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**Original article**

# VITAMIN $D_3$ LEVEL AND ITS RECEPTOR OF PATIENTS WITH PSORIASIS: A CASE CONTROL STUDY

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**ABSTRACT**

Psoriasis is a multi-factorial disease resulting in response to increased secretion of inflammatory cytokines or deficiency in certain vitamins such as vitamin $D_3$. This study aims to evaluate the levels of vitamin $D_3$ and its receptor (VDR) in psoriatic patients and healthy control, as well as to determine the ratio between vitamin/receptor and their relative risk in the pathogenesis of psoriasis. This study was designed as a case-control study and includes 45 psoriatic subjects and 45 healthy controls. The results of currents studies show a significant decrease in vitamin $D_3$, VDR levels and vitamin $D_3$/ VDR ratio when compared with the healthy control group. The relative risk for VDR levels with psoriasis was found to be positively significantly associated, whereas those for vitamin $D_3$ levels with psoriasis were insignificant. In conclusion, the relative risk for VDR is more than that for calicitriol and this supports the pathogenic role of VDR abnormality in psoriasis.

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## 1. Introduction: the history of perception

Psoriasis is considered a chronic inflammatory disease of the skin with immune background. It has a negative effect on the physical, emotional and psychosocial life of affected patients [1]. There are different triggering environmental factors such as infection or drugs of which may be secondary to the trauma or genetic factors [2]. The disease occurs in the different age groups with rare occurrences in those less than 10 years of age and greatly between 15-40 years. There is unknown course disease with continuous remission and exacerbation [1]. Today psoriasis is considered a systemic disease and includes many other situations from psoriatic arthritis to obesity and finally, metabolic syndrome, which increases the possibility of cardiovascular disease in psoriatic patients [2]. The etiology of psoriasis is unknown but there are different factors that participate in its initiation such as auto-immune, genetic, hormone and psycho-somatic issues [3]. There is an increase in the spreading of metabolic syndrome among psoriatic patients and it's independent of disease severity depending on the hospital case-control study [4]. It's a result of a combination of metabolic factors in the same patients such as obesity, dyslipidemia, hypertension, glucose intolerance, thrombotic and an inflammatory state [5,6].

A vitamin D derivative that can be applied topically was recently determined for treating patients with mild-moderate plaque psoriasis with minimal effect on calcium metabolism [7]. Calcipotriene ointment (50µg of calcipotriene per gram) when applied twice a day resulted in the clearly psoriatic lesion in 60% of chronic plaque psoriasis patients over the course of 8 weeks. Colorless ointment with no clothes painting was used but it caused mild irritation especially on the face [8].

There are two different types of vitamin D, the first type is $D_2$ (ergocalciferol) which presents in plants and fish and cannot synthesize in the human body, another form is $D_3$ (cholecalciferol) that presents in the human body. Full human vitamin $D_3$ requirement can be taken either from exposure to sunlight for enough time or by supplementation [9]. There are environmental factors such as alteration in the climax angle of the sun caused by latitude changing, season, or time of day which dramatically influences vitamin $D_3$ production on skin [10].

The vitamin $D_3$ receptor (VDR) is a member of the steroid/thyroid hormone receptor superfamily that acts to mediate the action of vitamin D's active form which is 1,25-dihydroxy vitamin $D_3$ and subsequently results in increasing or decreasing target gene transcription [11]. VDR is a nuclear receptor which binds to retinoid X receptor and acts as a heterodimer with one of its three isotypes. VDR has a high affinity for binding with $1,25(OH)_2$ $D_3$.

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The main function of the nuclear receptor is a ligand that binds to the specific substance to become an activated transcription factor to affect the specific process such as reproduction, development of metabolic process and finally immune modulator effect [11]. The nuclear receptor is very important in maintaining the normal physiological status of the body and many problems such as psoriasis, cancer, DM, and inflammation which are a result of inappropriate nuclear receptors such as function or number and inappropriate signaling [12].

The effect of calcitriol on psoriasis can occur through suppressing T-cell hyper-proliferation and its activation, increase induction of regulatory T-cell and regulation of cytokines production. Calcitriol also has an effect on B-cell development in addition to its regulatory role on maturation and migration of dendritic cells [13]. All cytokines production that is required for activation of Th1 and Th17 cell are inhibited by the active form of vitamin D while it stimulates the Th2 cell to produce IL-10. It is anti-inflammatory cytokines that inhibits the expression of inflammatory cytokines in psoriasis that include IL-2, IL-6, IL-8 and finally γ-interferon [13].

Liganding of vitamin $D_3$ with its receptor can inhibit the expression of pro-inflammatory cytokines which play a vital role in the stimulation of most of the cutaneous inflammation, proliferation and inhibition of keratinocyte and T-cell differentiation and these cytokines including IL-2, IL-6, IL-8, IFN γ and finally GM-CSF [14]. Liganding of VDR with the calcitriol lead to an increase in the level of IL-10 which has anti-inflammatory properties because the vitamin $D_3$ can increase the genetic expression for a gene that is responsible for increasing the receptor of IL-10 [15]. The anti-psoriatic activity of VDR result from their anti-proliferative, differentiated and immune-modulatory properties. Liganding of VDR with the calcitriol or its analogs can exhibit multiple anti-psoriatic effects in the psoriatic lesion and also influence the function and differentiation of keratinocyte, T-cell, and APC. Ligands of VDR can stimulate keratinocytes differentiation and inhibit its proliferation [16].

## 2. Material and methods

*Ethical Issues*

In the current study the ethical issues are based on the approval of the committee of College of Medicine at the University of Babylon, and the approval of the ethical committee of Babylon General Directorate of Health. All participants were assigned a consent to participate in this study.

*Date and Duration*

The study was performed from August 2017 to June 2018 in the Department of Chemistry and Chemistry Biochemistry, College of Medicine, the University of Babylon in association with the Department of Dermatology, Merjan Teaching Hospital in Hilla city, Iraq.

*Study Design*

The present study was designed as a case-control study. The sample size was determined according to the Daniel formula for sample size.

*Patients*

Forty-five patients were involved in this study. All patients were presented to the Department of Dermatology in Merjan Teaching Hospital in Hilla City.

All patients have chronic plaque psoriasis diagnosed by a dermatologist. Full patients history regarding age, sex, job, residence, sunlight exposure, family history, psychological stress, itching, duration, drug administration, co-morbidities are information collected in a questionnaire sheet from involved subjects according to the patient's interview.

*Control*

Forty-five control subjects were involved in this study. All these subjects were healthy and without any skin disease or another manifestation. All these control subjects are identical with patients in the age, sex, and BMI.

*Biochemical assessments*

Vitamin $D_3$ and vitamin D receptor level was determined according to the manufacturers manuals Cusabio® and Mybiosource® companies, respectively.

*Statistical Analysis*

The statistical analysis was applied by Excel 2013 and SPSS 2013 version 22. All the statistical values are expressed as the mean ± standard deviation (SD). Students t-test were used for estimating the probability (P value) with acceptable P value level >0.05 to determine the difference that presents in both patients and control group.

## 3. Results

*Physical Examination*

Ninety participants were included in this study and were classified into four groups: two groups belong to healthy control (male and female) while the other two groups are the psoriatic subjects and there is no significant difference in age among groups, as shown in Table 1. Forty-five adult patients were included in this study and classified according to gender into 34 (75%) adult psoriatic males and 11 (25%) adult psoriatic females. Results of the presented study show there is no significant difference in BMI between psoriatic and healthy control subjects, as shown in Table 1. According to the results of the presented study, there is a significant increase in PASI score in males more than females among psoriatic patients, as shown in Table 2. There is a significant difference in exposure to sunlight between psoriatic males and females when in males it is 4.6 hr/d and in females 1.3 hr/d.

| | Group | Both Genders | Male | Female |
|---|---|---|---|---|
| Age (years) Mean ±SD | Patients | 42.91 ± 14.19 | 42 ± 14.12 | 46.33 ±14.70 |
| | Control | 40.07 ±14.96 | 40 ± 14.58 | 41.44 ± 16.21 |
| P value | | 0.376 | 0.659 | 0.512 |
| BMI ($kg/m^2$) Mean ±SD | Patients | 24.34 ± 5.67 | 24.47± 6.20 | 23.92±3.70 |
| | Control | 22.52 ± 3.03 | 22.80±2.67 | 21.49±3.89 |
| P value | | 0.072 | 0.155 | 0.194 |

**Table 1 - Age and Body Mass Index of Participants.**

| Subjects | Mean PASI (%) | Mean± SD | P value |
|---|---|---|---|
| Male | 17.429 | 11.742 | 0.026 |
| Female | 7.933 | 6.571 | |

**Table 2 - Psoriasis Area and Severity Index (PASI) Score of Psoriatic Patients.**

*Biochemical Assessments*

Results of the presented study reveal that there are significant decreases in serum concentration of vitamin $D_3$, vitamin $D_3$ receptor and vitamin $D_3$/ vitamin $D_3$ receptor ratio of psoriatic when compared with control group, as shown in Table 3.

| Parameter | Subjects | Mean ± SD | P value |
|---|---|---|---|
| Vitamin $D_3$ (ng/ml) | Psoriatic group | 12.15 ±2.75 | 0.000 |
| | Control group | 34.23 ±8.40 | |
| Vitamin $D_3$ receptor (ng/ml) | Psoriatic group | 4.00 ±1.70 | 0.035 |
| | Control group | 4.95 ±2.30 | |
| Vitamin $D_3$/VDR Ratio | Psoriatic group | 3.03± 1.61 | 0.000 |
| | Control group | 6.91±3.65 | |

**Table 3 - Vitamin $D_3$, Vitamin $D_3$ Receptor Concentrations and Vitamin $D_3$/ Vitamin $D_3$ Receptor Ratio of Psoriatic and Control group.**

*Biochemical Parameter as a Risk Factor for Initiation the Disease*

After calculating the risk factor for vitamin $D_3$ deficiency in the current study, there was no significant association between vitamin $D_3$ and initiation of psoriasis because the relative risk (RR) factor was 1 and that means there is no association between vitamin $D_3$ deficiency and psoriasis initiation, while there was a significant association between VDR deficiency and initiation of psoriasis because the RR factor was 47.

## 4. Discussion

The statistical analysis involved in the presented study did not find any significant difference between the ages of the control group and the psoriatic group, nor significant differences between the age of both psoriatic males and females in both male and female healthy control. This finding was in agreement with a previous study done in Iraq for psoriatic patients [17]. The increasing number of affected males over females in the enrolled study was probably due to the genetic basis of the disease. This finding of the presented study was in agreement with the previous study [17].

Results of the presented study reveal the absence of significant difference in BMI between psoriatic and control group and that means psoriasis does not have any effect on Iraqi patients' BMI because the patients' BMI is still within the normal borderline after appearance of psoriatic onset and this finding was in agreement with vidulla *et al* [18] but disagreed with the Al-Ammar study [19]. Statistically, there is a significant relationship between PASI score and severity of psoriatic lesion and this was in agreement with Al-Ammar [19] and A. Johnston *et al.* [20] when both concluded the disease severity was decreased with decreasing PASI scores after follow up study for psoriatic patients. The author believes that this result is expected because the PASI score is a measure of the severity of the disease. Mean PASI score of both psoriatic males and females was 17.429 ±11.742 and 7.933 ± 6.571, respectively. Mean PASI score in males was higher than in females and this may be attributed to the increasing incidence of psoriasis among males more than females (distribution ratio 3:1) and also to a larger number of psoriatic males than females in the presented study.

Results of the present study reveal there was a significant difference in exposure to sunlight among both Iraqi males and females psoriatic patients when the sunlight exposure was1.33 ± 0.707 and 4.060 ±3.774 for psoriatic females and males, respectively. A significant decreasing also showed in PASI score after exposure to sunlight. The finding of the present study was in agreement with the previous study performed in Ohio, USA by E. Soyland *et al* [21] which concluded that there was a clinical improvement in psoriasis and a decrease in PASI score among psoriatic patients after exposure to sunlight; mainly due to the rapid reduction for inflammatory markers such as inflammatory cytokines produced by $T_h$ cell in response to decreasing numbers of $T_h$ cell in the lesional psoriatic skin in epidermis after exposure to light that results in these clinical improvements.

Smith *et al.* [22] explain the important role of vitamin $D_3$ in treatment of psoriasis and how its deficiency can result in hyperproliferation of human keratinocyte and initiation of psoriasis, the aforementioned studies show vitamin $D_3$ deficiency as a risk factor for the development of psoriasis. Another perspective of deficiency of vitamin $D_3$ among psoriasis patients may be that it results from limited sun exposure in response to the psychological status stemming from skin mutilation due to loss of self-body image that causes the affected individual psychological status to worsen which results in an increasing severity of vitamin $D_3$ deficiency status among these patients and an increasing severity of the disease.

Current study results were in agreement with the previous study done by Petra Mild *et al* [23] which reports a more significant decreasing in VDR than normal individuals in response to the genetic factors.

Another perspective within this present study is that psoriasis may initiate as a response to an abnormality in VDR either in its level due to deficiency or due to the genetical factors such as a mutation in genes that is coded for its expression or maybe as a response to receptor down-regulation that resulted from viral or bacterial infection or drugs.

To the best of our knowledge, no previous study investigated the value of vitamin $D_3$ / VDR (Vit-$D_3$/VDR) ratio, so to prove the results of the present study we calculated the Vit-$D_3$/VDR ratio for both patients and control group by the concentration of vitamin $D_3$ and VDR for both patients and control group and then compared them. There was a clear discrepancy in the ratio between both groups and the main cause for this discrepancy is mainly attributed to the differences in concentration of vitamin $D_3$ and its receptor among both groups when the patient's group has the lowest ratio as a result for calcitriol and its receptor deficiency. Vitamin $D_3$/VDR ratio has supported the results of vitamin $D_3$ and its receptor among patients and control group and is considered a confirmatory tool for the results of the presented study.

The opinion of the current study about this discrepancy in the value of risk factor is attributed to the important role of VDR that is involved in the action of vitamin $D_3$ because the calcitriol, or its analog, can express its action through VDR and any abnormalities in their structure or deficiency which may affect its role.

When making a comparison of the most overbalanced cause for initiation of psoriasis between calcitriol and its receptor, the receptor is more important than calcitriol because the calcitriol deficiency can be replaced by using the calcitriol supplements either from exposure to sunlight, dietary or industrial supplements while these cannot occur in the case of receptor abnormality.

The suggestion of this present study about this classification is that it is not necessary that all patients should have a VDR deficiency and the disease can result from calicitrol resistance in response to abnormal VDR receptors, even if present in a normal level or if the patients themselves were deficient in RXR. This is an important point because the RXR has the ability to bind with VDR after liganding of VDR with vitamin $D_3$ to bring it to hormone response element on the DNA and finally express the effect of vitamin $D_3$ and in the presence of any problems in RXR these processes cannot occur and the effect of calicitriol can be obscured.

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