Research Article

Association Of VDR (Apai Rs7975232) Polymorphism And Some Biochemical Parameters With Psoriasis In Iraqi Patients

Safana S. Dardouh[1], Mohammed A. Mohammed[1]*, Mohammad M.F. Al-Halbosiy[2]

[1]Biotechnology Department, College of Applied Science, University of Fallujah, Anbar, Iraq.
[2]Biotechnology Research Center, Al-Nahrain University, Baghdad, Iraq.

[1]E-mail: apsci.h2525@uofallujah.edu.iq , ORCID: 0009-0006-8661-8072
[1*] Mohammed.a.mohammed@uofallujah.edu.iq , ORCID: 0000-0001-9057-489X
[2] E-mail: mohammad.farhan@nahrainuniv.edu.iq , ORCID: 0000-0003-1373-4188
Corresponding author: Mohammed A. Mohammed

ABSTRACT

Background: Psoriasis is an inflammatory skin disease caused by genetic and environmental factors. Although data on Iraqi patients are poor, there may be a relation between the vitamin D receptor (VDR) gene and susceptibility to psoriasis. **Objective:** This study aims to analyze the association between the VDR ApaI (rs7975232) gene polymorphism and the tendency toward psoriasis in Iraqi patients and to evaluate serum levels of vitamin D3, ferritin, and zinc. **Method:** A case-control study was conducted on 45 patients with psoriasis and 35 age- and sex-matched control group. Genotyping of the Vitamin D receptor rs7975232 polymorphism was done by high-resolution melting (HRM) analysis. Automated analyzers tested serum vitamin D3, ferritin, and zinc levels. Statistical analyses were performed using GraphPad Prism software. **Results:** The allele frequency was considerably higher in patients (40.0%) than in the control group (24.3%), which conferred an elevated risk of psoriasis (OR = 2.07, 95% CI: 1.01–4.24, p = 0.046). AA carriers showed the lowest mean vitamin D3 level (15.0 ± 3.7 ng/mL, p = 0.0043) and highest mean ferritin level (223.6 ± 67.2 ng/mL, p = 0.0136). Levels of vitamin D3 and zinc were considerably lower in patients than in the control group (p<0.001 for both), and the highest mean ferritin level (p<0.001). **Conclusions:** The A allele of the VDR rs7975232 polymorphism was associated with increased susceptibility to psoriasis in Iraqi patients. AA carriers showed the lowest mean vitamin D3 and zinc levels and the highest mean ferritin level; however, genotype-related differences in these biochemical parameters were not statistically significant within the patient group.

Keywords: Psoriasis, VDR gene, ApaI polymorphism, vitamin D3, Ferritin, Zinc, Iraqi population.

INTRODUCTION:

Psoriasis is a persistent immune-mediated skin disorder characterized by recurrent exacerbations and chronic inflammation [1]. and also reported that it affects 2–3% of the world's population with a prevalence in Iraq of 2.3%, which is close to the global average [2]. Psoriatic lesions involves excessive proliferation of epidermal keratinocytes together with infiltration of inflammatory immune cell into the skin, primarily of the Th1/Th17 subsets, resulting in chronic inflammation and cytokine production, though the pathogenesis of psoriasis remains unclear despite extensive research [3],[4]. In addition, failure of regulatory T cell (Treg) activity may be a factor in chronic inflammation [4].

Previous studies revealed that its pathogenesis involves interactions between the different factors of Genetic vulnerability, immune system dysregulation and environmental triggering factors [2]. Psoriasis clinically manifests as scaly, erythematous plaques and patchy lesions in the skin, nails, and joints. This disease is frequently associated with pruritus and pain and the patients' health-related quality of life can be severely affected [5]. and is not sex specific, occurring in both sexes equally [6]. Several clinical variants of psoriasis have been described, including plaque, guttate, erythrodermic, pustular and site-specific forms palmoplantar, nail and scalp [7], with plaque psoriasis representing approximately 80–90% of all cases reported [8].

Vitamin D is a secosteroid hormone that undergoes binding to the vitamin D receptor (VDR) to become its active form, 1,25-dihydroxyvitamin D [1,25$(OH)_2$D]. Vit. D in psoriasis is involved in immunological responses, epidermal barrier function, and regulation of keratinocyte proliferation and differentiation [9]. Atopic dermatitis, vitiligo, alopecia areata, and psoriasis are among the dermatoses associated with decreased serum levels of 25-hydroxyvitamin D [25(OH)D] [10].

Vitamin D receptor (VDR) is a nuclear receptor protein, which is encoded by the VDR gene on chromosome 12 (12q13.11) [11]. The biological effects of active vitamin D are mediated by the vitamin D receptor (VDR), which contributes to the regulation of gene transcription, cellular proliferation, differentiation, and calcium

homeostasis [12]. Much of the research has focused on single-nucleotide polymorphisms (SNPs) in the VDR gene, with several defined by the restriction enzymes used to identify them[13]. Among over sixty identified polymorphisms, four restriction fragment length polymorphisms (RFLPs) are the most widely studied for their biological and clinical relevance: BsmI (rs1544410), ApaI (rs7975232), TaqI (rs731236) [14], and FokI (rs10735810) [15] (Figure 1).

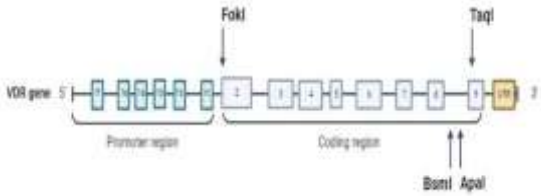


Figure 1. Schematic representation of the human VDR gene showing the four studied polymorphic sites: ApaI, FokI, BsmI, and TaqI.

The ApaI polymorphism (rs7975232) is located in the VDR gene's intron 8. Although this polymorphism does not directly change the amino acid sequence of the protein, it is believed to have an impact on gene expression, maybe through linkage disequilibrium with other functional variants or messenger RNA (mRNA) stability [14].
Biomarkers are essential for diagnosis, subclassification, prognosis, monitoring treatment, and advising therapy of inflammatory dermatoses. They have well established prognostic and response monitoring roles, but their utility in individualized therapy persists as a field of ongoing inquiry [16]. Zinc, an element with an important role in the enzymatic immune defense and antioxidant protection. Another study showed that the levels of zinc in serum are also reduced in patients with psoriasis and that this reduction may be linked to altered proliferation and inflammation of keratinocytes [17]. The results may suggest that zinc is a known biomarker that it can be correlated with the disease.
Ferritin is critical for maintaining iron homeostasis and also, has a role in several pathophysiological pathways. Being a key protein for intracellular iron storage it might reflect the severity and burden of psoriasis, with higher serum ferritin levels [18].

Literature Review

VDR polymorphisms have been investigated across a range of immune-mediated disorders because genetic variation in the receptor may contribute to differences in vitamin D signaling. Agliardi et al. (2023), in a narrative review of VDR single-nucleotide polymorphisms and autoimmunity, discussed the major VDR variants, including ApaI, in relation to immune-mediated diseases. The available evidence indicated that the relevance of individual VDR variants differed according to the disease and population examined, and their biological implications remain incompletely understood [19].
Previous research has examined VDR genetic variation not only in relation to disease susceptibility but also as a possible source of variability in biological and therapeutic responses. Usategui-Martín et al. (2022), in a systematic review and meta-analysis, evaluated whether common VDR polymorphisms influence the response to vitamin D supplementation. While significant effects were reported for some VDR variants, ApaI (rs7975232) was not significantly associated with supplementation response [14].
The possible clinical relevance of VDR polymorphisms has also been investigated in psoriasis treatment. Berna-Rico et al. (2023) reviewed pharmacogenetic studies of psoriasis and found that VDR variants have been evaluated as potential determinants of response to topical vitamin D analogues and phototherapy. For ApaI specifically, available evidence did not show a significant association with calcipotriol response in one of the populations studied. Overall, findings across VDR variants were inconsistent, limiting their current clinical application [20].
Nutritional and biochemical factors have been investigated through a separate line of psoriasis research. Patra and Harrison (2024) reviewed studies of trace elements and reported that zinc has been examined in relation to oxidative stress, serum concentrations, and clinical severity. However, results across studies were not uniform, with conflicting findings regarding trace-element levels and their relationship with psoriasis, indicating that this area remains incompletely defined [21].
Taken together, previous research shows that VDR variation and biochemical disturbances have each been investigated from different perspectives in psoriasis and related vitamin D research. However, the available

evidence does not yet provide a consistent picture of how these factors interact. This leaves scope for studies that assess genetic variation alongside biochemical measurements within the same patient population.

Significance of The Study

Previous studies have investigated the association between vitamin D receptor (VDR) gene polymorphisms and psoriasis susceptibility; however, the findings regarding the ApaI (rs7975232) polymorphism have been inconsistent across different populations[1][22][23]. Such variability highlights the importance of investigating this polymorphism in different ethnic and geographical populations. In Iraq, data concerning the association of VDR rs7975232 with psoriasis remain limited, particularly regarding its relationship with biochemical parameters. Therefore, the present study provides population-specific data by evaluating the association of the VDR ApaI (rs7975232) polymorphism with psoriasis susceptibility in Iraqi patients and simultaneously examining serum vitamin D3, zinc, and ferritin levels. The combined assessment of genetic variation and biochemical alterations may contribute to a better understanding of factors associated with psoriasis in the Iraqi population and provide a basis for larger studies to further clarify the potential role of VDR genetic variation in psoriasis.
Therefore, the present study aimed to evaluate the association between the VDR gene polymorphism (ApaI rs7975232) and psoriasis in Iraqi patients and to evaluate its association with serum levels of vitamin D3, zinc, and ferritin.

METHODOLOGY:

Study Design:
This case-control study was performed on a total of 80 Iraqi adults, including 45 patients with psoriasis and 35 control group. Following approval from the Iraqi Ministry of Health, participant recruitment and sample collection were carried out at the Dermatology Unit of AlFallujah Teaching Hospital, Anbar Province, during the period from August 2025 to December 2025.

Study Subjects:

Inclusion Criteria
Individuals enrolled in the patient group were adults aged 15–47 years with a clinically established diagnosis of psoriasis, ascertained by a specialist dermatologist, who had not been administered systemic immunosuppressive treatment in the three months before specimen collection. in the control group was apparently healthy subjects with no documented history of psoriasis, autoimmune diseases, or persistent inflammatory disorders, paired with patients with respect to age and sex.

Exclusion Criteria
Participants from both groups were deemed ineligible if they presented with a coexisting autoimmune disorder, were actively pregnant, had a prior diagnosis of chronic systemic disease, acute infection in the four weeks prior to enrollment, or ongoing use of micronutrient supplementation.

Sample Collection
Each participant had a venous blood sample (5 mL) taken with a disposable syringe. Samples were divided into two portions: three milliliters were transferred into gel tubes and allowed to clot at room temperature (20–25°C). Serum samples were isolated by centrifugation at 3000 rpm for 5 minutes and aliquoted into Eppendorf tubes and stored at –20°C until further analysis for biochemistry and immunological testing. while the remaining two milliliters were placed into EDTA tubes for genetic examination.

Routine Analysis
Serum vitamin D3 levels were quantified using a Cobas e411 immunoassay analyzer (Roche Diagnostics, Germany). Levels of ferritin and zinc were determined using automated chemistry analyzers (Roche Diagnostics, Germany). Every assay was carried out in compliance with the manufacturer's instructions.

Extraction of DNA
Genomic DNA was isolated from whole blood using the AccuPrep® Genomic DNA
Extraction Kit (Bioneer, Republic of Korea) according to the instruction manual.

Agarose Gel Electrophoresis of DNA

Agarose gel electrophoresis was used to assess the isolated genomic DNA's integrity. Red Safe nucleic acid stain was used after samples were electrophoresed on a 1% agarose gel made in 1× TBE buffer. Following electrophoresis at 70 V for 30 minutes, DNA bands were observed under ultraviolet illumination as shown in figure 2.

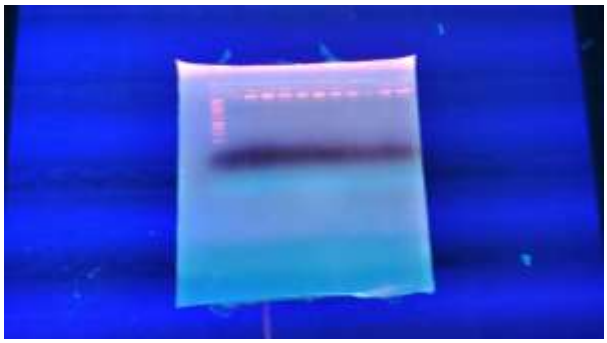


Figure 2. Agarose gel electrophoresis of representative genomic DNA samples. The first lane shows the DNA ladder, while the remaining lanes represent amplified PCR products from representative samples.

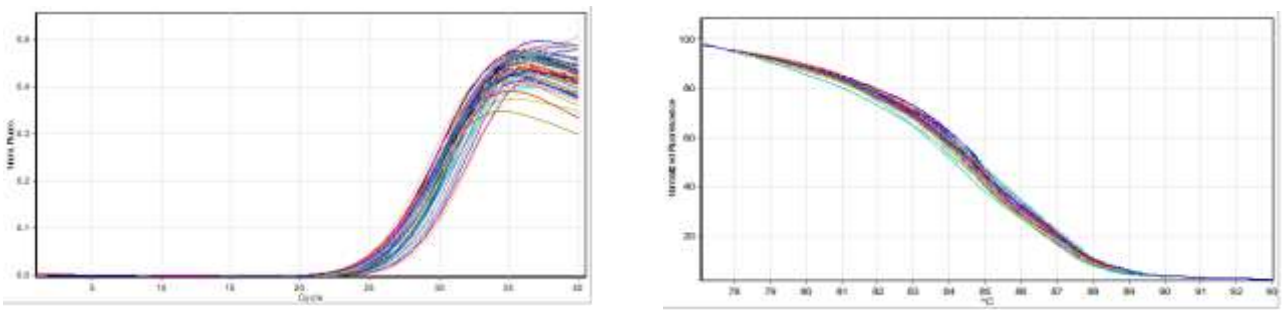
VDR ApaI rs7975232 polymorphism genotyping using HRM-PCR

High-resolution melting (HRM) analysis was used to genotype the VDR ApaI (rs7975232) polymorphism. To guarantee target specificity, particular primers were created using the
NCBI reference sequence. The forward primer sequence was 5'GGATAGAGAAGAAGGCACAGGA-3' (22 bp; Tm = 59.85°Cand an amplicon of 90 bp was produced using the reverse primer sequence 5'-CTGCCGTTGAGTGTCTGTGT-3' (20 bp; Tm = 59.94°C). Alpha DNA Ltd. (Canada) produced the primers, which were then diluted in water devoid of nuclease to create 100 µM stock solutions and kept at -20°C. 10 µL of stock was diluted in 90 µL of nuclease-free water to make functional solutions (10 µM), which were then kept at -20°C until needed.

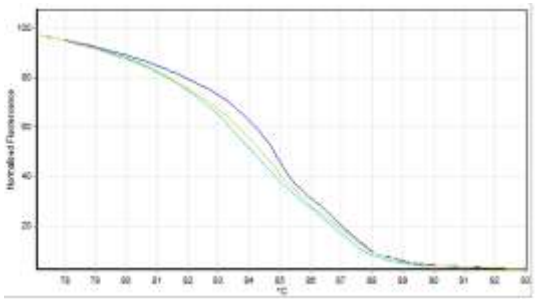
The TransStart® Tip Green qPCR SuperMix (Catalog No. AQ141-01, TransGen Biotech), which includes TipTaq DNA polymerase, dNTPs, EvaGreen I dye, and PCR enhancers, was used to perform PCR amplification for HRM analysis in a total volume of 20 µL. 10 µL of 2× SuperMix, 1 µL of forward and reverse primers (10 µM), 4 µL of genomic DNA (100– 200 ng per reaction), and 4 µL of nuclease-free water made up the reaction mixture.

Thermal cycling was performed on a Rotor-Gene Q Real-Time PCR System using the following conditions: 30 seconds at 94°C to activate the enzymes, followed by 40 cycles of amplification using the following cycle times: Denature at 94°C for 5 seconds, anneal for 15 seconds at 60°C; extend at 72°C for 20 seconds. After amplification, High Resolution Melting analysis was performed by increasing the temperature in increments of 0.2°C from 55°C to 95°C.

Rotor-Gene software (version 4.4) was used to create normalized melting curves and differential curves. Based on clustering of HRM curves, the genotypes were assigned as heterozygous (CA), homozygous mutant (AA), or homozygous wild-type (CC). The VDR gene's intronic region contains the rs7975232 (C>A) polymorphism (chromosome 12:47845054, GRCh38). The HRM analysis, including the amplification curve and normalized fluorescence curves, is presented in Figure 3.



(A) (B)



(C)

Figure 3. High-resolution melting (HRM) analysis of the VDR rs7975232 polymorphism. (A) Amplification curve of the VDR rs7975232 HRM assay. (B) Normalized fluorescence melting curves obtained from all analyzed samples. (C) Normalized fluorescence curves showing the melting profiles of the VDR rs7975232 genotypes.

Statistical Analysis

These data were statistically analyzed using GraphPad Prism Version 9.2 (GraphPad Software Inc., La Jolla, CA). Descriptive statistics were used to obtain demographic statistics using SPSS Version 24.0 (IBM Corp., Armonk, NY, USA). Data are expressed as means ± SD. Groups were compared with a post hoc test (Šidák) using two-way ANOVA. A p-value < 0.05 was significant; a p-value < 0.01 was extremely significant. Genotype frequencies were checked against the Hardy-Weinberg equilibrium, and allele and genotype frequencies were compared using the chi-square test (χ^2). To evaluate illness risk for the co-dominant, dominant, recessive, and over-dominant genetic models, odds ratios (OR) and 95% confidence intervals (CI) were calculated. Moreover, in order to assess the link between serum vitamin D3 levels, ferritin, and zinc in individuals with psoriasis, the Pearson correlation coefficient (r) was computed. A test of significance was used, and values were judged statistically significant when < 0.05 (two-tailed)

RESULTS:

The study population's clinical and demographic characteristics

A total of 80 participants were enrolled in the study, comprising 45 individuals with psoriasis and 35 age- and sex-matched control group. The age distribution was comparable between the two groups, confirming successful matching and minimizing the potential for confounding by demographic variables. No statistically significant differences in age distribution were observed between the groups (Table 1).

Table 1. Age distribution of the study groups.

Age groups (years)	Patients (%)	Control group (%)
15–25	44%	46%
26–36	38%	40%
37–47	18%	14%

Laboratory Parameters

Biochemical Parameters

The comparative analysis revealed statistical significance and marked changes in all measured biochemical parameters between psoriasis patients and the control group. These findings confirmed a marked disruption in vitamin D3, ferritin, and zinc homeostasis in the patient group, as summarized in (Table 2).

Table 2. Serum of vitamin D3, ferritin, and zinc levels in psoriasis patients and control group.

Parameter	Patients (Mean± SD)	Control group (Mean ± SD)	p value
Vit.D3 (ng/mL)	18.48 ± 5.92	66.42 ± 20.61	p < 0.001
Ferritin (ng/mL)	210.51 ± 48.40	95.22 ± 26.42	p < 0.001
Zinc (µg/dL)	30.86 ± 9.6	77.80 ± 25.77	p < 0.001

Age-stratified

Independent samples t-test demonstrated highly significant differences in serum ferritin, zinc, and vitamin D3 levels between psoriasis patients and the control group across all age groups ($p < 0.001$ for all) (Table 3).

Table 3. Biochemical parameter comparison between control group and psoriasis sufferers, broken down into age groups.

Parameter	Age group	Patients (Mean± SD)	Control group (Mean ± SD)
Ferritin (ng/mL)	15–25	177.0 ± 13.6	70.8 ± 6.6
	26–36	215.1 ± 34.4	106.6 ± 7.9
	37–47	284.5 ± 44.9	141.6 ± 5.2
Zinc (µg/dL)	15–25	39.8 ± 4.5	98.6 ± 23.6
	26–36	26.6 ± 3.9	64.0 ± 7.5
	37–47	17.4 ± 3.0	50.0 ± 2.7
Vit.D3 (ng/mL)	15–25	23.7 ± 3.8	84.8 ± 11.1
	26–36	16.1 ± 2.7	56.1 ± 9.2
	37–47	10.8 ± 2.1	36.4 ± 5.0

Association of the VDR rs7975232 (C/A) Polymorphism with Psoriasis Susceptibility

The results show that there are differences in the distribution of the VDR gene polymorphism rs7975232 (C>A; HGVS: NC_000012.12: g.47845054; ApaI site) between psoriasis and the control group. The Psoriasis patients, compared with the control group, have a higher prevalence of the homozygous AA genotype (15.6% vs 5.7%), a higher prevalence of the heterozygous CA Genotype (48.9% vs 37.1%), and a lower prevalence of the homozygous CC Genotype (35.6% vs 57.1%) for the VDR gene rs7975232 polymorphism.

The results showed that the A allele was more frequent in the patient population than in the control group (40% vs 24.3%) based on allele frequency analysis (Odds ratio of 2.07; 95% CI of 1.01 - 4.24; P-Value of 0.046). Various models of genetic inheritance were evaluated to determine if the genotype AA was more prevalent among patients than in the control group, with the recessive model (AA vs CC+CA) (15.6% vs 5.7%). Based on this model, there was a non-significant statistical difference in genotype prevalence (odds ratio (OR) = 3.04, 95% confidence interval (CI): 0.59-15.6, p-value (p) = 0.170). In the dominant model (CA+AA vs CC), patients had a greater proportion of combined genotypes (64.4%) than the control group (42.9%), but this was also not statistically significant (p=0.063). For the over-dominant model (CA vs CC+AA), patients had an increased frequency of the CA genotype compared with the control group (48.9% vs 37.1%); however, this result did not achieve statistical significance (OR=1.62, 95% CI: 0.65-4.05, p=0.305) (see Table 4).

Table 4: Shows the distribution of allele frequencies, genetic models, and VDR rs7975232 (C/A) polymorphism genotypes in psoriasis patients and the control group.

Genotypes	Patients (n=45) (%)	Controls (n=35) (%)	Odds ratio (95%CI)	χ^2	p-value
Co-dominant Model					
CC (wild)	16 (35.6%)	20 (57.1%)	Reference		
CA (Hetero)	22 (48.9%)	13 (37.1%)	2.12 (0.82–5.47)	2.47	0.116
AA (Mutant)	7 (15.6%)	2 (5.7%)	4.38 (0.79–24.1)	2.92	0.087
C	54 (60.0%)	53 (75.7%)	Reference		
A	36 (40.0%)	17 (24.3%)	2.07 (1.01–4.24)	3.97	0.046*
Recessive Model					
CC + CA	38 (84.4%)	33 (94.3%)	Reference		
AA	7 (15.6%)	2 (5.7%)	3.04 (0.59–15.6)	1.88	0.170
Dominant Model					
CC	16 (35.6%)	20 (57.1%)	Reference		
CA + AA	29 (64.4%)	15 (42.9%)	2.42 (0.96–6.08)	3.46	0.063
Over-dominant Model					
CC + AA	23 (51.1%)	22 (62.9%)	Reference		
CA	22 (48.9%)	13 (37.1%)	1.62 (0.65–4.05)	1.05	0.305

Hardy–Weinberg Equilibrium

The genotype frequencies of the VDR rs7975232 (C>A; ApaI) polymorphism were assessed for conformity with Hardy–Weinberg equilibrium in patients with psoriasis and healthy controls. Comparison of the observed and expected genotype counts revealed no significant deviation from Hardy–Weinberg equilibrium in either patients (χ^2 = 0.015, p = 0.901) or controls (χ^2 = 0.003, p = 0.953). These results indicated that the observed genotype distributions in both groups were consistent with Hardy–Weinberg expectations, as presented in Table 5.

Table 5. Hardy–Weinberg Equilibrium for rs7975232 (C/A) Polymorphism.

Polymorphisms	Groups		Wild (CC)	Hetero (CA)	Mutant (AA)	χ^2	P-value
rs7975232	Patients Genotype	Observed no.	16	22	7	0.015	0.901
		Expected no.	16.2	21.6	7.2		
	Control Genotype	Observed no.	20	13	2	0.003	0.953

		Expected no.	20.06	12.87	2.06		
	Total Observed		36	35	9		

Association of rs7975232 Genotypes with Biochemical Parameters

Classification by rs7975232 genotypes revealed consistent biochemical differences between psoriasis patients and the control group. Vitamin D3 levels were significantly reduced across all genotypes ($p < 0.0001$ for CC and CA; $p = 0.0043$ for AA). Ferritin levels were markedly elevated in patients for all genotypes ($p < 0.0001$ for CC and CA; $p = 0.0136$ for AA). Zinc levels showed significant reductions in CC and CA carriers ($p < 0.0001$), while the AA genotype exhibited a non-significant decrease ($p = 0.1296$) (Table 6, Figures 4–6).

Table 6. Biochemical Parameters Stratified by rs7975232 Genotypes.

Parameter	Genotype	Patients (Mean ± SD)	Control group (Mean ± SD)	p Value
Vitamin D3 (ng/mL)	CC	19.6 ± 6.3	66.9 ± 17.6	< 0.0001
	CA	18.8 ± 5.9	69.0 ± 15.6	< 0.0001
	AA	15.0 ± 3.7	46.5 ± 9.2	0.0043
p Value		0.6658	0.0594	
Zinc (µg/dL)	CC	32.9 ± 10.2	79.9 ± 27.4	< 0.0001
	CA	30.9 ± 9.8	77.9 ± 24.1	< 0.0001
	AA	25.3 ± 5.0	55.5 ± 4.9	0.1296
p Value		0.6260	0.1828	
Ferritin (ng/mL)	CC	208.9 ± 46.9	95.8 ± 25.5	< 0.0001
	CA	207.4 ± 44.3	88.8 ± 25.6	< 0.0001
	AA	223.6 ± 67.2	128.0 ± 28.3	0.0136
p Value		0.7004	0.4213	

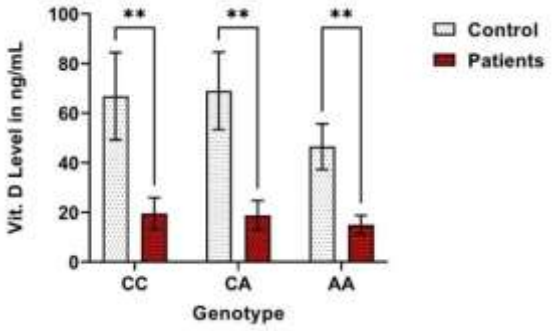


Figure 4. Serum vitamin D_3 levels in psoriasis patients and the control group stratified according to VDR rs7975232 genotypes. Error bars represent standard deviation. Sample sizes: Patients (CC = 16, CA = 22, AA = 7); Control group (CC = 20, CA = 13, AA = 2).

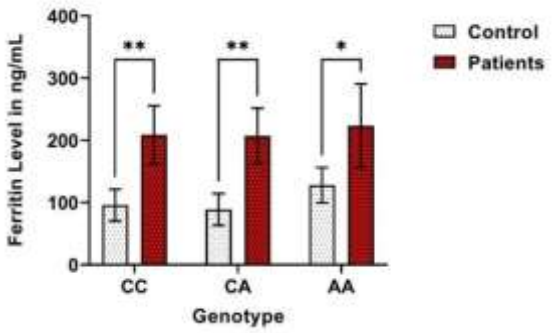


Figure 5. Serum ferritin levels in psoriasis patients and the control group stratified according to VDR rs7975232 genotypes. Error bars represent standard deviation. Sample sizes: Patients (CC = 16, CA = 22, AA = 7); Control group (CC = 20, CA = 13, AA = 2).

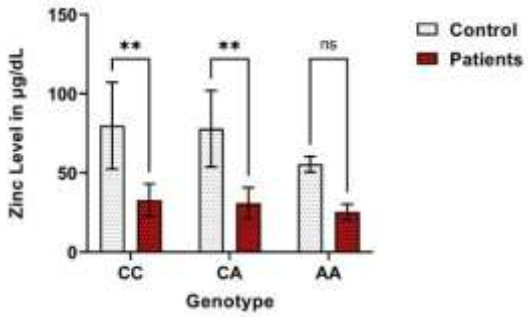


Figure 6. Serum zinc levels in psoriasis patients and the control group stratified according to VDR rs7975232 genotypes. Error bars represent standard deviation. Sample sizes: Patients (CC = 16, CA = 22, AA = 7); Control group (CC = 20, CA = 13, AA = 2).

Pearson Correlations

Pearson correlation coefficients among Vitamin D3, Zinc, and Ferritin in psoriasis patients are presented in (Figure 7).

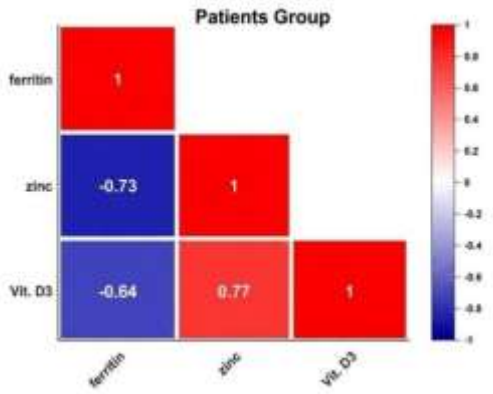


Figure 7. A heatmap showing the relationship between ferritin, zinc, and vitamin D3 in individuals who have psoriasis. The Pearson correlation coefficients are used to indicate the relationships. A red correlation indicates a positive relationship; a blue correlation indicates a negative relationship, and the amount of colour indicates how strong the correlation is. All relationships demonstrated are statistically significant ($p < 0.001$).

DISCUSSION

Psoriasis differs geographically, with 0.1% of people having it in East Asian populations and up to 1.5% in Western Europe [24]. The disease is not due to a single cause but rather a result of a complex interplay of genetic vulnerability, environmental factors and random occurrences [25].

Vitamin D3 Dysregulation in Psoriasis

Vitamin D has immunomodulatory effects through enhancing the function of regulatory T cells and reducing the production of pro-inflammatory cytokines such as IL-17A [26].

The mean level of 25(OH)D was significantly lower in the psoriasis group than in the control group (18.48 ± 5.92 ng/ml versus 66.42 ± 20.61 ng/ml, $p < 0.0001$). This is in accordance with previous studies (e.g., Bhat et al.) that have reported decreased levels of 25(OH)D in persons with psoriasis as compared to the control group [25]. The causes for the discrepancy could have been due to disparities between different gene populations from different areas of the world, lack of exposure to sunshine, and changes in feeding practices that could afford more research within those gene pools.

Vitamin D insufficiency may have played a role in the illness process, and it is possible that vitamin D levels are decreased in psoriasis patients.

Zinc Deficiency and Immune Imbalance

The present study suggested that the serum zinc level in patients with psoriasis (30.86±9.6 µg/dL) was significantly decreased compared with the control group (77.80±25.77 µg/dL)
($p<0.001$), which indicated a probable role of zinc deficiency in the etiology of psoriasis. Zinc is a necessary component for several cellular functions, such as protein synthesis, DNA repair, RNA repair, and enzymatic activity, and it plays a protective role against oxidative stress by lowering free-radical activity and avoiding lipid peroxidation. A meta-analysis by Lei et al. (2019) showed that zinc levels were considerably lower in psoriasis patients, while other studies showed inconsistent results or no significant difference, which may be related to the differences in nutrition, ethnicity, demographic characteristics, and methodology. There were several pathways that may have led to zinc deficiency in psoriasis. Increased use of zinc is owing to excessive keratinocyte proliferation within psoriatic lesions. Impairment of antioxidant defense mechanisms and immunological dysfunction may also have contributed to the reduction of systemic zinc availability[17].

Elevated Ferritin as an Inflammatory Marker

Ferritin is the main intracellular protein involved in iron storage and homeostasis Recent studies showed that psoriasis is associated with impaired iron metabolism. Increased iron accumulation has been found in psoriatic skin and is related to increased inflammatory activity, abnormal behavior of keratinocytes, and enhanced recruitment of immune cells [18]. In the current study, serum ferritin levels of psoriasis patients were significantly higher than the control group (210.51 ± 48.40 ng/mL vs 95.22 ± 26.42 ng/mL, $p < 0.001$). This supported previous studies that have demonstrated the association of elevated ferritin levels, systemic inflammation, and impaired iron metabolism in psoriasis [18].

Association of VDR rs7975232 (C/A) Polymorphism and Risk of Psoriasis

Distribution of the different genotypes was not statistically different between patients and control group. The most common genotype in patients was heterozygotes (CA, 48.9%) and in the control group wild-types (CC, 57.1%). The frequency of A allele was greater in patients (40.0%) than in the control group (24.3%) with an OR of 2.07 (95% CI: 1.01-4.24, $p = 0.046$). These data suggested that A allele may be associated with increased susceptibility to psoriasis in studied Iraqi community. Alhetheli et al. (2022) noted that the frequency of the AA genotype of the ApaI polymorphism was higher in psoriatic patients than in healthy persons, and the frequency of the A allele was also raised in psoriatic patients, compared with the control group. In addition, the current investigation showed a significant variation in serum vitamin D levels among the different genotypes of the ApaI polymorphism, where homozygous AA carriers had significantly lower serum levels than other genotypes [1].

Liu et al. (2020) revealed that the A allele of rs7975232 polymorphism was substantially more common in psoriasis patients than in the control group. Furthermore, carriers of the AA and GA genotypes were at a higher risk of psoriasis than CC genotype carriers. These results demonstrate the association of ApaI polymorphism with susceptibility to psoriasis [22]. Previous studies have reported inconsistent findings regarding the association between the rs7975232 (ApaI) polymorphism and susceptibility to psoriasis. Mohamed et al. (2022), in their review of previous findings, highlighted that studies conducted in Egyptian, Italian, Chinese, Croatian, and Japanese populations had reported no significant association between rs7975232 and psoriasis. In contrast to these earlier reports, their own case-control study demonstrated that rs7975232 was significantly more polymorphic among psoriasis patients than healthy controls, indicating variability in the association of this polymorphism with psoriasis across different populations [27].
Lee (2019) performed a recent meta-analysis including 16 studies with a total of 2086 psoriasis patients and 2182 control group and did not report any significant association of VDR ApaI polymorphism with susceptibility to psoriasis in general, Caucasian and Asian populations [23]. Conversely, the present investigation demonstrated a significant connection between allele A of rs7975232 and susceptibility to psoriasis in Iraqi participants. The discrepancy may be explained by ethnic differences, population-specific genetic background and geographical variation. In addition, the inconsistency among studies may also be related to differences in sample size, environmental exposures, and genotyping methods. Furthermore, rs7975232 is an intronic polymorphism that does not directly alter the amino acid sequence of the VDR protein. Therefore, its biological effect may be mediated through linkage disequilibrium with functional variants or by influencing mRNA stability and VDR expression. These mechanisms may partly explain the population-specific association observed in the present Iraqi cohort.

An association between VDR rs7975232 polymorphism and biochemical markers

When biochemical markers were analyzed according to genotype, we observed a very reliable pattern. For all three genotypes, biochemical markers were least favorable in patients compared to control group (Table 6).

The lowest mean vitamin D3 level was observed in AA carriers (15.0 ± 3.7 vs. 46.5 ± 9.2, p = 0.0043), while CC (19.6 ± 6.3 vs. 66.9 ± 17.6, p<0.0001) and CA carriers (18.8 ± 5.9 vs. 69.0 ± 15.6, p<0.0001) also showed significantly lower levels than the control group. These findings suggested a possible involvement of vitamin D3 deficiency in the pathology of psoriasis [25]. These findings were consistent with previous observations relating ApaI polymorphism to variance in serum vitamin D levels among psoriasis patients [1].

Zinc showed a similar directional pattern. CC carriers (32.9 ± 10.2 vs. 79.9 ± 27.4 µg/dL, p < 0.0001) and CA carriers (30.9 ± 9.8 vs. 77.9 ± 24.1 µg/dL, p < 0.0001) demonstrated significant reductions. Mean levels of zinc in AA were lowest (25.3+/−5.0 vs. 55.5+/−4.9 µg/dL) but did not reach significance (p = 0.1296). Although not statistically significant, AA carriers showed the lowest mean zinc concentration, which may have reflected a trend towards reduced zinc status in this genotype. Inflammation has been associated with redistribution and zinc deficit in psoriasis [17].

Ferritin moved in the opposite direction, elevated in psoriasis patients across all genotypes. CC carriers (208.9 ± 46.9 vs. 95.8 ± 25.5 ng/mL, p<0.0001) and CA carriers (207.4 ± 44.3 vs. 88.8 ± 25.5 ng/mL, p<0.0001) showed highly significant increases, while AA carriers exhibited the highest mean ferritin level among the studied genotypes (223.6 ± 67.2 vs. 128.0 ± 28.3 ng/mL, p = 0.0136) However, differences among patient genotypes were not statistically significant. Together, these results suggested that psoriasis patients have higher serum ferritin levels, which is in accordance with earlier observations that raised ferritin is correlated with psoriasis and dysregulated iron metabolism [18]. To our knowledge, there is no published research directly investigating the correlation between VDR rs7975232 genotypes and serum ferritin levels in psoriasis patients. AA carriers had the highest mean ferritin concentration in the present study, but further studies are needed to evaluate if this is a true genotype-related effect.

Age-Stratified Analysis of Vitamin D3, Zinc, and Ferritin

When the data from the psoriasis patients were collected using a similar age-stratification method, a definite directionality could be observed: the youngest patients had the highest vitamin D3 and zinc levels, and the older patients the lowest. The opposite result was observed for ferritin levels, where the lowest values were found in patients aged the youngest age and the highest at the oldest age, as summarized in (table 3).

Several physiological mechanisms may explain these age-related trends. In addition to decreased sun exposure and dietary deficiencies in vitamin D, aged skin's diminished capacity to produce vitamin D in the sun, decreasing precursor levels, and impaired renal conversion are the causes of vitamin D deficiency in older persons. These factors, in combination, may have contributed to immune senescence and to the low-grade chronic inflammatory situation known as inflammaging, which can make the organism more vulnerable to infections and age-related diseases [28].

Zinc deficiency also becomes more common with advancing age, partly because of reduced dietary intake and decreased intestinal absorption. Such deficiency may further contribute to immunosenescence and inflammaging in older individuals [29].

This is supported by Von Holle et al. (2025), who identified increased ferritin levels to be associated with faster biological aging [30]. The age-related rise in ferritin in patients with psoriasis may have been due to the combined effect of chronic inflammation and age-related physiological changes.

In general, the current findings indicated that as age advances, the biochemical parameters in psoriasis patients tend to deteriorate progressively with lower levels of vitamin D3 and zinc and higher levels of ferritin. These age-related variations may have reflected changes in nutritional status, immune function and inflammatory activity, highlighting the potential influence of aging on the metabolic anomalies associated with disease.

Correlation Analysis

Correlation analysis between the major biochemical markers was carried out in the patient cohort (Figure 7). In the psoriasis group, Pearson correlation analysis revealed a strong and statistically significant negative link between serum vitamin D3 and ferritin levels ($r = -0.64$, $p < 0.001$). The study demonstrated that increasing ferritin level is associated with lower vitamin D3 level in patients of psoriasis.

This inverse association might be related to the chronic inflammatory nature of psoriasis. Vitamin D is an important immunomodulatory hormone, modulating innate and adaptive immunological responses by suppression of Th1- and Th17-mediated inflammation and enhancement of regulatory T-cell activity [26]. Therefore, vitamin D deficiency may have played a role in the sustained immune activation and chronic inflammatory response that are characteristic of psoriasis pathogenesis.

The negative association detected in the current study may have been indicative of the total inflammatory load associated with the condition. Previous studies have indicated that vitamin D insufficiency is prevalent in psoriasis and has been associated with immunological dysregulation involved in disease pathogenesis [31],[32]. Thus, there was a tendency for patients with higher inflammatory burden to have lower vitamin D3 levels, together with higher ferritin concentration. Therefore, the negative association between vitamin D3 and ferritin found in this study may be owing to disease-associated inflammation rather than an independent change in iron metabolism. Therefore, the significant negative correlation between vitamin D3 and ferritin could reflect the impact of the underlying inflammatory processes in psoriasis on both markers, with lower vitamin D3 levels related to higher ferritin levels in patients with higher inflammatory burden.

Vitamin D3 and zinc were positively correlated ($r=0.77$, $p<0.001$). This showed that loss of serum vitamin D status is tightly associated with loss of serum zinc status suggesting the possibility of concurrent micronutrient shortages rather than separate micronutrient deficiencies. In addition, multiple studies have indicated that patients with psoriasis tend to have lower serum levels of zinc and vitamin D than normal.

A narrative analysis of the literature demonstrates that low blood zinc levels were reported in many instances in all the dermatoses studied (including psoriasis) and changed levels of zinc appear to be an intrinsic aspect of many of the chronic inflammatory/autoimmune dermatological illnesses [33]. Data have shown an inverse correlation between serum levels of calcium or zinc and the total surface area of psoriasis-affected plaques, indicating that zinc deficiency could be contributing to the severity of the disease in a systematic review of trace elements and their association with psoriasis [21]. The protective mechanism of zinc ions is assumed to be through their capacity to lower oxidative stress which has been identified as one mediator of the inflammatory response implicated in the pathophysiology of psoriasis [21]. The skin has vitamin D receptors and vitamin D–mediated signaling pathways that are involved in the maintenance of skin homeostasis [26],[32].These data suggested that cumulative evidence for the beneficial association between vitamin D3 and zinc, and indicate that perturbations of both micronutrients may have contributed to the immunological dysregulation and oxidative stress of psoriasis patients.

A substantial negative connection was seen between blood ferritin and zinc levels in patients with psoriasis ($r = -0.73$, $p < 0.001$). This finding might be explained by the opposite biological activity of these two indicators during chronic inflammation. Psoriasis is a disease of chronic immune activation and elevated secretion of pro-inflammatory cytokines that facilitates systemic inflammatory responses. Ferritin is an acute-phase reactant, whose synthesis is accelerated by inflammatory cytokines and increased ferritin levels can be regarded as a measure of disease activity [34].

On the other hand, Zinc is an essential trace element with many enzymatic, antioxidant and immunoregulatory functions [35] . In addition, Zinc is a cofactor of antioxidant enzymes and protects from oxidative stress, a known mediator of the inflammatory response responsible for the development of psoriasis. Low serum levels of zinc are associated with less activity of antioxidant enzymes and dysfunction of the cellular immune system[17],[21].

CONCLUSION

The A allele of the VDR ApaI (rs7975232) polymorphism may be associated with increased susceptibility to psoriasis in Iraqi individuals. The present study provides population-specific data on the association between VDR rs7975232 polymorphism and vitamin D3, zinc, and ferritin levels in Iraqi patients with psoriasis. The frequency of the A allele was significantly higher in patients than in the control group, indicating that this allele may be a genetic risk factor for psoriasis (OR = 2.07). AA carriers showed the lowest mean levels of vitamin D3 and zinc and the highest ferritin levels among the genotypes examined, which may have reflected a trend of a less favorable biochemical profile. Our findings suggest that VDR genetic variation may contribute to biochemical alterations associated with psoriasis. In conclusion, the present investigation provided more evidence for the possible role of VDR rs7975232 polymorphism in psoriasis in Iraqi patients. A larger sample size is needed to validate the findings and to investigate the underlying molecular pathways.

limitations

The present study has several limitations. First, the relatively small sample size (45 patients and 35 control group) may have limited the statistical power, particularly for subgroup analyses. Second, disease severity was not assessed using the Psoriasis Area and Severity Index (PASI); therefore, its association with VDR rs7975232 genotypes and biochemical parameters could not be evaluated. In addition, HRM genotyping was not confirmed by DNA sequencing, which should be considered when interpreting the genotype results. Finally, this study was conducted in a single geographical region, which may limit the generalizability of the findings to the broader Iraqi population. Further studies involving larger sample sizes from different provinces are recommended to confirm and validate the present findings.

Ethical statement

Approval to conduct the study and collect clinical samples was obtained from the Research Committee, Anbar Health Directorate, Iraqi Ministry of Health (Decision No. 2025058, dated 12 August 2025), which authorized the implementation of the study in the affiliated healthcare institutions. Subsequently, ethical approval was obtained from the Research Ethics Committee, College of Applied Science, University of Fallujah, Iraq (Reference No. AS-EC/0015, dated 13 January 2026). Written informed consent was obtained from all participants before sample collection.

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