Low Vitamin D in Psoriasis: Reality or Myth?
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Abstract
Context: Psoriasis is a chronic, systemic disease with the beneficial effect of topical vitamin D3 analogs, known for a long time. Low levels of vitamin D are increasingly found to be associated with the initial development of some autoimmune diseases. There are contradictory reports of low serum levels of vitamin D3 in the pathogenesis of psoriasis. Aims: (1) To determine the serum levels of vitamin D, calcium and C-reactive protein (CRP) in patients with psoriasis vulgaris, (2) To compare these levels with the serum levels of controls, and (3) To correlate them with the severity of the disease. Subjects and Methods: A hospital-based case–control study with 61 patients of psoriasis and 61 age- and sex-matched controls was undertaken. A detailed history was taken and examination including body mass index, Psoriasis Area and Severity Index (PASI) was done. Estimations of serum vitamin D, serum calcium, and CRP levels were done. Results: Mean 25(OH) vitamin D level was not significantly different between persons with and without psoriasis. Mean vitamin D level in cases was 18.41±9.41 and that in controls was 17.24±13.03 (P=0.63). However, vitamin D level were significantly lower in females than in males in both cases (P=0.02) and controls (P=0.006). There was no significant correlation between the severity of psoriasis and serum levels of vitamin D, serum calcium, and CRP. Conclusions: Serum level of vitamin D did not correlate with the severity of psoriasis in our study.

Key Words: C-reactive protein, Psoriasis Area and Severity Index, psoriasis vulgaris, serum calcium, serum vitamin D

What was known?
Contradicting evidence of an association between serum vitamin D levels and the severity of psoriasis vulgaris.

Introduction
Psoriasis is an immune-mediated polygenic skin disorder.\(^1\) Although the cause of psoriasis remains unknown, increasing evidence suggests that psoriasis is a complex disorder caused by the interaction of multiple genes, the immune system, and environmental factors.\(^2\) Its pathogenesis is not clear, but it is a known fact that there is activation of sectors of innate and adaptive immune responses.\(^3\) Vitamin D regulates both innate and adaptive immunity, and it is an established fact that lower levels of vitamin D are associated with the initial development of some autoimmune diseases and premature mortality.\(^4,5\) Vitamin D also plays a vital role in the metabolism of calcium. Hypocalcemia is a known risk factor in precipitating pustular psoriasis.\(^6,7\) C-reactive protein (CRP) has been recognized as one of the most sensitive markers of inflammation, and it is associated with cytokines responsible for skin inflammation. CRP may also be employed as a measure of disease severity in psoriatic patients along with the Psoriasis Area and Severity Index (PASI).\(^8\) The aims and objectives of this study were: (1) To determine the serum levels of vitamin D, calcium and CRP in patients with psoriasis vulgaris. (2) To compare these levels with the serum levels of controls. (3) To correlate them with the severity of the disease.

Subjects and Methods
This case–control study involving 122 patients was conducted in the outpatient department of Dermatology, Venereology, and Leprosy, of Justice K S Hegde Charitable Hospital, Deralakatte from October 2015 to March 2017.

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Sixty-one patients with psoriasis were enrolled in the study along with 61 age- and sex-matched controls. This study was commenced after obtaining the clearance from the Institutional Ethics Committee. Inclusion criteria were age >18 year, patients with chronic plaque-type psoriasis who have not received topical treatment in the previous month or systemic therapy over the past 3 months. Age- and sex-matched controls without psoriasis vulgaris attending dermatology outpatient department for minor ailments without any inflammatory disorder were included in the study. Other types of psoriasis, those on treatment with vitamin D supplements or phototherapy, chronic inflammatory diseases such as multiple sclerosis, inflammatory bowel disease, rheumatoid arthritis, lupus erythematosus, cutaneous lymphoma, nonmelanoma skin cancer, or any other cancer were excluded from the study.

After fulfilling the selection criteria, all patients were counseled about the study and informed written consent was obtained. A detailed history and complete physical examination including the extent of disease, type of lesion, body mass index (BMI), PASI of the patients along with the local examination of the psoriatic plaques were undertaken. Investigations done included the estimation of serum vitamin D [25(OH) vitamin D] level, serum calcium level, CRP level, and complete hemogram.

The severity of PASI score was graded as mild, moderate, and severe with scores of <5, 5–10, and >10, respectively. A revised BMI for Asian Indians recommended by the World Health Organization was considered as the reference value and interpreted as follows - <18.5 kg/m² as underweight, 18.5–23 kg/m² as normal 23–27.5 kg/m² as overweight, and 27.5 kg/m² or higher as obese. Deficiency, insufficiency, and normal levels of serum vitamin D was considered at levels <20 ng/ml, 20–30 ng/ml, and 30–100 ng/ml, respectively.

**Statistical analysis**

The data collected were entered into Microsoft Excel spreadsheet and analyzed using IBM SPSS Statistics, version 22 (IBM Corp, Armonk, NY, USA). Descriptive data were presented in the form of frequency, the percentage for categorical variables and in the form of mean, median, standard deviation, and quartiles for continuous variables. Kruskal–Wallis test, Fisher’s exact test, and Chi-square test were also done to determine the differences in various study variables among cases and controls. Spearman’s correlation test was used to test the correlation between study variables. A value of \( P<0.05 \) was considered statistically significant.

**Results**

A total of 61 patients with psoriasis and 61 age- and sex-matched controls were enrolled in this study. Among the 122 individuals participated, 94 (77%) were male and 28 (23%) were female with a male-to-female ratio of 3.36:1. The average age was 44.12±13.15 years in cases and 43.15±13.15 years in controls. Majority of the psoriatic patients (41.0%) belonged to the age group of 50–65 years [Tables 1 and 2].

Out of 61 patients, two patients had associated psoriatic arthritis (3.3%), 23 (37.27%) had nail involvement and 49 (80.3%) had scalp involvement along with body lesions. Forty-five (73.7%) patients had psoriasis for <5 years duration whereas 16 (26.2%) had psoriasis for more than 5 years. The mean duration of psoriasis was 73.38±91.20 months [Table 2].

**Table 1: Demographic and clinical characteristics of the participants**

| Group                  | Study n (%) | Control n (%) |
|------------------------|-------------|---------------|
| Age                    |             |               |
| 18-33                  | 17 (27.9)   | 17 (27.9)     |
| 33-49                  | 19 (31.1)   | 19 (31.1)     |
| 50-65                  | 25 (41.0)   | 25 (41.0)     |
| Sex                    |             |               |
| Female                 | 14 (23.0)   | 14 (23.0)     |
| Male                   | 47 (77.0)   | 47 (77.0)     |
| Duration (years)       |             |               |
| <1                     | 16 (26.2)   | -             |
| 1-5                    | 29 (47.5)   | -             |
| >5                     | 16 (26.2)   | -             |
| PASI                   |             |               |
| <5 (mild)              | 15 (24.6)   | -             |
| 5-10 (moderate)        | 22 (36.1)   | -             |
| >10 (severe)           | 24 (39.3)   | -             |
| BMI                    |             |               |
| Underweight            | 4 (6.6)     | 3 (4.9)       |
| Normal                 | 22 (36.1)   | 37 (60.7)     |
| Overweight             | 14 (23.4)   | 16 (26.2)     |
| Obese                  | 21 (34.4)   | 5 (8.2)       |
| Psoriasis type         |             |               |
| CPP                    | 61 (100)    | -             |
| CPP + psoriatic arthritis | 2 (3.3)    | -             |
| CPP + Nail involvement | 23 (37.27)  | -             |
| CPP + Scalp involvement| 49 (80.3)   | -             |
| CRP                    |             |               |
| Normal                 | 55 (90.16)  | 57 (93.44)    |
| High                   | 6 (9.84)    | 4 (6.56)      |
| Serum Vitamin D        |             |               |
| Deficient              | 39 (63.9)   | 41 (67.2)     |
| Insufficient           | 14 (23.0)   | 10 (16.4)     |
| Sufficient             | 8 (13.1)    | 10 (16.4)     |
| Serum calcium          |             |               |
| Normal                 | 61 (100)    | 59 (97.72)    |
| Hypocalcemia           | 0           | 2 (3.27)      |

CPP: Chronic plaque psoriasis, PASI: Psoriasis Area and Severity Index, BMI: Body mass index, CRP: C-reactive protein
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Thirteen (21.3%) patients consumed alcohol and 5 (8.2%) patients smoked on a regular basis, and it was significantly ($P=0.01$) less in controls consisting of only 2 (3.3%) individuals consuming alcohol and none smoking.

Thirty-five (57.4%) cases had a BMI $\geq 23$ kg/m$^2$ which comes under the overweight and obese category, whereas it was only 21 (34.4%) in control group. A normal BMI was seen in 22 (36.1%) cases, and 37 (60.7%) controls. There was a significant difference ($P=0.009$) in mean BMI in patients with psoriasis and those without psoriasis [Tables 1 and 2].

Among 61 patients with psoriasis 39.3% had severe disease. The mean PASI in patients with psoriasis was 9.25±5.87. There was a significant association between duration of the disease and severity of psoriasis ($P=0.02$) [Tables 1 and 2].

The mean CRP level in cases was 3.54±6.89 and that in controls was 1.97±2.79. Although not statistically significant, the estimated level of CRP was higher in patients with psoriasis compared to those without the disease [Table 2]. Serum calcium level was within normal range among 61 (100%) patients and 59 (96.7%) controls.

In our study population, 86.9% of patients with psoriasis and 83.6% of patients without psoriasis had lower levels of vitamin D. There was no significant difference in the mean levels of vitamin D among cases and controls ($P=0.10$). We found that psoriasis patients with severe disease were among those with vitamin D deficiency. However, it was not statistically significant ($P=0.67$) [Figure 1]. While correlating the severity of disease with vitamin D levels, we did not find a statistically significant correlation between the two ($r=-0.19$, $P=0.15$). There was no significant association between vitamin D levels and CRP among patients with psoriasis and among controls ($P=0.43$ and $P=1.00$, respectively) [Figure 2]. There was no significant relationship between serum vitamin D levels and BMI levels in cases ($P=0.27$) and controls ($P=0.44$). No significant association was found between serum vitamin D levels and duration of the disease ($P=0.11$)

The relation between severity of the disease given by PASI and serum levels of vitamin D, calcium, CRP in cases are presented in Table 3.

**Discussion**

Psoriasis is a chronic, systemic disease that affects 1–3% of the global population.

Multiple factors are involved in the pathogenesis of psoriasis. It is a known fact that genetic predisposition in psoriasis is vitamin D dependent if the genes have vitamin D receptor in their promoter region. In addition, the vitamin D metabolism may be abnormal in psoriasis. Vitamin D was found to up-regulate anti-inflammatory cytokines such as interleukin (IL-10) and down regulate or inhibit pro-inflammatory cytokines such as IL-6 and TNF-$\alpha$. In psoriatic skin, the cytokines IL-1, IL-6, and TNF-$\alpha$ are up-regulated. $^{[1]}$ 1,25(OH)$_2$D$_3$, an

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**Table 2: Mean and standard deviation of various parameters in patients with psoriasis and those without psoriasis**

| Parameter          | Patients with psoriasis | Controls without psoriasis |
|--------------------|-------------------------|-----------------------------|
| Age (years)        | 44.11±4.11              | 43.15±3.15                  |
| Hemoglobin (g/dl)  | 14.03±1.59              | 13.74±1.92                  |
| Total count (c/cumm) | 6905.57±1631.78        | 7224.59±1831.0              |
| BMI (kg/m$^2$)     | 23.34±3.50              | 21.93±2.22                  |
| PASI               | 9.25±5.87               | 0                           |
| CRP (mg/L)         | 3.54±6.89               | 1.97±2.79                   |
| Vitamin D (ng/ml)  | 18.41±9.41              | 17.24±13.03                 |
| Calcium (mg/dl)    | 9.74±0.61               | 9.55±0.56                   |

PASI: Psoriasis Area and Severity Index, BMI: Body mass index, CRP: C-reactive protein

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**Figure 1:** Serum levels of vitamin D, calcium and C-reactive protein in relation with severity of psoriasis

**Figure 2:** Levels of Vitamin D in relation to the severity of C-reactive protein among cases and control
active metabolite of vitamin D is known to regulate both innate and adaptive immunity and also has a role of modulation of dendritic cells.\textsuperscript{[2,4,10-12]} There are conflicting reports of clinical improvement in psoriatic lesions following oral supplement of vitamin D with a few studies showing good improvement and others showing none.\textsuperscript{[10,11,13]} We observed that majority of our study population had low serum levels of vitamin D. Vitamin D deficient subjects had the severe form of the disease. However, a correlation could not be made between the severity of the disease and serum levels of vitamin D. Various studies showing association/no association between serum vitamin D levels and psoriasis are given in Table 4.

| Table 3: Relation between severity of the disease given by Psoriasis Area and Severity Index and serum levels of vitamin D, calcium, C-reactive protein among cases |

| PASI (case) | Serum calcium | Total (%) | Fishers exact test |
|-------------|---------------|-----------|--------------------|
|             | Normal (%)    | Hypocalcemia (%) |                  |
| Mild        | 15 (100.0)    | 0          | 15 (100.0)         | -                  |
| Moderate    | 22 (100.0)    | 0          | 22 (100.0)         |                    |
| Severe      | 24 (100.0)    | 0          | 24 (100.0)         |                    |

| PASI (case) | CRP | Total (%) | Fishers exact test |
|-------------|-----|-----------|--------------------|
| Normal (%)  |     |           |                    |
| Mild        | 13 (86.7) | 2 (13.3) | 15 (100.0)         | \( P=0.64 \)      |
| Moderate    | 21 (95.5) | 1 (4.5)  | 22 (100.0)         |                    |
| Severe      | 21 (87.5) | 3 (12.5) | 24 (100.0)         |                    |

| PASI (case) | Serum vitamin D | Total (%) | Fishers exact test |
|-------------|-----------------|-----------|--------------------|
|             | Deficient (%)   | Insufficient (%) | Sufficient (%) |
| Mild        | 9 (60.0)        | 4 (26.7) | 2 (13.3)           | 15 (100.0)         | \( P=0.67 \)      |
| Moderate    | 12 (54.5)       | 6 (27.3) | 4 (18.2)           | 22 (100.0)         |                    |
| Severe      | 18 (75.0)       | 4 (16.7) | 2 (13.1)           | 24 (100.0)         |                    |

PASI: Psoriasis Area and Severity Index, CRP: C-reactive protein

| Table 4: Various studies showing association/no association between serum levels of vitamin D and psoriasis |

| Study by | Place of study | Cases (n) | Control (n) | Mean value (ng/ml) | \( P \) |
|----------|----------------|-----------|-------------|--------------------|--------|
|          | Studies showing association between vitamin D and psoriasis |
| Gisondi et al.\textsuperscript{[10]} | Italy | 145 | 141 | Cases - 20.7±11.3 | Control - 37.1±27.6 | 0.001 |
| Orgaz-Molina et al.\textsuperscript{[14]} | Spain | 43 | 43 | Cases - 24.4±7.80 | Control - 29.5±9.38 | 0.007 |
| Atwa et al.\textsuperscript{[9]} | Egypt | 43 | 40 | Cases - 11.7±1.74 | Control - 24.5±9.3 | 0.000 |
| Chandrashekar et al.\textsuperscript{[15]} | Puducherry, India | 43 | 43 | Cases - 13.3±6.9 | Control - 22.4±18.4 | 0.004 |
| Al-Mutairi et al.\textsuperscript{[16]} | Kuwait | 100 | 100 | Cases - 31.5±14.41 | Control - 53.5±19.6 | 0.005 |
|          | Studies showing no association between vitamin D and psoriasis |
| Zuchi et al.\textsuperscript{[3]} | Brazil | 20 | 20 | Cases - 23.5±7.60 | Control - 22.3±3.10 | 0.7356 |
| Wilson\textsuperscript{[5]} | USA | 148 | 5693 | Cases - 24.2±1.5 | Control - 23.6±0.9 | 0.37 |
| Morimoto et al.\textsuperscript{[17]} | Japan | 34 | 24 | Cases - 22±7 | Control - 21±15 | NS |
| Maleki et al.\textsuperscript{[18]} | Iran | 50 | 43 | Cases - 14.9±6.31 | Control - 12.5±4.54 | 0.21 |
| Solak et al.\textsuperscript{[19]} | Turkey | 43 | 41 | Cases - 21.2±8.7 | Control - 25.2±14.1 | 0.120 |

NS: Not significant
The findings of low vitamin D in both the cases and the controls in male patients make us ponder about its role in the pathogenesis of psoriasis. Vitamin D deficiency of 70–100% was observed in studies conducted in different parts of India in seemingly healthy individuals. Along with low intake, insufficient sun exposure, vegetarian diet with high phytate/calcium ratio, genetic, and epigenetic factors have been postulated for this observation. Thus, we speculate Indian population could have been acclimatized to the relatively low level of vitamin D and hence, any significance drawn from the finding of low levels may be erroneous.

Intracellular calcium plays a major role in the differentiation and proliferation of keratinocytes. In psoriasis, intensification and extension of lesions are seen following decrease in levels of calcium. There are many reports of the occurrence of generalized pustular psoriasis and erythroderma, severe forms of psoriasis in association with mild hypocalcemia.

There was no significant difference in mean levels of serum calcium in mild, moderate, and severe psoriasis (P=0.83). As none of the cases of psoriasis had abnormal serum calcium level, the relation between severity of the disease and serum calcium level could not be assessed. Similarly, Gisondi et al. also did not find any difference in the mean serum calcium level of psoriatic patients and controls ([9.5±0.4 mg/dl and 9.3±0.3 mg/dl] (P=0.2)). Contradictory to our study, Solak et al. observed significantly low mean serum calcium level in psoriasis patients as compared to controls [(9.4±0.4 mg/dl and 9.7±0.2 mg/dl) (P=0.006)].

In this study, 9.8% of the cases and 6.6% of the controls had CRP levels above 6 mg/L. We found a significant difference between mean levels of CRP among cases and controls (P=0.002). However, we could not correlate significantly between CRP levels and the severity of psoriasis (r=0.12, P=0.36). This finding was contradictory to a previous study which had shown a significant relation between CRP and disease severity. We believe this is because of remitting and relapsing nature of the disease and also at what point estimation of CRP was done. Estimation, during an active state of the disease, might give a higher CRP value. As the study patients were chronic plaque psoriasis, ongoing low-grade chronic inflammation was speculated for raised CRP in our patients.

A study observed that CRP had a positive correlation with PASI, neutrophils and its activation products elastase and lactoferrin, total leukocyte and specific inhibitor of elastase alpha-1 antitrypsin. This strengthens the association between psoriasis and increased level of inflammatory mediators. Hence, CRP may be used as a blood marker for severity along with the visual aid of PASI. However, another study did not show a significant relation between CRP and PASI, and it concluded that there is no single tool for assessing the severity of psoriasis. They supported the hypothesis that a combination of inflammatory markers with different coefficients is required like that of the combination of PASI score along with plasma levels of elastase and CRP.

The limitations of this study include its small sample size; hence, this may not be the actual reflection of the general population. As this study was conducted throughout the year, seasonal changes which can cause variation in levels of vitamin D were not considered. Finally, dietary factors which might contribute to the blood level of calcium and a certain extent to vitamin D were not considered.

Conclusion
The severity of psoriasis did not correlate with vitamin D and CRP levels

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Conflicts of interest
There are no conflicts of interest.

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