Association of Serum vitamin D levels, Psoriasis and the Effect of Oral D supplementation on Clinical improvement of Disease

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Abstract

\textbf{Background:} Psoriasis is a chronic inflammatory skin disease mediated by the immune system. Hyper-proliferation with incomplete differentiation of epidermal keratinocytes and decreased keratinocyte apoptosis characterize psoriasis lesions. A role in the pathogenesis of various skin diseases for vitamin D includes psoriasis, were reported. Physiologically speaking, the active form and receptor of vitamin D regulate keratinocyte differentiation and proliferation, cutaneous immune system balance, and the apoptosis process. \textbf{Aims:} Evaluate the serum levels of vitamin D in psoriatic patients and to investigate the beneficial effect of oral D supplementation in the treatment of this disease. \textbf{Subjects and method:} This Case study included fifty-eight (58) Iraqi patients with Psoriasis and undergoing biologic therapy who were recruited from the Center of Dermatology and Venereology, Medical city, during the period from September 2019 to February 2020. IL-17 A and hs-CRP were measured in the patients’ serum by Enzyme-Linked Immunosorbent Assay technique Whereas, serum 1,25 (OH) D was measured by using Cobas e 411 analyzers. [PASI] Score, [BMI], [WC], and percentage of sun exposure were be evaluated and reported to be correlated with blood measurements. \textbf{Results:} The mean (±SD) value of serum 25OHVD levels of the placebo group was significantly higher compared to that of the oral vitamin supplement group (P=0.0001) before the supplement. The mean value of serum 25OHVD levels of group vitamin D supplement (after) was significantly increased when compared with that of (before) (P <0.0001) after three months of follow up of VD supplementation. \textbf{Conclusion:} Iraqi psoriatic patients suffer from vitamin D deficiency. An appropriate oral dose of vitamin D supplements can raise vitamin level in the serum to a normal value and, at the same time, be used as adjuvant therapy.

\textbf{Keywords:} Serum, vitamin D, Psoriasis

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Introduction:

Psoriasis is a chronic, immune-mediated, systemic, inflammatory disease wherein skin changes are the most visible sign. It occurs in approximately 1% to 3% of the world population\[1\]. It is often accompanied by physical symptoms of itching, physical irritation, pain, and soreness that increase with disease severity. These symptoms limit a patient’s ability to perform basic tasks [2]. Psoriasis is associated with comorbidities, such as psoriatic arthritis, obesity, metabolic syndrome, cardiovascular, and cerebrovascular diseases [3]. The pathogenesis of psoriasis involves a complex interaction between the immune system and the two main factors that affect the onset and exacerbation of the disease: environmental factors and genetic disposition. Approximately one-third of patients with psoriasis have a first-degree relative with the genetic condition [4].

The Psoriasis Area and Severity Index (PASI) is a widely used tool for evaluating the severity and extent of psoriasis [5].

Etanercept is a dimeric, soluble fusion protein used as a TNF-α inhibitor that was approved to use in psoriasis [6].

In psoriasis, vitamin D is involved in the maintenance of cutaneous barrier homeostasis. Several studies identified an association between polymorphisms of vitamin D receptor (VDR) and psoriasis susceptibility [7]. The A-1012G promoter polymorphism of the VDR gene is associated with psoriasis risk through a lower expression of VDR mRNA, favoring conditions that may alter the cutaneous barrier and the development of psoriatic lesions [8].

The active metabolite of vitamin D exerts an anti-inflammatory effect on the inflammatory profile of human monocytes/macrophages [9]. Down-regulating the expression and production of several pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, IL-8, and IL-17 [3].

Subjects and method:

This case study was carried out at the Department of Biochemistry, College of Medicine, University of Baghdad, and at Center of Dermatology and Venereology / Medical City, during the period from 9-9- 2019 to end of February 2020. It included 70 patients with psoriasis disease diagnosed by Consultant Dermatologist. They aged (17 - 70 years) and with different disease duration. Twelve of these patients were excluded from this study because some of them had psoriasis area severity index (PASI) score less than 7.5, and others took vitamin D supplements recently. The reminder 58 psoriatic patients were on biologic therapy Enbrel (etanercept) 50 mg.

The patients were classified into two ages-, gender-, and -PASI score-matched groups:
Group 1 (G1): It involved 33 patients aged 17 - 64 years.
Group 2 (G2): It included 25 patients aged 18 – 70 years.

Five milliliters of the blood sample was collected from a peripheral vein of each patient. The second blood sample was aspirated from each patient of G2 after completing their defined doses of vitamin D supplementation for 12 weeks. The sample was separated by centrifugation at 3000 rpm for 10 minutes to get serum after remaining to clot at room temperature for 10 - 15 minutes. And the separated serum was stored at -20 ºC for measurements of Interleukin 17, hs-CRP, and 25OHD.

IL-17 A and hs-CRP were measured in the patients’ serum by Enzyme-Linked Immunosorbent Assay technique. Whereas, serum 1,25 (OH) D was measured by using Cobas e 411 analyzer. Psoriasis Area and Severity Index [PASI] Score, Body mass index [BMI], waist circumference [WC], and percentage of sun exposure were be evaluated and reported to be correlated with blood measurements.

All analyses were performed with Statistical Package for the Social Sciences (SPSS) version 25 and XLSTAT add on Microsoft excel 2010 software. Students t-test and ANOVA tests were used for comparison between different groups mean. Pearson’s correlation was used to evaluate how the different biomarkers were related to each other. When the P-value was less than 0.05 it was considered as significant.

Results:

Table 1.1 shows the mean (±SD) values of demographic parameters for entire group of psoriatic patients before three months follow up of Vitamin D (VD) supplementation. The mean value of age was (38.40±12.34 years), and that of duration of psoriasis disease was (15.47±7.97 years). The table also shows the mean value of biologic therapy duration usage before starting this study was (17.55±8.79 month), and those of BMI, WC and sun exposure % were (30.07± 6.33 Kg/m2, 104.27± 16.45 cm, and 8.66±14.58 %; respectively). Similarly, it shows the mean value of PASI score before VD supplement (16.11±9.74). The mean value of serum 25OHVD concentrations was (14.46± 6.60 ng/ml), that of IL-17 (156.96±173.37 pg/ml), and of hs-CRP was (4.637+1.224 µg/ml).
Table 1.1: Mean (±SD) Values of Demographic and Parameters for Entire Group of Psoriatic Patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient group (n=58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (F/M)</td>
<td>22/ 36</td>
</tr>
<tr>
<td>Age (Year)</td>
<td>38.40±12.34</td>
</tr>
<tr>
<td>Duration of Psoriasis (years)</td>
<td>15.47±7.97</td>
</tr>
<tr>
<td>Duration of biologic therapy (month)</td>
<td>17.55±8.79</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>30.07±6.33</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>104.27±16.45</td>
</tr>
<tr>
<td>Sun exposure %</td>
<td>8.66±14.58</td>
</tr>
<tr>
<td>PASI score before D supplementation</td>
<td>16.11±9.74</td>
</tr>
<tr>
<td>25OHVD (ng/ml)</td>
<td>14.46±6.60</td>
</tr>
<tr>
<td>IL-17A (pg/ml)</td>
<td>156.96±173.37</td>
</tr>
<tr>
<td>hs-CRP (µg/ml)</td>
<td>4.64±1.22</td>
</tr>
</tbody>
</table>

Table 1.2 shows the mean (±SD) values of the demographic and measured parameters of the subgroups of patients before VD supplementation (G1; consisted of 33 patients and G2; involved 25 patients). The mean values of age, BMI, duration of disease, and duration of biologic therapy treatment were comparable and did not differ significantly between the two subgroups of patients. The important fact in these two subgroups of patients was that the mean (±SD) value of PSAI of two subgroups (G1: 16.00± 9.15, and G2: 16.26± 10.83) did not differ significantly and nearly in exact comparable. The mean (±SD) value of serum 25OHVD levels of G1 was significantly higher compared to that of G2 (16.63± 6.99 ng/ml, 11.59± 4.99 ng/ml; respectively, P=0.0001). However, the mean values of serum IL-17 levels of G1 and G2 (168.62± 200.79 pg/ml, 191.89± 285.63 pg/ml; respectively) and those of hs-CRP concentrations (4.67±1.32 µg/ml, 4.60± 1.13 µg/ml; respectively) did not differ significantly between these two subgroups of patients.

Table 1.2: Mean (±SD) Values of Demographic and Measured Serum Biochemical Markers (25OHVD, IL-17, hs-CRP) of Subgroups Before Vitamin D Supplementation

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Table 1.3 shows the mean (±SD) values of measured biochemical parameters of G2 of patients before and after three months of follow up of VD supplementation. The mean value of serum 25OHVD levels of G2 after was significantly increased when compared with that of before (31.52± 5.70 ng/ml, 11.59± 4.99 ng/ml; respectively, P <0.0001). The mean value of serum IL-17 levels did not differ significantly between G2 before and after (191.89± 285.63 pg/ml, 177.91± 258.32 pg/ml; respectively). Similarly, the mean value of serum hs-CRP levels was comparable between G2 before and after (4.60±1.1 µg/ml, 4.46±0.92 µg/ml; respectively).

Table 1.3: Mean (±SD) Values of Measured Serum Biochemical Parameters (25OHVD, IL-17, hs-CRP) of G2 of Patients Before and After VD Supplementation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>G2 before (n=25)</th>
<th>G2 after (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vit D (ng/ml)</td>
<td>11.59±4.99</td>
<td>31.52± 5.70*</td>
</tr>
</tbody>
</table>

T-test revealed significant increase of 25OHVD levels in G1 compared to G2 (p=0.0001), NS: non-significant differences in age, BMI,WC, sun exposure, duration of disease, duration of therapy, PASI score, IL-17, and hs-CRP levels between G1 and G2 (before VD supplement).
Table 1.4 show the mean (±SD) values of the PASI score of G1 (placebo group) and G2 (VD supplementation group) before and after three months of follow up period.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>G1 Before (n=33)</th>
<th>G1 After (n=33)</th>
<th>G2 Before (n=25)</th>
<th>G2 After (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASI score</td>
<td>16.00±9.15</td>
<td>18.72±10.56</td>
<td>16.26±10.83&lt;sup&gt;NS&lt;/sup&gt;</td>
<td>15.42±11.47</td>
</tr>
</tbody>
</table>

The results of present study found significant positive correlations between serum levels of hs-CRP and values of PASI score (r= 0.778, p= 0.0001) as well as significant negative correlation between serum levels of hs-CRP and serum 25OHVD concentrations in entire studied group (r= -0.265, p=0.045). Also, there were significant positive correlation between serum hs-CRP concentrations and PASI score values in G2 before VD supplementation (r=-0.771, p= 0.0001) and after VD supplementation (r= 0.538, p= 0.006). In addition, there was significant negative correlation between serum 25OHVD levels and serum hs-CRP concentration in G2 after VD supplementation (r= -0.412, p= 0.041). In G1 in which their patients did not taken VD supplementation, there was significant positive correlation between serum levels of hs-CRP and values of PASI score (r= 0.803, p= 0.0001) as well as significant positive correlation between serum levels of hs-CRP and serum concentrations of IL-17 (r= 0.352, p= 0.044). In G1, there was also significant negative correlation between serum 25OHVD levels and PASI values (r= 0.389, p= 0.025).
Discussion:

The mean value of age of psoriatic patients in the current study was found to be (38.40 year) which is near that found by El-ashmawy et al. (2018) who stated the mean of age of their psoriatic patients to be (31.60 year) [10].

The mean value of waist circumference (WC) of patients in the present study was found to be 104.27 cm. Other studies observed a mean of WC value of their patients to be 98.28 cm [11] and 85.36 [12].

Similarly, the mean value of BMI of psoriatic patients of the current study was (30.07 kg/m2) which reflects that Iraqi psoriatic patients are obese. This finding was higher than that reported by previous studies [11-13].

Obesity is an important risk factor for psoriasis [14]. The relationship between the two conditions is probably bidirectional, with obesity, mainly visceral obesity, predisposing to psoriasis [15].

The present study found that the mean value of sun exposure % of patients was (8.66 %) which is less than that observed by other studies [16-17]. The epidermis is the natural source of vitamin D synthesis by the action of ultraviolet light (UV) B of the sun or other UVB sources.

The mean value of serum IL-17A levels of psoriatic patients of the present study (156.96±173.37 pg/ml). The mean value of serum IL-17A levels in Iraqi healthy individuals was reported to be 22.7±4.97 pg/ml and 32.29 ± 20.18 pg/ml [18-19]. Mousa & Hassan (2020) stated that the mean value of serum IL-17A levels of their psoriatic patients was (895.066±105.171 pg/ml) [20] and that of (Dhalimi, 2013) was (265.39±806.76 pg/ml) [18]. While Razzaq et al. (2015) found the mean of IL-17A of their psoriatic patients was (42.38 ± 12.35 pg/ml) [19].

IL-17A is a very important cytokine in sustaining inflammation in psoriatic plaques. It influences the recruitment of inflammatory cells, enhances keratinocyte proliferation, and inhibits keratinocyte differentiation. IL-17A is undetectable in normal skin; however, it was detected in skin lesions in allergic contact dermatitis and psoriasis Vulgaris [21].

The mean value of hs-CRP levels of patients in the current study was (4.64±1.22 µg/ml). It is considered high when compared with normal values. (Jain et al., 2017) and (Gupta et al., 2019) found the mean of serum hs-CRP levels in their psoriatic patients was (4.8 mg/l) and (6.82 mg/l), respectively. The inflammatory state in psoriasis releases pro-inflammatory cytokines, which stimulate the liver to produce acute phase reactants. C-reactive protein is one such acute phase reactant [22-23].

The result of the present study showed a decrease in the PASI value of the VD supplemented group after 3 months even this decrease did not reach significant value, while the placebo group revealed an increase in PASI value after the same period. Also, the percentage of decreased in PASI value in the VD group is 4.27%, while in placebo group PASI value was an increase of 16.2%. Disphanurat et al.
(2019) reported that at a 3-month follow-up, the mean PASI score in the vitamin D (30,000 IU/ week) psoriatic group was decreased, whereas the mean PASI in placebo was increased. These authors suggested that vitamin D2 is a good adjunctive treatment to standard therapy [16]. Lee & Song (2018) demonstrated that circulating 25(OH) D levels are lower in patients with psoriasis, and that a small but statistically significant negative correlation exists between 25(OH) D levels and psoriasis severity [24]. A recent study conducted by Ingram et al. (2018) concluded a direct benefit of vitamin D supplementation for psoriasis could not be determined [25]. However, these authors suggested a relationship between 25(OH) D and psoriasis severity, at least in some subgroups. Ala-Houhala et al. (2014) concluded that patients with psoriasis received continuous oral cholecalciferol supplementation; narrow-band ultraviolet NB-UVB exposure increased serum 25 (OH) D concentrations. PASI score improved in these patients with psoriasis [26].

The mean values of IL-1A and hs-CRP levels were decreased after VD supplementation although these changes did not approach the significant level. A similar finding was observed by Disphanurat et al. (2019) who did not found a significant decline in hs-CRP at 3- and 6-months of VD supplementation [16].

Conclusion:

Iraqi psoriatic patients suffer from vitamin D deficiency. an appropriate oral dose of vitamin D supplements can raise vitamin level in the serum to a normal value and at the same time be used as an adjuvant therapy in addition to recommended therapy to improve the clinical condition of patients and also maintain the improvement of this disease when used alone like in shortness of biologic therapy availability.

Recommendations:

1- Large size sample of psoriatic patients.
2- Doses of 50,000 IU/ week for 3 and 6 month follow up study.

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