TaqI polymorphism T/t genotypes at the vitamin D receptor gene (VDR) are associated with increased serum vitamin D levels in mild and moderate psoriasis vulgaris: A pilot study

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Abstract

Background: Several types of polymorphisms in vitamin D receptor (VDR) have been found in psoriasis.

Aim: This study looked at the role of the TaqI polymorphism in the VDR gene as a factor in changing plasma 25-hydroxyvitamin D [25(OH)D] levels in psoriasis patients and to see if it had any relationship with disease severity.

Subjects and Methods: Clinical examination, serum 25(OH)D level measurement, molecular studies and TaqI genotyping by PCR and RFLP were performed for the two groups.

Results: The T/t genotypes of TaqI polymorphism genotypes were most common in patients, while the t/t genotypes were more abundant in healthy subjects. The T allele was high in the patient group in comparison with the normal subjects, but there were no significant differences ($p = 0.421$). Patients with T/T TaqI genotypes had higher levels of 25(OH)D than those with T/T and t/t ($p = 0.004$). Moderate psoriatic patients with the T/t genotype had relatively high 25(OH)D levels compared with moderate patients with the T/t and t/t genotypes ($p = 0.001$).

Conclusion: The increase in 25(OH)D titers in moderate patients is greater than that in mild and severe patients. T/t genotypes are associated with increased 25(OH)D levels in moderate and mild patients.

Keywords

psoriasis, TaqI polymorphism, VDR, vitamin D

INTRODUCTION

Psoriasis is a repetitive, immune-mediated inflammatory condition defined by clearly delineated, erythematous papules and plaques enveloped in silvery-white scales.1 Psoriasis affects 2–4% of the world’s population. People of both genders suffer equally, while the disorder primarily affects individuals between the ages of 20 and 30, and 50 and 60.2

Vitamin D3 (cholecalciferol) in its natural state is mainly synthesized in the skin and acquired through nutrition.3,4 Its bio-active form, 1,25-dihydroxyvitamin D [1,25-dihydroxycholecalciferol or 1,25 (OH) 2D3], which acts through a specialized vitamin D receptor (VDR), is implicated in various operations, such as transcriptional regulation of various genes to facilitate their genomic activity on calcium homeostasis, aging, immune function, immune modulation, cell growth, proliferation and differentiation.5–12

The VDR, a member of the nuclear steroid receptor subgroup, has many polymorphisms: BsmI, TaqI, ApaI, and FokI, and they correspond to VDR gene polymorphisms and vulnerability to atopic dermatitis, asthma and psoriasis.13–18
To the best of our knowledge, no research on the distribution of VDR gene polymorphisms in psoriasis or changes in serum vitamin 25(OH)D levels (sVDLs) has been conducted in Saudi Arabia. Therefore, researchers are interested in conducting this study to determine whether polymorphisms in the vitamin D receptor gene play a key role, especially TaqI, in the risk of psoriasis. Therefore, this study investigated the role of the TaqI polymorphism in the VDR gene as a factor in changing sVDLs in psoriasis patients and evaluated its possible relationship with clinical outcomes.

2 | SUBJECTS AND METHOD

2.1 | Subjects

This comparative case–control study was carried out in the Dermatology Outpatient Department for a year. It was carried out in accordance with the Helsinki Declaration guidelines and was authorized by the Local Ethical Committee. Before enrollment, all subjects provided written informed consent after being briefed on the purpose and nature of the study.

2.1.1 | Inclusion criteria

Adult male and female patients of any age with a clinically established diagnosis of psoriasis but with no systemic involvement were eligible.

2.1.2 | Exclusion criteria

Patients on vitamin D therapy, pregnant, lactating, or with malignancies, active liver disease or renal disorders were excluded.

In terms of subject count, we conducted a pilot study and used a small number of subjects as a “feasibility” study. It is a small-scale preliminary study conducted prior to large-scale quantitative research to assess the potential for a future study evaluating the TaqI polymorphism and its association with psoriasis severity. This has allowed us to forecast an adequate sample size, budget for it, and strengthen the study design before embarking on a full-scale project.

A total of 118 patients (64 males and 54 females) were enrolled, and the diagnosis was performed through clinical and physical examinations. Patients were divided into three groups based on the body surface area affected: severe psoriasis vulgaris involving more than 10% of the body surface; moderate psoriasis vulgaris involving 5–10% of the body surface; and mild psoriasis vulgaris involving less than 5% of the body surface.19

The remaining 94 subjects were healthy participants who were gender and age aligned to the psoriasis group (58 males and 36 females); they had no clinical evidence of psoriasis or any other autoimmune condition. Patients were recruited from the clinic when searching for medical advice. Controls were selected from close associates of the cases, such as friends and relatives who were attending with the patients or healthy escorts of dermatology patients attending the dermatology outpatient clinic.

Both groups underwent comprehensive physical and clinical assessments, genetic analysis and vitamin D estimations.

2.2 | Genomic DNA extraction

Anticoagulant Na2EDTA was used to gather samples of blood. The QIAamp® DNA BloodMini Kit was used to purify genetic DNA from 200 L of whole blood in accordance with the Blood guidelines.

2.3 | Detection of TaqI polymorphism using PCR-RFLP

To genotype the TaqI polymorphism, a genomic DNA fragment was amplified using the polymerase chain reaction (PCR) technique and a couple of oligonucleotide primers: the upstream primer sequence was 5′-CAGAGCATGGACAGGGAGCAA-3′ and the downstream primer sequence was 5′-CACTTCGACACAGGGGGCGTTAGC-3′. The primers were uploaded to the gene bank database at https://www.ncbi.nlm.nih.gov/tools/primer-blast/. Denaturation at 94°C for 3 min was followed by 35 cycles at 94°C for 60 s, 63°C for 60 s, and 72°C for 2 min, with one final extension cycle at 72°C for 5 minutes, using 100–200 ng of genomic DNA. PCR products (740 bp) were digested with TaqI restriction enzyme (Fermentas, Lithuania) at 65°C for 3 h before being loaded onto a 3% agarose gel stained with ethidium bromide. The homozygous TT (absence of the specific TaqI restriction site) produced bands at 245 and 495 bp. The homozygous Tt had fragments of 205, 245 and 290 bp, while the heterozygous Tt had fragments of 495, 205, 245 and 290 bp.20

2.4 | Serum vitamin D concentration measurements

Patients’ baseline sVDLs were determined. Blood samples were obtained from veins and analysed using the Roche Cobas e411 in less than 24 h (Roche Diagnostics System, Switzerland). According to the Food and Nutrition Board of the Institute of Medicine, sVDLs were classified as adequate (>20 ng/ml), inadequate (12–20 ng/ml) and deficient (12 ng/ml).21

2.5 | Statistical analysis

The Statistical Package for Social Sciences, version 20.0, was used to perform statistical analysis (SPSS Inc., Chicago, Illinois, USA). To assess the mean and percentage differences, an analysis of variance (ANOVA) testing was performed between more than two means. t-Tests and chi-squares were used; p > 0.05 was regarded as insignificant. Additionally, quantitative data are represented as a mean ±
standard deviation (SD), whereas qualitative data are articulated as the percentage and frequency.

3 | RESULTS

The TaqI gene polymorphism was investigated in 118 psoriasis patients (64 males and 54 females) and 94 control healthy individuals (58 males and 36 females). There was no clinical evidence or family history of psoriasis or an autoimmune condition in the healthy individuals. Table 1 displays the clinical and general data for all patients and healthy individuals.

In this study, we looked at the TaqI polymorphism of the VDR gene in 118 patients and 94 control healthy individuals (Figure 1).

A comparative of TaqI gene polymorphism genotypes in patients and control healthy individuals revealed that T/t in patients (45.8%) was the most prevalent, followed by t/t (28.8%), and then T/T (25.4%). In control healthy individuals, the most common genotype was t/t (44.6%), while the frequencies of T/t and T/T genotypes were 29.9 and 25.5%, respectively (Table 2). The allele frequency did not differ significantly between patients and control healthy individuals. The T allele was found to be more prevalent in patients than in healthy subjects (48.3 vs. 40.4%), with no significant differences ($p = 0.421$). Furthermore, there were no significant differences in the frequency of the t allele ($p = 0.883$) between patients and healthy individuals (Table 3). Serum vitamin D levels in T/t patients were statistically significantly higher ($p = 0.004$; Table 4).

When serum vitamin D levels were compared, the different clinical types of psoriasis, serum vitamin D levels were found to be higher in patients with moderate psoriasis vulgaris than in patients with mild and severe psoriasis vulgaris patients ($p = 0.032$ Table 5). The T/T genotypes were compared between clinical types, finding that serum vitamin D levels do not differ by $p = 0.723$. When comparing t/t genotypes between clinical types, the same results were observed; $p = 0.004$. Table 6 shows that there are significant differences between the T/t genotypes and the variable clinical types.

Only 12 of the 38 patients with severe psoriasis vulgaris had T/T genotypes, whereas 13 of the 32 patients with moderate psoriasis vulgaris had T/t genotypes; t/t genotypes were found in 19 of the 48 moderate patients. Vitamin D levels were higher in patients with moderate psoriasis vulgaris than in patients with severe and mild psoriasis vulgaris ($p \leq 0.001$; Table 7A). When we compared serum vitamin D levels in six patients with severe psoriasis vulgaris t/t, 13 moderate patients with T/t and eight mild patients with T/T, we discovered that T/T in moderate patients had higher levels of serum vitamin D than severe t/t and mild T/T ($p \leq 0.001$; Table 7B). There was no significant variation noted when we compared severe psoriasis vulgaris patients with T/T genotypes with T/T moderate patients and

**TABLE 1** General and laboratory characteristics of psoriatic patients and healthy subjects

| Parameters                     | Patients N (118) mean±SD | Healthy subjects N (94) mean±SD | p-Value |
|-------------------------------|--------------------------|---------------------------------|---------|
| Age                           | 42.36 ± 6.8              | 38.23 ± 58                      | 0.687   |
| Male/female (N, %)            | 64 (54%)/54 (46%)        | 58 (61.7%)/36 (38.3%)           | 0.325   |
| Severe psoriasis vulgaris (N, %) | 38 (32.2%)            | —                               | NA      |
| Moderate psoriasis vulgaris (N, %) | 32 (27.1%)         | —                               | NA      |
| Mild psoriasis vulgaris (N, %)  | 48 (40.7%)              | —                               | NA      |
| Presence of family history (N, %) | 73 (61.9%)           | —                               | NA      |
| Absence of family history (N, %) | 45 (38.1%)            | —                               | NA      |
| Serum vitamin D level (ng/ml)  | 20.4 ± 2.64             | 43.5 ± 3.56                     | 0.001*  |

SD, standard deviation; N, Number.

*Highly significant difference ($p \leq 0.001$); NA, not applicable.
### TABLE 3  Comparison of allele frequency in psoriatic patients and healthy subjects

| Allele frequency | Patients (N, %) | Healthy subjects (N, %) | p-Value |
|------------------|----------------|-------------------------|---------|
| T                | 114 (48.3%)    | 76 (40.4%)              | 0.421   |
| t                | 122 (51.7%)    | 112 (59.6%)             | 0.883   |

### TABLE 4  Comparison of serum vitamin D and TaqI gene genotypes in psoriatic patients

| Parameters | T/T (N = 30) | T/t (N = 54) | t/t (N = 34) | p-Value |
|------------|--------------|--------------|--------------|---------|
| Serum vitamin D level (ng/ml; mean ± SD) | 15.5 ± 6.89 | 28.01 ± 7.45 | 15.7 ± 9.56 | 0.004** |

SD, standard deviation.
**Mild significant differences (p ≤ 0.005).

### TABLE 5  Comparison of serum vitamin D level and variable clinical types of psoriasis in our patients

| Parameters | Severe psoriasis vulgaris (N = 38) | Moderate psoriasis vulgaris (N = 32) | Mild psoriasis vulgaris (N = 48) | p-Value |
|------------|-----------------------------------|-------------------------------------|----------------------------------|---------|
| Serum vitamin D level (ng/ml) (mean ± SD) | 16.7 ± 8.19 | 28.32 ± 7.77 | 15.8 ± 9.32 | 0.032** |

**Mild significant differences (p ≤ 0.005).

### TABLE 6  Comparison of serum vitamin D level, variable clinical types of psoriasis and the same TaqI genotypes in our patients

| Parameters | N [mean serum vitamin D level (ng/ml) for severe patients ± SD] | N [mean serum vitamin D level (ng/ml) for moderate patients ± SD] | N [mean serum vitamin D level (ng/ml) for mild patients ± SD] | p-Value |
|------------|-----------------------------------------------------------------|-----------------------------------------------------------------|-----------------------------------------------------------------|---------|
| T/T        | 12 (18.66 ± 6.7)                                                | 10 (14.86 ± 5.8)                                                | 8 (12.98 ± 3.6)                                                 | 0.723   |
| T/t        | 20 (15.64 ± 2.56)                                               | 13 (38.5 ± 4.8)                                                | 21 (29.91 ± 3.87)                                              | 0.004** |
| t/t        | 6 (14.68 ± 2.65)                                                | 9 (18.8 ± 5.8)                                                 | 19 (16.9 ± 2.88)                                               | 0.324   |
| Total      | 38 (16.3 ± 8.19)                                                | 32 (24.5 ± 7.77)                                               | 48 (20.6 ± 9.32)                                               | 0.032** |

118 patients

**Mild significant differences (p ≤ 0.005).

### TABLE 7  Comparison of serum vitamin D level, variable clinical types, and different TaqI genotypes in our patients

| A           | Severe psoriasis vulgaris (N = 12) with T/T genotype | Moderate psoriasis vulgaris (N = 13) with T/t genotype | Mild psoriasis vulgaris (N = 19) with t/t genotype | p-Value |
|-------------|------------------------------------------------------|-----------------------------------------------------|--------------------------------------------------|---------|
| Serum vitamin D level (ng/ml; mean ± SD) | 18.66 ± 6.7 | 38.5 ± 4.8 | 16.9 ± 2.88 | ≤0.001* |

B

| B           | Severe psoriasis vulgaris (N = 6) with t/t genotype | Moderate psoriasis vulgaris (N = 13) with T/t genotype | Mild psoriasis vulgaris (N = 8) with T/t genotype | p-Value |
|-------------|-----------------------------------------------------|-----------------------------------------------------|--------------------------------------------------|---------|
| Serum vitamin D level (ng/ml; mean±SD) | 18.66 ± 6.7 | 38.5 ± 4.8 | 12.98 ± 3.6 | ≤0.001* |

C

| C           | Severe psoriasis vulgaris (N = 20) with T/t genotype | Moderate psoriasis vulgaris (N = 10) with T/T genotype | Mild psoriasis vulgaris (N = 19) with t/t genotype | p-Value |
|-------------|-----------------------------------------------------|-----------------------------------------------------|--------------------------------------------------|---------|
| Serum vitamin D level (ng/ml; mean±SD) | 15.64 ± 2.56 | 14.86 ± 5.8 | 16.9 ± 2.88 | 0.998   |

D

| D           | Severe psoriasis vulgaris (N = 20) with T/T genotype | Moderate psoriasis vulgaris (N = 9) with T/t genotype | Mild psoriasis vulgaris (N = 8) with T/t genotype | p-Value |
|-------------|-----------------------------------------------------|-----------------------------------------------------|--------------------------------------------------|---------|
| Serum vitamin D level (ng/ml; mean±SD) | 15.64 ± 2.56 | 18.8 ± 5.8 | 12.98 ± 3.6 | 0.998   |

*High significant differences (P ≤ 0.001).
TaqI was chosen for several reasons: first, there have been no investigations into patients with psoriasis in Saudi Arabia (this is the first report); and second, there have been no reports on its association with psoriasis severity in Saudi Arabia. It was also chosen owing to its TaqI polymorphism and its role in vitamin D formation. In future studies, we intend to investigate the role of other polymorphisms in psoriasis and their association with disease severity one at a time.

In comparison, research published in Egypt and Croatia found no role for the VDR in psoriasis. 25-27 There have been various studies on VDR polymorphisms in psoriasis in many populations, 22-24,27-31 but nobody has conducted one on the Saudi population. We investigated the genetic impact of TaqI genotypes on serum 25-hydroxyvitamin D [25(OH)D] levels in psoriasis vulgaris patients in Saudi Arabia. Our study agreed with previous studies that supported the role of VDR gene polymorphisms in psoriasis etiopathogenesis. 22-24 In this study, we discovered that the TaqI polymorphism is associated with psoriasis.

T/t and t/t findings were significantly higher in patients than in controls. The allele frequency did not differ significantly between patients and healthy subjects. The results showed that the T allele was more prevalent in patients than in healthy subjects. This is consistent with the results of Açıkbası et al., in a study conducted on 204 participants. 18 Our findings contradict the findings of Halsall et al., 22 who reported that the T allele and T/T genotype are linked with the vitamin D3 reaction. It is well recognized that societies’ ethnic composition and genetic background significantly impact the VDR genotype distribution.

In contrast to our findings, the T/T genotype frequency was greater in patients than in healthy subjects in our previous research on Japanese psoriasis patients 29 and Asian and Turkish populations. 32 There are two possible explanations for the obvious disparity between these previous findings and ours. Initially, the size of the healthy subject population in our study was quite large. Second, Saudi Arabia has geographically distinct areas with variable climatic, ideological, social, economic and genetic variations, and the country’s population diversity complicates genetic analysis.

Our results indicate that T/t genotype patients have statistically elevated serum vitamin D levels, showing psoriatic cell resistance to vitamin D. Serum vitamin D levels were greater in moderate psoriasis vulgaris patients than in mild and severe psoriasis vulgaris patients, with \( p = 0.032 \). We looked into the relationship among TaqI genotypes, serum vitamin D levels and different clinical types of psoriasis. Significant differences were found between the T/t genotype and the variable clinical types (\( p = 0.004 \)). However, when comparing the T/T and t/t genotypes between the variable clinical types (\( p = 0.723 \) and 0.324, respectively), serum vitamin D levels did not change.

Vitamin D levels were greater in patients with moderate psoriasis vulgaris than in those with severe and mild psoriasis vulgaris (\( p = 0.001 \)). We discovered that Tt in moderate patients has higher serum vitamin D levels than severe T/T and mild T/T (\( p = 0.001 \)).

When we compared the T/t genotypes in patients with severe psoriasis vulgaris with the T/T genotypes in moderate patients and the tt genotypes in mild patients, there was no discernible difference. The same results were discovered between severe psoriasis vulgaris with T/t genotypes, moderate patients with Tt and mild patients with T/T. Despite the few patients with psoriasis studied, this is the first study to show that the T allele is more prevalent in Saudi patients with psoriasis than in healthy subjects. We hypothesized that the alleles of the polymorphic regions of the VDR gene were closely

### Table 8

Comparison of serum vitamin D level, different TaqI genotypes and the same clinical types in our patients

| Parameters                        | Severe psoriasis vulgaris \( (N = 12) \) with T/T genotype | Severe psoriasis vulgaris \( (N = 20) \) with T/t genotype | Severe psoriasis vulgaris \( (N = 6) \) with t/t genotype | \( p \)-Value |
|-----------------------------------|----------------------------------------------------------|----------------------------------------------------------|----------------------------------------------------------|--------------|
| Serum vitamin D level (ng/ml; mean±SD) | 18.66 ± 6.7                                              | 15.64 ± 2.56                                             | 14.68 ± 2.65                                             | 0.897        |
| Moderate psoriasis vulgaris \( (N = 10) \) with T/T genotype | Moderate psoriasis vulgaris \( (N = 13) \) with T/t genotype | Moderate psoriasis vulgaris \( (N = 9) \) with t/t genotype | \( p \)-Value |
| Serum vitamin D level (ng/ml; mean±SD) | 14.86 ± 5.8                                              | 38.5 ± 4.8                                               | 18.8 ± 5.8                                               | 0.0001*      |
| Mild psoriasis vulgaris \( (N = 8) \) with T/T genotype | Mild psoriasis vulgaris \( (N = 21) \) with T/t genotype | Mild psoriasis vulgaris \( (N = 19) \) with t/t genotype | \( p \)-Value |
| Serum vitamin D level (ng/ml; mean±SD) | 12.98 ± 3.6                                              | 29.91 ± 3.87                                             | 16.9 ± 2.88                                              | 0.0001*      |

*High significant differences \( p \leq 0.001 \).
linked to calcipotriol sensitivity or non-sensitivity. This study discovered that the frequency of the T/t genotype was significantly greater in the Saudi study group than in healthy subjects. 

The treatment response of patients with psoriasis to the antiproliferative effect of vitamin D3 is strongly linked to the transcriptional level of VDR mRNA. As a result, Saudi psoriasis patients with the T allele may be resistant to calcipotriol therapies. Because patients with psoriasis have both joint and connective inflammatory reactions, their non-responsiveness to calcipotriol may be correlated with the heterogeneity and severity of their psoriasis, which must be investigated. In addition to topical therapy, these patients may need systemic immunomodulatory entities to enhance therapeutic outcomes. Only a few research findings have shown the role of VDR polymorphism analysis in predicting the clinical response to calcipotriol. Halsall et al. revealed that the T allele was initially proposed to be significantly interrelated with the calcipotriol response in psoriasis patients, but only the T/T genotype was significant. According to our findings, the T/t and tt genotypes, as well as the T allele, were more common in the study group than in the controls. The disparity between the research findings could be attributed to the use of a range of therapeutic agents at different concentrations, population numbers and the genetic backgrounds of the populations investigated. In this study, we discovered that the VDR gene TaqI polymorphism is linked to an increased risk of developing psoriasis in the Saudi population. We focus on providing evidence of genetic susceptibility in Saudi psoriasis patients by demonstrating a correlation between TaqI polymorphism and psoriasis. Serum vitamin D levels were significantly higher in T/t patients with moderate and mild psoriasis vulgaris, particularly compared with other genotypes (T/T and t/t) in the same clinical type. This was consistent with the findings of Liu’s meta-analysis study.

Finally, this study found that VDR TaqI polymorphism increases psoriasis vulnerability in the Saudi population. More research into the connections between VDR polymorphisms and psoriasis vulnerability is needed, based on these findings. To explore the specific role of VDR gene polymorphisms in psoriasis pathogenesis, larger scale studies in larger populations are necessary.

5 | CONCLUSION

The research was based on the difference in vitamin D levels between patients and healthy subjects; the study also discovered a difference in vitamin D levels with different TaqI genotypes. Furthermore, moderate patients had higher increases in vitamin D levels than mild and severe patients. T/t genotypes are also linked to higher vitamin D levels in moderate and mild patients.

5.1 | Limitations

The limitations of this study are that, first, the small number of patients does not cover all regions of Saudi Arabia, and second, we recommend investigating other VDR polymorphism genotypes.

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Nil.

CONFLICTS OF INTEREST

There are no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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