A case-control study was conducted during January 2022 to June 2022 in Melmaruvathur Adhiparasakthi Institute of Medical Sciences and Research Hospital, Tamil Nadu, India. Total 80 participants (40 patients with PMLE eruptions and 40 normal healthy volunteers), of both sexes aged between 40-60 years were included. Serum 25-OH Vitamin D levels were estimated for participants and the data obtained were analysed by using Student's t-test and Chi-square test as tests for significance and Odds ratio by logistic regression as test for outcome association.

**Results:** Amongst the total 80 participants, 40 in each case and control group, mean age in case group was 50.08±5.21 years and in control group was 49.80±5.68 years. The results of the study showed significantly reduced serum 25-OH vitamin D levels (30.13±7.39 ng/mL) among cases compared to controls (34.50±6.05 ng/mL) (p=0.005). It further showed significant positive B (0.160) slope for sunlight exposure and significant negative B (-0.556) slope for serum vitamin D levels with odds of occurrence to PMLE disease state increases by 17.4% for every unit increase in sunlight Ultraviolet (UV) exposure {Odds ratio: 1.174 (C.I: 1.088-1.266)} and decreases by 42.6% for every unit increase in Vitamin D levels {Odds ratio: 0.574 (C.I: 0.446-0.738)}.

**Conclusion:** Most PMLE patients were found to have significantly lower Vitamin D levels with majority in the pre-deficient zones. These findings suggest Vitamin D could be a cost effective alternative prospect in both PMLE diagnostics and therapeutics in future after thorough trial validations.

**Keywords:** Cholecalciferol predeficiency, Dermatological disease, Immune suppression, Maculopapular lesion

## INTRODUCTION

Polymorphic Light Eruptions (PMLE) are immune mediated dermal maculopapular eruptions that occurs after sun exposure [1]. Despite being common condition, the aetiology of eruptions are still largely unknown. Global prevalence of the disease is 10-20% [1] with varied numbers across countries, while the national prevalence stands at between 2-13.5% in India [2].

Vitamin D, a fat soluble vitamin which is better known for its skeletal role, also plays multifocal extraskeletal biological functions. Its deficiency has become increasingly prevalent even in tropical countries like India with estimates around 490 million people [3] Lowered Vitamin D levels has been gaining attention in many dermatological diseases of varied pathologies. Beyond, being an immune and inflammatory modulator, research studies on Vitamin D levels in PMLE are still lacking both on a global and national scale. There are only a few published literature regarding associations of Vit-D in PMLE [4,5].

The justifications towards the need for the study extends across multiple fronts. On the aetiological front, PMLE is a disease of many unknowns, which includes unknown aetiology, unknown phototrigger, unknown photoantigen, unknown genetic predisposition and unknown pathogenesis. On the clinical front, PMLE remains a common, distressful and recurring itch, affecting quality of life for patients with lifestyle restrictions that deprive them of sun exposure benefits, lifelong recurrences, even leading to mental illness states [6]. On the diagnostic front, PMLE still remains a diagnosis of exclusion as its multiple morphological presentations causes clinical overlap to other photodermatoses. This results in mistaken diagnosis and treatment diversions often ending in unwanted consequences. On the management front, the indiscriminate use of oral corticosteroids, immunosuppressants for its control lands up in intolerable adverse effects. There is also far but real carcinogenic risk involved under present first line management options (phototherapy/photochemotherapy) among PMLE patients [7].

Further, there is absence of testing for vitamin D levels and vitamin D supplementation in general global management consensus towards PMLE [8]. The present study will further to the knowledge on the role of vitamin D in pathophysiology of the illness. The study also might serve as a key to unravel the importance of vitamin D testing and a path for further trials on vitamin D supplementation in PMLE patients. The study design is to test the null hypothesis statement that the Vitamin D levels have no association with disease status of patients with PMLE. The aim of the study was to estimate the levels of serum 25-OH vitamin D levels among patients with PMLE in Melmaruvathur Adhiparasakthi Institute of Medical Sciences and Research Hospital, Melmaruvathur, Tamil Nadu, India.

## MATERIALS AND METHODS

A case-control study was conducted during January 2022 to June 2022 in Melmaruvathur Adhiparasakthi Institute of Medical Sciences and Research Hospital, Melmaruvathur, Tamil Nadu, India. The study was commenced after obtaining formal approval from Institutional Research and Ethics Committee (Reference no: MAPIMS/IEC/52/2021/196(12)2021). Informed consent was obtained from all participants before the conduct of study.

**Inclusion Criteria:** Patients aged between 40-60 years, irrespective of gender, with PMLE eruptions based on clinical diagnosis (new onset itchy maculopapular rash on sun exposure) who presented to the Dermatology Outpatient Department (OPD), Adhiparasakthi

hospitals were included as cases. Normal healthy volunteers were enrolled as controls from Master health section, Adhiparasakthi hospitals.

**Exclusion criteria:** Patients with other dermatological diseases, liver disease, renal disease, on Vitamin D supplements were excluded.

**Sample size calculation:** The minimum sample size calculated for the study by institutional statistician using formula [$n=\{(\sigma1/2+\sigma2/2)^2 (Z1-\beta+Z1-\alpha/2)^2\}/d^2$] was 42 [21 for each group] with 80% power and 95% confidence interval. Sample size was calculated using OpenEpi software [4]. A simple random sampling was followed to enroll the study subjects.

The study participants were 80 which includes 40 cases (patients with PMLE) and 40 controls (normal healthy volunteers). Clinical history including sun exposure, diet history, lifestyle activities was obtained and baseline clinical examination was conducted before drawing blood sample.

### Procedure

A 5 mL of venous blood by Venepuncture (under aseptic precautions) non fasting state was analysed for serum 25-OH cholecalciferol levels. Estimation of serum 25-OH Vitamin D levels was done by Electrochemiluminescence Immunoassay (ECLIA) [9] using Roche Cobas e411 analyser. Vitamin D deficiency and insufficiency are defined at levels <20 ng/mL and 30-20 ng/mL respectively, toxicity findings are noted at levels >150 ng/mL. Normal reference range for serum 25-OH vitamin D levels is 20-65 ng/mL [10].

## STATISTICAL ANALYSIS

The data obtained from the study were tabulated and analysed for Student's t-test and Chi-square test as tests for significance and Odds ratio by logistic regression as test for outcome association using Statistical Package for Social Sciences (SPSS) version 18.0.

## RESULTS

Total of 80 participants, 40 in each group were analysed. Mean age in case group was 50.08±5.21 years and in control group was 49.80±5.68 years. Demographic characteristics such as age, gender distribution, sunlight exposure, diet history and physical activity showed no statistically significant difference between the two groups [Table/Fig-1]. Serum 25-OH vitamin D levels were found to be significantly reduced among patients with PMLE (30.13±7.39 ng/mL) when compared to healthy controls (34.50±6.05 ng/mL) as in [Table/Fig-2].

Logistic regression analysis showed significant positive B (0.160) slope (regression coefficient) for sunlight exposure and significant negative B (-0.556) slope (regression coefficient) for serum Vitamin D levels [Table/Fig-3]. The odds of occurrence to PMLE disease state increases by 17.4% for every unit increase in sunlight exposure and decreases by 42.6% for every unit increase in Vitamin D levels.

| Parameters | Group 1 (Cases) (N=40) | Group 2 (Controls) (N=40) | Test statistic | p-value |
|---|---|---|---|---|
| **Age** (years) | 50.08±5.21 | 49.80±5.68 | 0.226 | 0.822 |
| **Male** (N (%)) | 25 (62.5%) | 28 (70%) | $\chi2$=0.503 | 0.478 |
| **Female** (N (%)) | 15 (37.5%) | 12 (30%) | | |
| **Average sunlight exposure per day** (minutes) | 54.38±23.21 | 50.63±22.79 | 0.729 | 0.468 |
| **Diet history** | | | | |
| Carbohydrate intake (g/day) | 347.13±23.77 | 352.25±27.87 | -0.885 | 0.379 |
| Lipid intake (g/day) | 32.5±6.4 | 32±5.03 | 0.388 | 0.699 |
| Protein intake (g/day) | 45.88±6.59 | 44±5.08 | 1.424 | 0.158 |
| **Physical activity** | | | | |
| Sedentary lifestyle (N (%) | 14 (35%) | 16 (40%) | 0.213 | 0.818 |
| Active lifestyle (N (%)) | 26 (65%) | 24 (60%) | | |

**[Table/Fig-1]:** Demographic data of cases (n=40) and controls (n=40); Quantitative variables between the two groups were compared using Independent sample t-test (p-value) and Qualitative variables using Chi-square test ($\chi2$ ); *p≤0.05 was considered to be significant

| Analyte | Group 1 (Cases) | | | Group 2 (Controls) | | | t-statistic | p-value |
|---|---|---|---|---|---|---|---|---|
| | Categories | N (%) | Mean±S.D | Categories | N (%) | Mean±S.D | | |
| Serum 25-OH vitamin D (ng/ml) | Sufficient | 17 (42.5%) | 30.13 ± 7.39 | Sufficient | 29 (72.5%) | 34.50±6.05 | -2.89 | **0.005*** |
| | Insufficient | 18 (45%) | | Insufficient | 11 (27.5%) | | | |
| | Deficient | 5 (12.5%) | | Deficient | - | | | |

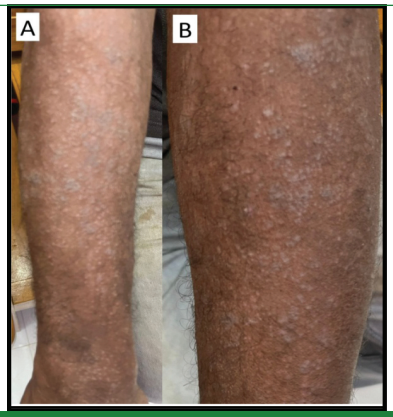
**[Table/Fig-2]:** Serum 25-OH vitamin D levels among study participants. Vitamin D cut off levels for each category: (Sufficient:≥30 ng/mL Insufficient: 20-30 ng/mL Deficient:≤20 ng/mL). Statistical significance between the two groups were compared using Independent sample t-test (p-value);. * p≤0.05 was considered to be significant; Total N=40 in each group

| Variables | B | S.E | p-values | Exp (B) | 95% CI for Exp (B) | |
|---|---|---|---|---|---|---|
| | | | | | Lower | Upper |
| Serum Vitamin D | -0.556 | 0.129 | **<0.001*** | 0.574 ‡ | 0.446 | 0.738 |
| Age | 0.102 | 0.069 | 0.138 | 1.107 | 0.968 | 1.267 |
| Gender | 0.126 | 0.689 | 0.855 | 1.134 | 0.294 | 4.374 |
| Sunlight exposure | 0.160 | 0.039 | **<0.001*** | 1.174 †: | 1.088 | 1.266 |
| Carbohydrate intake | -0.019 | 0.014 | 0.188 | 0.981 | 0.954 | 1.009 |
| Lipid intake | 0.070 | 0.058 | 0.224 | 1.073 | 0.958 | 1.201 |
| Protein intake | -0.066 | 0.063 | 0.291 | 0.936 | 0.828 | 1.058 |
| Lifestyle | -1.137 | 0.777 | 0.143 | 0.321 | 0.070 | 1.471 |

**[Table/Fig-3]:** Logistic Regression model for exposure outcome association between the predictor independent variables and the outcome dependent variable (PMLE disease state). B-regression coefficient; SE: standard error; Sig. p-value; Exp(B): Odds ratio; CI: Confidence interval; * p≤0.05 was considered to be significant; †: OR>1; ‡: OR< 1; p-values are significant

## DISCUSSION

Polymorphic Light Eruption (PMLE) is an acquired idiopathic photo dermatosis with possible genetic predisposition. The commonest clinical presentation of the disease is smooth topped erythematous papular rashes on the sun exposed areas [Table/Fig-4]. Study done by Gruber-Wackernagel A et al., [4] proposed Vitamin D insufficiency as cause towards resistance against immunosuppression by UV in PMLE.




**[Table/Fig-4]:** Polymorphic Light Eruptions. A, Macular eruptions on wrist and forearm B, Maculopapular eruptions on the forearm

Similar findings were reported by other studies, strengthening the role of vitamin D in PMLE [4,11-13]. Though the present study did not establish vitamin D deficiency among PMLE patients with only 12.5% of cases being deficient, yet most (45%) of the cases were found in pre-deficiency/insufficiency states for vitamin D. This clearly indicates preliminary states progressing towards Vitamin D deficiency having strong associations with PMLE disease. Hence the null hypothesis that vitamin D levels have no association with disease status of PMLE patients can be rejected.

Resistance to UV mediated immune suppression remains a primary event in PMLE pathogenesis. Many factors are responsible for this resistance which includes alterations in Antigen Presenting Cells (APCs) like dendritic and Langerhans cells, Regulatory T cells (Tregs) suppression, participation of Toll Like Receptors (TLR), involvement of several cytokines and subsequent inflammatory components, all pointing towards aberrations of antigen presentation to aberrations of immunological responses to it. Other abnormalities in PMLE includes mast cell recruitment, oxidative stress, failure in apoptosis and dermal microbiome dysbiosis. Not surprisingly, vitamin D has strong footprints at all corners of these stresses and aberrations. The literature evidences systematically rolls through each aspects both from Ultraviolet Radiation (UVR) side and Vitamin D side in PMLE [14-29].

Langerhans cells, as a part of Skin Immune System (SIS) act as agents for dermal immune surveillance. Together with dendritic cells, they perform primary function of antigen presentation to Tregs. UVR exposure causes epidermal Langerhans cell abnormalities [14] and dendritic cell alterations [15] affecting their function. Resistance observed in PMLE patients makes them resurface back leading to immunological activation. On the other hand, Vitamin D appears to have a functional link between APCs and Tregs. Vitamin D affects both the structure and function of Langerhans cells [15] and dendritic cells [16], thus, modulating the immunological role.

Further, the immunological response is determined by the type of T cell recruitment with the induction of Tregs suppressing the response, whereas the induction of Effector T cells (Teffs) activating the response. UVR exposure creates proportionality differences between Tregs and Teffs that leads to suppression of immune response. Resistance to UVR mediated immune suppression observed in PMLE patients causes Cluster Differentiation (CD) 4+ and CD8+ T cells infiltrations [17], a possible delayed type hypersensitivity response to possible photoallergen. Pathological findings also confirm the presence of dense perivascular infiltrate involving predominantly dendritic cells and Tregs [18]. On the contrary, all the immunological cells including lymphocytes also express Vitamin D receptors [19]. As Vitamin D plays the role of mediator of T cell regulation, so has profound potential in modulating immunological processes. Immunomodulatory effect of Vitamin D has been noted through downregulation of expression of TLRs [20].

In deflective contrast to the results of the present study, studies like Schweintzger NA et al., [5] did not conclusively established any role of vitamin D among PMLE patients. Possible reason includes non-Vitamin D pathways mediating UVR related immunological mechanisms as both Vitamin D dependant and independent pathways exist. This suggests that Vitamin D independent pathways could serve a predominant role in pathogenesis among certain PMLE patients [5].

But logistic regression analysis of the present study shows significance of Vitamin D dependent pathway indirectly as there were significant Odds association for Sunlight (UV) exposure and serum Vitamin D levels [among independent predictor variables] towards PMLE disease state [outcome dependent variable] in an inverse manner. Beyond this, there seems to be additional causes behind PMLE pathogenesis. UVR exposure increases mast cell density in papillary dermis of PMLE lesions which is evidenced by dermal oedema. A known hypersensitivity mediator, mast cells, also are known to switch over from immunosuppressive mediation to pro-inflammatory mediation with activation of Tregs and Teffs, respectively, depending on the role it performs. While UVR exposure leads to keratinocyte necrosis which activates TLR-3 as proinflammatory signal [21]. Vitamin D decreases inflammation [22] by regulating Tregs through FOXP3 (Forkhead box P3) expression and by interfering with signalling of inflammatory cytokines Tumor Necrosis Factor-alpha (TNF$\alpha$) and Nuclear Factor Kappa Beta (NF$\kappa\beta$) [23].

Oxidative stress seems to contribute to PMLE lesions. While UVR exposure initiates Reactive Oxygen Species (ROS) formation with modification of redox status because of genetic modifications that compromises antioxidant capacity [24]. Vitamin D counters by increasing intracellular pool of glutathione and inducing ROS scavenging enzymes like Super Oxide Dismutase (SOD) [25].

Apoptosis failure in PMLE creates a conducive milieu towards formation of potential auto antigen and downstream immunological mechanisms [26]. While UVR exposure takes the blame for it by lowering gene expression related to apoptotic cell clearance, Vitamin D counters by triggering apoptosis in cells via induction of apoptotic calcium signal that recruits downstream effectors and proteases [27].

Dermal microbiome dysbiosis has been observed in PMLE. While UVR exposure causes microbiome abnormalities [28] Vitamin D and its VDR signalling has been shown to be modulating it. Vitamin D appears to be a critical intermediary player in the interconnections between immune system and microbiome [29].

Negating these immune inflammatory abnormalities, photochemotherapy and corticosteroids remain mainstay treatment options in PMLE. But given its modulation role, vitamin D could be a better safety option in restoration, avoiding the adverse events of the former. Though the present study population were not followed up with therapeutic vitamin D supplementation, other studies [11,30] showed the prophylactic role of vitamin D in PMLE patients with significant results. Vitamin D could do this by increasing Treg numbers that can suppress any excessive immune responses [31]. Possibly, vitamin D deficients and pre-deficients could not mount this immune suppression resulting in resistance ultimately leading to PMLE disease state.

### Limitation(s)

The study lacks parallel aetiological justifications as investigations like Treg number counts, oxidative stress markers, apoptotic gene polymorphisms, inflammatory cytokine levels were not measured. It also lacks cellular presence evidences as PMLE lesional skin biopsies were not taken citing invasiveness which could have otherwise proved strong immunological pathogenesis. Seasonal variations on Vitamin D levels were not included in the study. This might affect both dependant and predictor variables, a possible confounder that the study did not addressed. Presence of UV mediated immune suppression in healthy controls and its reversal (resistance to UV mediated immune suppression) in PMLE patients were not evidently established. Above all, the study lacks clinical extrapolation as follow up Vitamin D supplementation with correlation on regression of PMLE lesions was not done.

## CONCLUSION

Sunlight (UV) exposure is at the cross roads for both PMLE lesions and Vitamin D synthesis creating easy expectations for Vitamin D levels on the higher end in PMLE patients. But on the contrary, most PMLE patients were found to have significantly lower Vitamin D levels with majority in the predeficient zones. Pathogenetic involvement of Vitamin D is evidently obvious through multiple mechanisms from antigen presentation through T cell regulation to immunological manifestations of PMLE lesions. There seems to exist a constant fight between UV exposure and Vitamin D which snowballs into confluence of stresses where UV exposure finds a cause to create it, and Vitamin D yielding a solution whatsoever. Being a measurable analyte and a healthy supplement, Vitamin D could further serve as a laboratory tool in PMLE diagnostics and a supplemental option in PMLE therapeutics following thorough validations in future.

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**PARTICULARS OF CONTRIBUTORS:**

1. Professor, Department of Biochemistry, Melmaruvathur Adhiparasakthi Institute of Medical Sciences and Research [Affiliated to TNMGRMU, Guindy, Melmaruvathur, Tamil Nadu, India.
2. Assistant Professor, Department of Biochemistry, Government Medical College, Omandurar Government Estate [Affiliated to TNMGRMU, Guindy], Chennai, Tamil Nadu, India.
3. Assistant Professor/Consultant, Department of Biochemistry, Tamil Nadu Government Multi Super Speciality Hospital, Omandurar Estate [Affiliated to TNMGRMU, Guindy], Chennai, Tamil Nadu, India.

**NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:**
K. Gunanithi,
Flat No.104, Malligai Block, Invicon SSP Flats, Krishna Nagar, 6th Street, West Tambaram, Chennai-600 045, Chennai, Tamil Nadu, India.
E-mail: gunamededu@gmail.com



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- iThenticate Software: Nov 21, 2022 (9%)

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