RESEARCH ARTICLE

Serum Vitamin D Levels at Different Stages of Acne Vulgaris Patients Treated with Isotretinoin: A Prospective Study

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Abstract:

Background: Acne vulgaris is a common chronic inflammatory skin disorder of pilosebaceous units. Isotretinoin (13-cis retinoic acid) is the most effective multifunctional treatment for moderate-to-severe and nodulocystic acne. Vitamin D plays a role in the immune system, and its deficiency might contribute to the pathogenesis of acne.

Objective: To investigate whether isotretinoin improves serum 25-hydroxyvitamin D levels in acne vulgaris patients.

Methods: This prospective cohort study included 68 patients with acne vulgaris. Lipid profiles, liver function tests, and serum 25-hydroxyvitamin D [25(OH)D] levels were measured at baseline and three months after starting isotretinoin treatment.

Results: There was a significant increase in serum vitamin D levels three months after starting isotretinoin treatment in mild acne patients (P=0.0003).

Conclusion: Vitamin D levels are altered in acne vulgaris. Isotretinoin therapy is associated with an increase in vitamin D levels, which was statistically significant in mild acne patients. Considering the role of vitamin D in acne, effective treatment with isotretinoin might highlight vitamin D as a possible target for acne therapy or as a biomarker for disease activity and remission.

Keywords: Acne vulgaris, Vitamin D, Vitamin D deficiency, Isotretinoin, Acne therapy, Isotretinoin therapy.

1. INTRODUCTION

Acne Vulgaris (AV) is a common primary inflammatory skin disorder of pilosebaceous units. Clinically, AV is characterized by open-and-closed comedones, papules, pustules, and nodules [1, 2]. AV affects both genders equally, and it usually starts in adolescence between 14 and 17 years of age in females and 16 and 19 years of age in males; however, its emergence may be delayed until 25 to 30 years of age. The time at which AV fades varies [3]. The pathogenesis of acne involves four primary factors: increased sebum production, increased follicular hyperkeratinization, colonization with cutibacterium acnes (formerly known as propionibacterium acnes), and inflammatory process [4].

Several treatment modalities have been used to treat AV. Topical therapies include antibiotics, azelaic acid, benzoyl peroxide, and retinoids. Systemic treatments include antibiotics, hormonal therapy, and isotretinoin [5].

Isotretinoin (13-cis-retinoic acid) is a systemic non-aromatic retinoid that is highly effective in the treatment of nodulocystic and moderate-to-severe acne, and it affects all four underlying factors of AV pathogenesis. Therefore,
isotretinoin is regarded as the most effective medication currently available for acne, and it is also an effective treatment for many other dermatological conditions [6]. Isotretinoin is indicated mainly for severe cases of acne but can be used in moderate cases to minimize scarring. The recommended dose for isotretinoin treatment is 0.5–1 mg/kg daily, with a cumulative dose between 120 and 150 mg/kg [7, 8]. Isotretinoin has many side effects, the most important of which are its hepatotoxicity, psychological effects, social effects, teratogenicity, and xerosis [9].

Vitamin D is a fat-soluble steroid hormone derived from dietary intake and synthesized through the skin via exposure to sunlight. Vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol) are manufactured through solar ultraviolet B radiation (UVB). Absorption of UVB radiation in the skin leads to the conversion of provitamin D to pre-vitamin D, followed by the production of vitamin D3 [10].

Vitamin D has both anticomedogenic and antioxidant properties; it demonstrates a regulatory effect on the immune system, proliferation, differentiation of sebocytes and keratinocytes. Therefore, its deficiency may contribute to the pathogenesis of acne [11, 12].

In this study, the effect of isotretinoin in the improvement of serum vitamin D levels in AV patients is explored. It is known that this is the first study in the Kingdom of Saudi Arabia to address this issue.

2. MATERIALS AND METHODS

2.1. Subjects

This prospective cohort study was conducted in the outpatient dermatology clinic at Qassim University, Saudi Arabia, between October 2016 and March 2017. The Medical Research Ethics Committee in the College of Medicine at Qassim University approved the study with the approval number 15/18/13. The study was conducted in the cold weather seasons to minimize the effect of seasonal variation on vitamin D levels. Of the enrolled AV patients (n=68), 30.88%, 38.24%, and 30.88% had mild, moderate, and severe acne, respectively.

Before initiating the study, a written informed consent was received from the participants after explaining the aim, value, and necessary steps in a simplified manner and the potential side effects of isotretinoin drugs.

Acne was graded and classified as mild, moderate, or severe. Mild acne was marked by <20 comedones, <15 inflammatory lesions, or a total lesion count <30. Moderate acne was characterized by 20–100 comedones, 15–50 inflammatory lesions, or a total lesion count of 30–125. Severe acne required >5 pseudocysts, a total comedones count >100, a total inflammatory count >50, or a total lesion count >125 [13].

All 68 subjects completed a data collection form to provide their demographics, family history of acne, sun exposure >2 hours/day, age of onset, duration of disease, site of acne (face, chest, or back), past medical history, and other relevant variables.

Inclusion Criteria: Patients from 15 to 35 years of age with AV, irrespective of sex, and who did not opt for acne treatments for at least the previous four weeks and patients who were unresponsive to conventional topical therapies or systemic antibiotics (other than systemic isotretinoin) were included in this study.

Exclusion Criteria: Pregnant and breastfeeding, patients taking vitamin D supplements for any reason, and patients who were on a concurrent treatment for acne were excluded.

2.2. Treatment

All patients were treated with isotretinoin (0.5–1 mg/kg/d) adjusted to 30–40 mg/day for three months. Serum beta HCG tests were performed for all female patients before starting the treatment.

2.3. Biochemical and Laboratory Analysis

2.3.1. Serum Vitamin D Concentration Measurements

Patients had their baseline serum 25-hydroxyvitamin D (25(OH)D) concentrations measured. Blood samples were collected from veins and analyzed within 24 h of sampling using the Roche Cobas e411 (Roche Diagnostics System, Switzerland). Based on the guidelines of the Food and Nutrition Board of the Institute of Medicine, 25(OH)D serum levels were categorized into adequate (>20 ng/ml), inadequate (12–20 ng/ml), or deficient (<12 ng/ml) categories [14].

2.3.2. Lipid Profile Measurements

Estimation of lipid profile: Plasma levels for triglycerides (TG) and Total Cholesterol (TC) were measured by standardized enzymatic procedures, using kits supplied by Roche Diagnostics (Mannheim, Germany) on the Olympus AU 400 automated clinical chemistry analyzer.

2.3.3. Liver Function Test measurements.

Serum AST was estimated using the Aspartate Aminotransferase (AST) Activity Assay Kit Catalog Number MAK055 (Sigma-Aldrich, USA). Serum ALT was evaluated using the Alanine Aminotransferase Activity Assay Kit Catalog Number MAK052 (Sigma-Aldrich, USA).

2.3.4. Statistical Analysis

Recorded data were analyzed using the Statistical Package for Social Sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). An analysis of variance (ANOVA) test was performed between more than two means t-tests and chi-squares to analyze the mean and percentage differences. A significance level of P<0.001 was considered highly significant, and P ≥0.05 was deemed to be insignificant. Furthermore, the quantitative data were expressed as a mean ± Standard Deviation (SD), while the qualitative data were expressed as frequency and percentage.

3. RESULTS

The study included 68 patients with AV (41 females and 27 males). Table 1 presents the participants’ baseline demographics and clinical characteristics [15].
The study reveals an overall non-significant increase in vitamin D levels, lipid profiles, and liver enzymes in all patients regardless of disease severity three months after starting isotretinoin treatment (Table 2).

Table 2. Comparison between means ± SD of serum concentration of vitamin D [25 (OH) D], lipid profiles, and liver enzymes before and 3 months after isotretinoin treatment in patients with acne vulgaris.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Before treatment</th>
<th>After 3 months of treatment</th>
<th>T-Test P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum vitamin D level (ng/ml)</td>
<td>28.8±7.9</td>
<td>33.4±6.8</td>
<td>0.327</td>
</tr>
<tr>
<td>Serum AST (u/l) (mean±SD)</td>
<td>26.6±10.7</td>
<td>32.5±9.0</td>
<td>0.132</td>
</tr>
<tr>
<td>Serum ALT (u/l) (mean±SD)</td>
<td>102.23±12.3</td>
<td>106.46±16.6</td>
<td>0.838</td>
</tr>
<tr>
<td>Triglyceride (mg/dl) (mean±SD)</td>
<td>170.5±13.9</td>
<td>236.8±18.4</td>
<td>0.412</td>
</tr>
</tbody>
</table>

SD=Standard deviation, AST=Aspartate Aminotransferase, and ALT=Alanine Aminotransferase.

At baseline, the vitamin D level was 26±9.4ng/ml for patients in the mild acne group and 31.4±6.9ng/ml for patients in the moderate acne group, while in patients with severe acne, it was 28.4±6.7 ng/ml. There were no significant variations in serum vitamin D levels between the mild, moderate, and severe acne groups (P=0.067), as levels were maintained post-treatment with isotretinoin (P=0.773). Three months after starting isotretinoin treatment, an increase in the mean value of serum vitamin D levels in mild, moderate, and severe acne was reported (35.6±6.5, 32.14±7.1, and 32.9±4.9, respectively).

However, this was only significant in the mild acne group (P=0.003; Tables 3 and 4).

Table 3. The relationship between acne vulgaris severity patients and serum concentration of vitamin D [25 (OH) D] before and 3 months after isotretinoin treatment.

No significant change in lipid profile mean values were detected in all subgroups mild, moderate, and severe acne throughout the study while in liver enzymes, only serum AST were significant in severe acne vulgaris after treatment with P-value 0.011 (Table 5).
Table 5. Comparison between means ± SD of lipid profiles, and liver enzymes at baseline and 3 months after isotretinoin treatment in patients with mild, moderate, and severe acne vulgaris.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>At baseline</th>
<th>3 Months</th>
<th>T-test P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild Acne (N=21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum AST (u/l) (mean±SD)</td>
<td>24±1.14</td>
<td>24±2.3</td>
<td>0.353</td>
</tr>
<tr>
<td>Serum ALT (u/l) (mean±SD)</td>
<td>29±5.7</td>
<td>28±2.3</td>
<td>0.987</td>
</tr>
<tr>
<td>Triglyceride (mg/dl) (mean±SD)</td>
<td>60±2.8</td>
<td>66.5±1.5</td>
<td>0.759</td>
</tr>
<tr>
<td>Cholesterol (mg/dl) (mean±SD)</td>
<td>132±12.1</td>
<td>143±13.5</td>
<td>0.432</td>
</tr>
<tr>
<td></td>
<td>Moderate Acne (N=26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum AST (u/l) (mean±SD)</td>
<td>23.2±4.8</td>
<td>25±4.6</td>
<td>0.484</td>
</tr>
<tr>
<td>Serum ALT (u/l) (mean±SD)</td>
<td>22±7.6</td>
<td>29±6.2</td>
<td>0.247</td>
</tr>
<tr>
<td>Triglyceride (mg/dl) (mean±SD)</td>
<td>111±12.8</td>
<td>140±11.6</td>
<td>0.392</td>
</tr>
<tr>
<td>Cholesterol (mg/dl) (mean±SD)</td>
<td>165±13.2</td>
<td>171±12.7</td>
<td>0.368</td>
</tr>
<tr>
<td></td>
<td>Severe Acne (N=21)</td>
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<td></td>
</tr>
<tr>
<td>Serum AST (u/l) (mean±SD)</td>
<td>28.5±8.3</td>
<td>41±2.3</td>
<td>0.011**</td>
</tr>
<tr>
<td>Serum ALT (u/l) (mean±SD)</td>
<td>30±2.3</td>
<td>41.5±5.6</td>
<td>0.222</td>
</tr>
<tr>
<td>Triglyceride (mg/dl) (mean±SD)</td>
<td>132±18.5</td>
<td>104±15.3</td>
<td>0.479</td>
</tr>
<tr>
<td>Cholesterol (mg/dl) (mean±SD)</td>
<td>180±9.7</td>
<td>197±1.3</td>
<td>0.463</td>
</tr>
</tbody>
</table>

N = Number, SD = Standard deviation, AST = Aspartate Aminotransferase and ALT = Alanine Aminotransferase.
** mild significant differences P ≤ 0.005

There is an established interaction between these receptors. RXR exerts a dimerizing effect on VDR receptors, and heterodimers can also be formed between them (VDR/RXR) [17]. In addition to the impact on RXR responsive genes, RXR selective retinoids could also influence vitamin D responsive genes. Furthermore, vitamin D could also regulate RXR responsive genes [18]. Although isotretinoin has a low affinity to retinoid receptors, it is converted intracellularly, demonstrating an agonist effect on RAR and RXR receptors [19].

Systemic isotretinoin is a potent acne treatment that affects all four pathogenic factors of the disease, suppressing sebum production and the abnormal desquamation of the sebaceous follicle epithelium and decreasing cutibacterium acne and inflammation [20]. Systemic isotretinoin also demonstrates an inhibitory effect on Th17 development and IL-17 [21].

The results of this study revealed that there was an increase in vitamin D levels after three months of isotretinoin treatment, with a significant difference in the mild acne group only (P=0.0003). What is interesting, no existed theoretical explanation by authors behind this which could be further investigated by future studies. Our results were nearly similar to El-Hamd et al. study [22]. On the other hand, a study by Moravej H et al. showed no effect on serum vitamin D levels after recommended dose of oral isotretinoin [23], while the result of another study of Ertugrul et al. showed increased 1,25-dihydroxyvitamin D levels and decreased 25-hydroxyvitamin D levels after isotretinoin treatment [24]. The possible rationale behind the contradicting results of these studies is that there might be differences in inclusions and exclusions criteria or in other methodologies’ sittings of those studies that had affected the results.

The results of our study and other studies focus on the active role of vitamin D deficiency and its effect on the development of AV, which can be illustrated by the role of cutibacterium acne in increasing the gene expression of immunological factors to block vitamin D production [25, 26].

This highlights the promising role of vitamin D in AV treatment. In our results, the absence of statistically significant differences between vitamin D and AV severity is mostly due to the small sample size.

The results in this study for lipid profiles and liver function showed an insignificant increase after three months of oral isotretinoin treatment which is similar to other studies [22].

CONCLUSION

Vitamin D plays a role in acne pathogenesis and its level are altered in acne vulgaris. Serum 25-hydroxyvitamin D levels increased after three months of oral isotretinoin therapy, and the effect was significant in mild acne patients. Oral isotretinoin and its influence on vitamin D serum levels in acne patients might highlight vitamin D as a possible target for acne therapy. Furthermore, vitamin D might be considered a biomarker for disease activity and remission.

Further studies on a larger scale are needed to address the effect of isotretinoin in improving vitamin D levels and the exact role of vitamin D deficiency in the pathogenesis of acne, as well as the possible therapeutic effect of vitamin D preparations in acne vulgaris.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Medical Research Ethics Committee in the College of Medicine at Qassim University approved the study with the approval number 15/18/13.

HUMAN AND ANIMAL RIGHTS

No Animals were used in this research. All human research procedures followed were in accordance with the ethical
standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

CONSENT FOR PUBLICATION

Informed consent was obtained from all the participants.

AVAILABILITY OF DATA AND MATERIALS

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

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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