

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

Gülbahar Saraç<sup>1</sup>, Tuba Tülay Koca<sup>2</sup>, Serpil Şener, Gülden Hakverdi<sup>3</sup>

<sup>1</sup>Department of Dermatology Inonu University, Malatya, Turkey

<sup>2</sup>Department of Physical Medicine and Rehabilitation, Sütçü İmam University, Kahramanmaraş, Turkey

<sup>3</sup>Department of Biostatistics, Cumhuriyet University, Sivas, Turkey



This work is licensed under a Creative Commons Attribution 4.0 International License

Received: 2018-01-06

Accepted: 2018-01-18

UDC: 616.1

*J Clin Med Kaz* 2018;1(47):25-28

**Corresponding Author:** Tuba Tülay KOCA, MD, Assistant Prof. Physical Medicine and Rehabilitation, Sütçü İmam University, Kahramanmaraş, Turkey  
E-mail: tuba\_baglan@yahoo.com

## 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  $\pm$  standard deviation) age, 23.55 $\pm$ 5.58 years. Eight patients dropped out of the study. The patients' (mean  $\pm$  standard deviation) 25'(OH) vit D3 level was 18.28 $\pm$ 9.92 before treatment and 13.28 $\pm$ 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

## ЖАСӨСПІРІМДІК БЕЗЕУЛЕРІ БАР ПАЦИЕНТТЕРДЕ D 25-ГИДРОКСИДӘРҮМЕН ДЕҢГЕЙІНЕ ИЗОТРЕТИНОИН-МЕН 6 АЙ ТЕРАПИЯ ЖАСАУДЫҢ ӘСЕРІ

Гюльбахар Сарач<sup>1</sup>, Туба Тюля Кока<sup>2</sup>, Серпиль Шенер, Гюльден Хакверди<sup>3</sup>

<sup>1</sup>Дерматология бөлімі, Инёню атындағы университеті, Малатья, Түркия

<sup>2</sup>Физиотерапия және оңалту бөлімі, Сутчу Имам университеті, Кахраманмараш, Түркия

<sup>3</sup>Биостатистика бөлімі, Кумхурнет университеті, Сивас, Түркия

### ТҰЖЫРЫМДАМА

**Мақсаты:** Безеу – терінің пилосебацей кешеніне жағымсыз әсер етуші созылмалы ісіп қызару ауруы. Изотретиноин – синтетикалық 13-цис-ретинолды қышқылдың байланысуы және безеулерді емдеу үшін тиімді дәрі болып табылады. Клиникалық зерттеулерде D дәрумені деңгейіне изотретиноинді ұзақ мерзімді және қысқа мерзімді қабылдаудың жағымсыз әсері және сүйек тіні метаболизмі оны пайдалануды шектейді. Бұл зерттеуде жасөспірімдік безеулері бар пациенттерде D дәрумені деңгейіне изотретиноинмен терапиялау әсері зерделенді.

**Әдістері:** Бұл зерттеуге Малатья қаласындағы Ғылыми-зерттеу ауруханасының Дерматология клиникасына жасөспірімдік безеулер клиникалық диагнозымен келген тоқсан пациент қатысты. Өткен айда қандай да бір жүйелі дәрілерді қабылдаған пациенттер зерттеуге енгізілмеді. D дәрумені метаболизміне әсер етуші кальций, сілтілі фосфатаза мен паратиреоидты гормон көрсеткіштерінде қалыпты жағдайдан ауытқушылығы бар пациенттер де зерттеуге қосылмады. Пациенттер 120 мг/кг жалпы мөлшерлеу мақсатында изотретиноиннің 0,5-тен 1.0 мг/кг-ға дейінгі (дене салмағының бір келісіне) мөлшерін қабылдады. Пациенттерде 25-гидроксидәруменнің D3 [25'(OH) vit D3] деңгейін емдеу алдында және терапияның алтыншы айында өлшеді.

**Нәтижесі:** Зерттеуге қатысқан 90 пациенттің арасында 51 (56.7%) әйел, және 39 (43.3%) еркек болды, жас диапазоны 16 жастан 50

жасқа дейін құрады (орташа±дәлсіздік), 23.55±5.58 жас. Сегіз пациент зерттеуден шығып қалды. Пациенттерде 25-гидроксидәрумен D3 деңгейі (орташа±дәлсіздік) емдеуге дейін 18.28±9.92 құрады және терапияның алтыншы айында (p=0.000) 13.28±7.78 құрады.

**Қорытынды:** D дәрумені деңгейіне изотретиноиннің жағымсыз әсері және сүйек тіні метаболизмі өткендегі зерттеулерде көрсетілген. Бұл зерттеу изотретиноинмен ұзақ мерзімді терапиядан өткен пациенттерде 25-гидроксидәрумен D3 деңгейі айтарлықтай төмендеді (p>0.000).

**Негізгі сөздер:** D дәрумені, жасөспірімдік безеулер, сүйек тіні метаболизмі

## ВЛИЯНИЕ 6-МЕСЯЧНОЙ ТЕРАПИИ ИЗОТРЕТИНОИНОМ НА УРОВЕНЬ 25-ГИДРОКСИВИТАМИНА D У ПАЦИЕНТОВ С ЮНОШЕСКИМИ УГРЯМИ

Гюльбахар Сарач<sup>1</sup>, Туба Тюля Кока<sup>2</sup>, Серпил Шенер, Гюльден Хакверди<sup>3</sup>

<sup>1</sup>Кафедра дерматологии, Университет им. Инёню, Малатья, Турция

<sup>2</sup>Кафедра физической медицины и реабилитации, Университет Сутчу Имам, Кахраманмараш, Турция

<sup>3</sup>Кафедра биостатистики, Университет Кумхуриет, Сивас, Турция

### РЕЗЮМЕ

**Цели:** Угри - хроническое воспалительное заболевание, негативно воздействующее на пилосебацейный комплекс кожи. Изотретиноин это производное соединение синтетической 13-цис-ретиноевой кислоты и является эффективным лекарством для лечения угрей. В клинических исследованиях, негативное воздействие длительного и кратковременного приема изотретиноина на уровень витамина D и метаболизм костной ткани ограничивает его использование. В данном исследовании изучено влияние терапии изотретиноином на уровень витамина D у пациентов с юношескими угрями.

**Материалы и методы:** В данном исследовании приняло участие девяносто пациентов с клиническим диагнозом юношеские угри, которые обратились в Дерматологическую клинику Научно-исследовательской больницы Малатяи. Пациенты, которые принимали какое-либо системное лекарство в предыдущем месяце не были включены в исследование. Пациенты с отклонениями от нормы в таких показателях, как кальций, щелочная фосфатаза, и паратиреоидный гормон, которые влияют на метаболизм витамина D, также не были включены в исследование. Пациенты принимали от 0.5 до 1.0 мг/кг (на один килограмм веса тела) дозы изотретиноина, с целью общей дозировки 120 мг/кг. Уровень 25-гидроксивитамина D3 [25'(OH) vit D3] у пациентов измеряли перед лечением и на шестой месяц терапии.

**Результаты:** Среди 90 пациентов, участвовавших в исследовании, было 51 (56.7%) женщин, и 39 (43.3%) мужчин, возрастной диапазон составил от 16 до 50 лет (среднее ±погрешность), 23.55±5.58 лет. Восемь пациентов выбыли из исследования. Уровень 25-гидроксивитамина D3 у пациентов (средний ± погрешность) составил 18.28±9.92 до лечения и 13.28±7.78 на шестой месяц терапии (p=0.000).

**Заключение:** Негативное влияние изотретиноина на уровень витамина D и метаболизм костной ткани был показан в предыдущих исследованиях. Данное исследование показало, что уровень 25-гидроксивитамина D3 у пациентов, прошедших долговременную терапию изотретиноином значительно снизился (p>0.000).

**Ключевые слова:** витамин D, юношеские угри, метаболизм костной ткани

## 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 pathology [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.

The group of patients who were excluded from these criteria and were volunteers were 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. Vitamin D levels were measured by immunoassay technique. 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.

## 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' (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<0.001). Normal value of 25'(OH) vit D3 is 20-30 ng/mL according to our laboratory. Our group was normally distributed by gender (p=0,347) and abnormally distributed by age (p=0,01) (Table 1).

**Table 1** 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)		0.001
Before treatment	18.28 (9.92)	
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 D<sub>3</sub> levels, but they did not observe a pronounced effect on 25'(OH) vit D<sub>3</sub> 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 D<sub>3</sub> and serum calcium levels and an increase in 1,25-dihydroxyvitamin D<sub>3</sub>, 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 D<sub>3</sub> 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.

## References

1. Saraç G, Koca TT, Şener S, Cenk H. A Comparison of Vitamin D Levels in Patients with Acne Vulgaris and Healthy Individuals. *J Clin Med Kaz.* 2017; 2(44):33-35.
2. Blasiak RC, Stamey CR, Burkhart CN, Lugo-Somolinos A, Morrell DS. High-dose isotretinoin treatment and the rate of retreat, relapse, and adverse effects in patients with acne vulgaris. *JAMA Dermatology.* 2013; 149(12):1392-8.
3. Bhambri S, Del Rosso JQ, Bhambri A. Pathogenesis of acne vulgaris: recent advances. *J Drugs Dermatol.* 2009; 8(7):615-8.
4. Tekin NS, Ozdolap S, Sarikaya S Keskin SI. Bone mineral density and bone turnover markers in patients receiving a single course of isotretinoin for nodulocystic acne. *Int J Dermatol.* 2008; 47(6):622-5.
5. Khatri KA, Garcia V: Light-assisted hair removal in patients undergoing isotretinoin therapy. *Dermatol Surg.* 2006; 32:875-7.
6. Mahrle G, Bauermeister-Jasso K, Enderer K. Roaccutane in acne and rosacea. *Z Hautkr.* 1985; 60(1-2); 120; 125-34.
7. Kindmark A, Rollman O, Mallmin H, Petren-Mallmin, Ljunghall S. Oral isotretinoin therapy in severe acne induces transient suppression of biochemical markers of bone turnover and calcium homeostasis. *Acta DermVenereol.* 1998; 78(4):266-9.
8. Goodman G: Managing acne vulgaris effectively. *AustFamPhysician.* 2006; 35:705-9.
9. Sinclair W, Jordaan HF: Acne guideline 2005 update. *S Afr Med J.* 2005; 95:881-92.
10. Özmen İ, Köse O. Vitamin D and Skin. *Turkish Journal of Dermatology.* 2008; 2:77-83.
11. Rodland O, Aksnes L, Nilsen A, Morken T. Serum levels of vitamin D metabolites in isotretinoin treated acne patients. *Acta Derm Venereol.* 1992; 72(3):217-9.

12. Ertuğrul DT, Karadağ AS, Tatal E, Akın KO. Does isotretinoin have effect on vitamin D physiology and bone metabolism in acne patients? *Dermatologic Therapy*. 2011; 24:291-95.
13. Halverstam CP, Zeichner J, Lebwohl M. Lack of significant skeletal changes after long-term, low-dose retinoid therapy: case report and review of the literature. *J Cutan Med Surg*. 2006; 10(6):291-9.
14. Trifiro G, Norbiato G. Type I collagen N-telopeptide variation in adolescents receiving oral isotretinoin for severe acne. *J Pediatr EndocrinolMetab*. 2002; 15(1):35-9.
15. Vestergaard P, Rejnmark L, Mosekilde L. High-dose treatment with vitamin A analogues and risk of fractures. *Arch Dermatol*. 2010; 146(5):478-82. doi: 10.1001/archdermatol.2010.59.

**How to cite this article:** Gülbahar Saraç, Tuba Tülay Koca, Serpil Şener, Gülden Hakverdi. Effect of 6-month isotretinoin treatment on 25-hydroxyvitamin D levels in patients with acne vulgaris. *J Clin Med Kaz*. 2018; 1(47):25-28