ORIGINAL ARTICLE

Effects of Oral Isotretinoin on Serum Vitamin D Metabolites and Other Biochemical Markers of Bone Turnover and Calcium Homeostasis in Severe Acne

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Abstract

Background: Few studies have investigated on vitamin D metabolites Serum levels, and calcium homeostasis in humans receiving retinoids, despite a substantial amount of literature concerning retinoid-induced osteoporosis in animals. We prospectively measured vitamin D metabolites serum levels and calcium homeostasis and radiographic bone changes in short course treatment with oral isotretinoin in severe acne.

Methods: 1,25-dihydroxy vitamin D and 25-hydroxy vitamin D, calcium, phosphate, Parathyroid hormone and axial spine , femoral neck radiographies were measured in 30 nodulocystic acne patients (17 -28 years) before and after twenty weeks of treatment with oral isotretinoin at the recommended dose (0.75 -1 mg/kg/day) .

Results: vitamin D metabolites, calcium, phosphate, Parathyroid-hormone did not change significantly and hyperostosis and other sclerotic change were not observed in any patients.

Conclusion: Short course treatment with oral isotretinoin at the recommended dose did not lead to any significant changes in serum vitamin D metabolites, calcium, phosphate and Parathyroid hormone and has no effects on bone radiography in acne patients. *(Iran J Dermatol 2008;11: 108-112*)

Keywords: isotretinoin, nodulocystic acne, calcium, phosphate, PTH, vitamin

Introduction

One of the concerns of dermatologists is complications resulting from administration of oral isotretinoin in patients with nodulocystic acne. By affecting all factors inducing acne, this medication is effective in its treatmen[1,2]. Due to its high efficiency, isotretinoin leads to long-term improvement of the lesions in most cases, although it may lead to such complications as lip fissure, mucosal dryness, xerosis, conjunctivitis, itching, muscular, arthritic and bone pains[3,4]. It has skeletal complications comparable to hypervitaminosis A, and diffuses idiopathic skeletal hyperostosis[5-10]. More observed symptoms include hyperostosis, ossification of ligaments, osteoporosis, periostal thickening, decreased cortical thickness, and early fusion of epiphysis[10-12]. These osseous changes result mainly from long term treatment, although partial changes have also been observed following short term treatment of nodulocystic acne at a low dosage[13]. Some studies have mentioned no clinically significant osseous changes after short term (20 weeks) treatment with isotretinoin[14]. Oral isotretinoin for treating acne may lead to changes in serum levels of hydroxy vitamin D, calcium, phosphate, and PTH, and vitamin D metabolites[15,16], but some studies have not mentioned these changes[17,18]. For a better understanding of the effects of synthetic retinoids on bone, we prospectively investigated bone radiography and calcium metabolism in 30 patients who received a short course of (20 weeks) isotretinoin for nodulocystic acne. We also measured the serum levels of 1.25 dihydroxy vitamin D, 25 hydroxy vitamin D, calcium, phosphate, PTH and radiographic bone changes before and after the treatment with oral isotretinoin in nodulocystic acne patients.

Patients and Methods

This study was a clinical trial before and after treatment. Thirty patients with nodulocystic acne were referred from the dermatology sections of Shaheed Beheshti Medical University; each participant gave a written informed consent and was instructed not to make notable changes in their diets or to take supplemental vitamin A, vitamin D or calcium. Subjects were limited to the ages between 17 and 28 to minimize age related bone changes. Twenty one (70%) were females who did not take oral contraceptive because of the confounding effects of estrogen on retinoids and 9 (30%) were male. Acne was clinically diagnosed by a dermatologist[1] and nodulocystic type was determined by its clinical criteria[1].

Inclusion criteria: boys and girls and nonpregnant, nonlactating women with severe nodulocystic acne, were candidates for receiving oral Isotretinoin (Ro-accutane; Roche Company, Switzerland). Females of childbearing potential were required to use two separate and effective methods of birth control and also not to take estrogen compound pill and had to have a negative serum pregnancy test 1 week before the start of isotretinoin therapy, which began on the second or third day of menstrual cycle.

Exclusion criteria: included musculoskeletal, endocrine, renal and gasterointestinal disorders, sarcoidosis, a history of recent blood transfusion, receiving anticonvulsants, glucocorticoids, erythromycin, tiazid diuretics, acetazolamide, antiacids containing calcium carbonate, vitamin A supplement, minerals, laxatives, thyroid hormone treatment, recent history of drug or alcohol abuse, recent history of psychiatric disorders, mood or depressive disorders, previous therapy with oral retinoids, any metal implants or bone disease, weight less than 30 kg and over 100 kg, diabetes mellitus, clinical rickets, sever scoliosis, current or history of severe back injuries, or presence of hyperostosis at baseline, estrogen, progesterone , androgen and tetracycline during the last two months.

25 hydroxy vit D, 1,25 dihydroxy vit D and calcium, phosphate, and Parathyroid hormone (PTH) and bone radiographic changes (axial, cervical, thoracic, lumbar spine and femoral neck) were measured before and 20 weeks after the treatment.

Laboratory method

Blood samples (10cc) of patients following 12 hours of fasting were taken before and 20 weeks after the treatment and were frozen and examined simultaneously for 1.25 dihydroxy vitamin D, 25 hydroxy vitamin D, calcium, phosphate, parathyroid hormone, and albumin level (for modification of total calcium values). Other standardized laboratory tests including complete blood cell count, serum chemistry; FBS, fasting serum lipids and liver function profile were done before the start of the treatment and one month after and then every two months up to the end of the treatment period.

Metabolites of vitamin D were measured using Competitive ELISA Method with the help of a monoclonal antibody by DRG Kit, Germany. Normal spectra of these metabolites are as follows:

1.25 (OH)2 vit. D: 39-139 pm

25-OH vit. D: 47-144 nm

PTH was measured using Sandwich ELISA with the help of two monoclonal antibodies by DRG Co. USA. Its normal spectrum is as follows:

PTH= 8.8-76.6 pg/ml

Calcium was measured by Chemical Colorimetry and its normal value is as follows:

Ca= 8.6-10.3mg/dl

Phosphate was measured by Chemical Colorimetry and its normal value is as follows:

P= 2.5-5 mg/dl

Albumin was measured by Chemical Colorimetry and its normal value is as follows:

Alb= 3.5-5.2 g/dl.

All patients were prescribed with isotretinoin produced by Roche, Switzerland (Ro-accutan) first at the dose of 1 mg/kg/day and then after two months at the dose of 0.75 mg/kg/day, accumulated dose being 120 mg/kg/day. After twenty weeks, blood samples (10cc peripheral venous blood) were taken from the patients and the above-mentioned indicators were measured using the same method at the same time with the samples collected before treatment.

Radiographic assessment of the axial spines and femoral neck

Before treatment , radiographies of anterior-posterior and lateral axial spine (cervical, thoracic, lumbar)and femoral neck were taken at the first visit as a screen for the development of hyperostosis, ossification of ligaments, osteopenia, periostal thickening, decreased cortical thickness in Shohada Tajrish Hospital (Simens, 50s polydoros) which were then reported by a radiologist .Twenty weeks after the treatment, a second radiography was taken and was compared with the baseline radiography blindly by the same radiologist.

Statistical analysis

Data was analyzed using McNemar's statistical test. P values <0.05 were considered significant.

Results

Values of 1,25 dihydroxy vitamin D, 25 hydroxy vitamin D, calcium, phosphate, and PTH have been provided in table 1, separately before and after the treatment with oral isotretinoin, which indicate that 25 hydroxy vitamin D was lower than normal in 3 patients (10%) before the treatment and in 1 patient (3.3%) twenty weeks after the treatment (p=0.7). 1,25 dihydroxy vitamin D was lower than normal in 1 patient before the treatment (3.3%, P=0.9) and in two patients after the treatment; however, McNemar's test indicated that the changes were not statistically significant. Calcium decreased in 4 patients (13.3%) after treatment (p=0.2). McNemar's test indicated that this difference was not statistically significant, too (p=0.2).

Phosphate levels were normal in all patients before and after the treatment. The status of parathyroid hormone levels were the same. Those serum levels that were lower than normal before the treatment reached basic levels after the treatment.

Radiographic assessment of the axial spines and femoral neck

Post treatment hyperostosis, ossification of ligaments, osteopenia, periostal thickening, and decreased cortical thickness were assessed by comparing the axial spine and femoral neck radiography at the baseline and twenty weeks after the treatment blindly by the same radiologist. Hyperostosis and other sclerotic changes in the axial spines and femoral neck were uniformly absent both at baseline and twenty weeks after the treatment and patients had no radiographic changes before and after the treatment.

Discussion

Our study indicated that short term (twenty weeks) administration of oral isotretinoin did not lead to changes in serum levels of 1.25 dihydroxy vitamin D, 25 hydroxy vitamin D, calcium, phosphate, PTH as well as radiographic findings.

The first study on serum changes following the administration of isotretinoin in human was conducted by Rodland et al. on 11 patients in 1992 in Norway, which led to a decrease in serum levels of 1,25 dihydroxy vitamin D ($p<0.10$) and an increase in molar ratio of 24, 25 dihydrxy vitamin D to 25 hydroxy vitamin D ($p<0.05$)[15]. Results obtained from the studies conducted by Rodland are consistent with the results obtained from animal models[19-20]. Our study indicated that administration of Isotretinoin in patients with nodulocystic acne did not lead to changes in serum levels of 1.25 dihydroxy vitamin D, 25 hydroxy vitamin D, calcium, phosphate, and PTH. Since no changes were observed in calcium, phosphate, 25 hydroxy vitamin D, and PTH, our study was similar to Rodland's study, but decreased levels of 1.25 dihydroxy vitamin D in his study were inconsistent with ours. Rodland's study was a comprehensive study, but his number of patients was less than our study (11 vs. 30) and also in statistical calculations, their values were statistically significant, but they were paraclinically in a normal spectrum.

In one study conducted by Margolis et al., it was found that administration of oral isotretinoin led to no changes in hip density and serum levels of osteocalcin, PTH, calcium, 25-hydroxy vitamin D and also calcium and hydroxy prolin in urine before and after treatment. In Margolis' study, 20 patients were included with an accumulative dose of 122 mg/kg/day of Isotretinoin. His results on serum levels of calcium, PTH, and 25-hydroxy vitamin D before and after treatment were similar to our study[17].

In another study, Kindmark et al. investigated the early effects of oral isotretinoin therapy on bone turnover and calcium homeostasis in nodulocystic acne patients. The effects on bone metabolism were correlated to radiological and bone mineral density measurements following drug therapy for six months. In this study, serum levels of calcium initially had a significant decrease following the administration of isotretinoin ($p<0.05$), reached its minimum on the 5th day, and level of PTH increased

Table 1: *Biochemical markers of bone metabolism before and after 20 weeks of treatment with oral isotretinoin in patients with nodulocystic acne*

	Ca		P		PTH		25 OH Vit D		$1.25(OH)_2$ Vit D	
	Mean Level	Abnormal	Mean Level	Abnormal	Mean Level	Abnormal	Mean Level	Abnormal	Mean Level	Abnormal
Before Treatment	8.94±1.8	---	3.64±0.53	---	15.2±4.9	---	54.6±9.1	3	76.1±26.4	1
After Treatment	8.75±0.48	4	3.82±0.58	---	28.3±12	---	57.7±11.5	1	84.9±25.9	2

severely ($p<0.05$) but reached its basic level within 14 days as treatment continued. This study was conducted on 11 patients and indicated no significant roentgenological changes or effects on bone mineral density. In our study, bone mineral densitometry was not done for patient but their radiographic results are similar to our study. Kindmark suggests that in spite of increased levels of PTH, isotretinoin has inhibitory effects on bone turnover indicating that this medication has a direct effect on bone tissues[18].

Furthermore, Leachman et al. investigated the effect of isotretinoin on bone density and calcium metabolism. They showed decreased bone density without any changes in metabolism of calcium .This study was conducted on 18 patients and 14 controls, in whom serum levels of calcium, PTH, 25 hydroxy vitamin D, and 1.25 dihydroxy vitamin D concentrations did not change over time before and after treatment in either group. These investigators found no significant changes in lumbar spine BMD or femoral neck BMD in either group[16]. In this study, the absence of measurable alterations of calcium metabolism is the same as our study.

In another study, DiGiovanna JJ et al. concluded that a short course of isotretinoin treatment at the recommended dose for severe acne has no clinically significant effects on lumbar spine and total hip BMD and the laboratory parameters in adolescents (12-17 years). However, they reported no radiographic changes in cervical spine for hyperostosis and other sclerotic changes at both baseline and final visit[14]. Their laboratory and radiological results are similar to our study. In researches on animal models, decreased levels of 1,25 dihydroxy vitamin D, 25 hydroxy vitamin D, calcium, phosphate, PTH after administration of Retinoids may be due to the inhibitory effect of retinoid on α hydroxylation of vitamin D in kidneys[21]. Another suggested mechanism is through the direct effect of retinoid on bone matter, leading to increased osteoclastic absorption of bone[22]. Trechsel-Fleisch suggested that retinol directly led to decreased synthesis of vitamin D in rats[23]. Stimulated osteoclastic absorption of bone could be a primary effect and decreased 1,25 dihydroxy vitamin D only a secondary one, so we can expect increased serum levels of calcium and decreased serum levels of PTH. These calcium and phosphate changes have also been reported by Frankel[19].

Our study showed that administration of oral isotretinoin in patients with nodulocystic acne after 20 weeks of treatment did not lead to serum changes in vitamin D metabolites, calcium, phosphate, and PTH as well as axial spine and femoral neck radiographic findings. It is possible that longer exposure or higher doses of isotretinoin be associated with significant measurable alterations of calcium metabolism, hyperostosis and osteoporosis. In addition, some isotretinoin effects such as acne improvement last after the discontinuation of the therapy; therefore, it is possible that these effects continue on bone and calcium metabolism. We conclude that a short-term course of therapy for acne has no significant effects on vitamin D metabolites, calcium, phosphate, and PTH as well as bone changes.

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