Effect of 6-month isotretinoin treatment on 25-hydroxyvitamin D levels in patients with acne vulgaris

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Abstract

Objectives: Acne is a chronic inflammatory disease that affects the pilosebaceous units of the skin. Isotretinoin is a derivative of the synthetic 13-cis-retinoic acid and is an efficient drug for acne treatment. In clinical studies, the negative effects of long-term and short-term isotretinoin use on vitamin D levels and bone metabolism restrict its use. In this study, the effect of isotretinoin treatment on vitamin D levels was examined in patients with acne vulgaris.

Material and Methods: Ninety patients with clinically diagnosed acne vulgaris who came to the Malatya Research and Training Hospital Dermatology Clinic participated in this study. Patients who had been using any systemic drug for the previous month or who had any systemic disease were not included in the study. Patients with abnormalities in calcium (Ca), alkaline phosphatase (ALP), and parathyroid hormone (PTH) levels, which affect vitamin D metabolism, also were not included in the study. Patients were treated first with 0.5 to 1.0 mg/kg (per kilogram of body weight) doses of isotretinoin, with the aim of total dosage of 120 mg/kg. The patients' 25-hydroxy vitamin D3 [25'(OH) vit D3] levels were measured before treatment and at the sixth month of treatment.

Results: Among the 90 patients who participated in the study, 51 (56.7%) were female, and 39 (43.3%) were male, with an age range of 16 to 50 years (mean ±standard deviation) age, 23.55±5.58 years. Eight patients dropped out of the study. The patients' (mean ± standard deviation) 25'(OH) vit D3 level was 18.28±9.92 before treatment and 13.28±7.78 at the sixth month of treatment (p=0.000).

Conclusion: The negative effect of isotretinoin on vitamin D levels and bone metabolism has been shown in previous studies. In this study, 25'(OH) vit D3 levels decreased significantly in patients treated with isotretinoin in the long term (p>0.000).

Keywords: vitamin D, acne vulgaris, bone metabolism

ZhaoSpirmidik Beseuleri Bar Pacientterde D 25-Gidrokсидорумен Denegiine Izotretnoind Men 6 Ayr Terapiya Jasaudyn Esery

Maksat: Bezee – teriiin pilosebacei keshenine jacketzysiz owr eutshu sosyalmalys cip zyzyru averu. Izotretnoin – sintetikalik 13-cis-retinolqdy 3qyshlyqdy baiylansyqy jene bezuuerdery emdeu uziin tizmidin deri bolyp tablyady. Klinikalik zertteuellerde D darumenin demekine izotretnoindindei baytymqy jene 3qyshka baytymdik abaylady. Bezm qyzyruqy jene zertteuellerde jene 3qyshka qaynqqyna 3qyshka jene demekine benzemez ekstremaline. Bulet zertteu jazoespirimdik bezueleyi bar pacientterde D deruneni denegiine izotretnoindikmen terapiyqy jene zertteu sardapendey.

Qammad: Bulet zertteu jazoespiromidik bezueleyi bar pacientterde D darumenin demekine izotretnoindikmen terapiyqy jene zertteu sardapendey.

Qytqyrmdamda

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Introduction
Acne is a chronic inflammatory disease that affects the pilosebaceous units of the skin. Increased sebum secretion, abnormal follicular keratinization, microbial colonization, and inflammation were thought to play a role in acne pathogenesis [1]. Isotretinoin is a systemically used retinoic acid derivative that affects many factors that play a role in acne pathogenesis. Isotretinoin has many adverse effects on various systems, most commonly mucocutaneous adverse effects, as well as adverse effects on the musculoskeletal system [2]. The most common side effect of isotretinoin on the skeletal muscle system is myalgia. Low back pain, arthralgia, osteoporosis and osteophyte formation are rarely reported. In this study, 25-hydroxyvitamin D3 [25'(OH) vit D3] levels in patients who used isotretinoin for acne vulgaris diagnosis was investigated. We examined the effects of isotretinoin on vitamin D metabolism.

Material and Methods
Ninety patients with clinically diagnosed acne vulgaris who came to the Malatya Public Hospital Dermatology Clinic participated in this study. Patients who had been using any systemic drug for the previous month or who had any systemic disease were not included in the study. Patients with abnormalities in calcium (Ca), alkaline phosphatase (ALP), and parathyroid hormone (PTH) levels, which affect vitamin D metabolism, also were not included in the study. In addition, the pregnancy status was precisely excluded by looking at b-hCG before treatment. Patients who had a metabolic disorder related to vitamin D in their history and were treated for vitamin D supplementation, were not included.

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Results
Among the 90 patients who participated in the study, 51 (56.7%) were female, and 39 (43.3%) were male, with an age range of 16 to 50 years (mean ± standard deviation) age, (23.55±5.58 years). Lesions appeared only on the face in 53 (58.8%) patients, on both the face and the back in 27 (30%) patients, and only on the back in 10 (11.1%) patients. Eight patients dropped out of the study as they showed treatment incompatibility. The patients’ 25'(OH) vit D3 levels were measured before treatment and at the sixth month of treatment.

Statistical analyses were done by using SPSS Statistics version 23.0. Consistency of the normal distribution of variable was tested by Kolmogorov-Smirnov. For variables not showing normal distribution, Wilcoxon (non-parametric) test was used for dependent variables and a Mann-Whitney U test was used for independent variables. To analyze the difference between age and gender ANCOVA test is used. Statistical significance was indicated at p<0.05.

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Among the 90 patients who participated in the study, 51 (56.7%) were female, and 39 (43.3%) were male, with an age range of 16 to 50 years (mean ± standard deviation) age, (23.55±5.58 years). Lesions appeared only on the face in 53 (58.8%) patients, on both the face and the back in 27 (30%) patients, and only on the back in 10 (11.1%) patients. Eight patients dropped out of the study as they showed treatment incompatibility. The patients’ 25'(OH) vit D3 levels were measured before treatment and at the sixth month of treatment. Statistical analyses were done by using SPSS Statistics version 23.0. Consistency of the normal distribution of variable was tested by Kolmogorov-Smirnov. For variables not showing normal distribution, Wilcoxon (non-parametric) test was used for dependent variables and a Mann-Whitney U test was used for independent variables. To analyze the difference between age and gender ANCOVA test is used. Statistical significance was indicated at p<0.05.
The descriptive data of the study group:

|                  | Mean (SD), min-max | P    |
|------------------|-------------------|------|
| Study group, N=91|                   |      |
| Age              | 23.55 (5.58), 16-50| 0.01 |
| Gender           |                   | 0.347|
| Female           | 51, 56.7%         |      |
| Male             | 39, 43.7%         |      |
| Vit D (ng/mL)    | 18.28 (9.92)      | 0.001|
| Before treatment | 0.001             |      |
| After treatment  | 13.28 (7.78)      |      |

Discussion

Acne vulgaris is a skin disease with chronic social and psychological effects, which especially affects adolescent individuals, and it has a multifactorial etiology characterized by papules, pustules, cysts, and comedones on the skin [3]. Isotretinoin is a synthetic 13-cis-retinoic acid derivative and an effective drug used in acne treatment [4]. The US Food and Drug Administration approved the drug in 1982 [5]. The pharmacological effect is accomplished by changing the lipid composition of the skin surface by decreasing the sebaceous gland size and production of sebum. Bacterial skin flora levels decrease depending on changes in sebaceous factors. The most common effect of the drug is on the mucocutaneous system because it decreases sebaceous gland size. Mucosal dryness and elevated triglyceride levels are observed in almost all patients. Mucocutaneous adverse effects are challenging for patients but do not require treatment cessation [6].

Although dietary vitamin A is required for normal growth and development, long-term and high-dose use of vitamin A derivatives (retinoids) may have undesirable effects on the skeletal system. Although isotretinoin does not have any effect on X-ray diffraction and bone mineral density measurements, it has a direct inhibitory effect on bone turnover [7]. Isotretinoin was shown to cause premature epiphysis closure in laboratory animals [8]. Long-term and high-dose use of the drug can cause hyperostosis and spinal ligament calcification similar to that seen in diffuse idiopathic skeletal hyperostosis (DISH) [9]. The drug also is related to osteoporosis. A pronounced effect of isotretinoin on bone mineral density was not observed with use of one dose and short-term applications [4].

The importance of vitamin D has been increasing over time, and it is the most widely studied vitamin in recent years. Vitamin D was known to regulate calcium and bone metabolism, and recent advances also showed that it has regulatory effects on cell growth and differentiation of various tissues by means of immunomodulation [10].

There are a limited number of studies in the literature related to the long-term effect of isotretinoin on vitamin D. In their study, 11 patients with cystic acne, Rodland et al [11] observed a decrease in 1,25-dihydroxyvitamin D3 levels, but they did not observe a pronounced effect on 25'(OH) vit D3 levels after three months of isotretinoin treatment. Ertugrul et al [12] examined levels of vitamin D and bone metabolites in 50 patients with nodulocystic acne after isotretinoin treatment for three months. At the end of three months of treatment, they observed a significant decrease in 25'(OH) vit D3 and serum calcium levels and an increase in 1,25-dihydroxyvitamin D3, bone ALP, and PTH levels [13]. Trifiro et al [14] detected a decrease in urinary levels of N-telopeptide of type I collagen (N-Tx) level in urine of adolescents who underwent short-term use of isotretinoin treatment. N-telopeptide of type I collagen exists in all tissues because it consists of especially bone and cutaneous tissue type I collagen, and N-telopeptide is a bone degradation inhibitor in metabolic bone diseases [14]. It is recommended to avoid sunlight during the treatment of isotretinoin. This also can lead to the development of osteoporosis and the formation of fractures. Vestergaard P and colleagues [15] showed that risk of fracture is not associated with vitamin A analogue treatment.

**Limitation of the study:** The mean level of the vit D in the study group was also low before the treatment. Our study group includes premenopausal and postmenopausal women with a wide range of age. These could also have affected the end result.

Conclusion

It was shown in recent studies that isotretinoin has an effect on vitamin D and bone metabolism. In this study, we showed that 25'(OH) vit D3 levels decreased significantly in patients treated with isotretinoin in the long term. Bone biopsy should be performed before and after treatment to detect any effect of isotretinoin on bone metabolism and vitamin D levels. If isotretinoin produces adverse effects, vitamin D supplementation may be required to reduce the negative effects of the drug on bone metabolism.

**Disclosures:** There is no conflict of interest for all authors.

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