Effect of a single course of isotretinoin therapy on bone mineral density in adolescent patients with severe, recalcitrant, nodular acne

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Background: Adverse changes in bone have been reported for patients undergoing high-dose, long-term (several years) isotretinoin therapy for disorders of cornification. The effect of short-term (4-5 months) therapy at the lower dose recommended for acne on bone development in younger, growing adolescent (12-17 years) patients has not been well studied.

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Objective: The purpose of the study was to evaluate the effect of a standard, single course of isotretinoin (Accutane) therapy on bone mineral density (BMD) of the lumbar spine and hip in adolescents ages 12 to 17 years with severe, recalcitrant, nodular acne.

Methods: In this open-label, multicenter study, 217 adolescents (81 girls) with severe, recalcitrant, nodular acne were enrolled and treated with isotretinoin twice daily with food at the recommended total dose of approximately 1 mg/kg for 16 to 20 weeks. BMD in the lumbar spine and hip was measured at baseline and at the end of therapy by dual energy radiograph absorptiometry.

Results: There was no clinically significant mean change in BMD measured at the lumbar spine (+1.4%, range: −4.9% to +12.3%) or total hip (−0.26%, range: −11.3% to +15.0%). Hyperostosis was not observed in any patient. Typical efficacy expected in the treatment of acne was observed.

Conclusions: A 16- to 20-week course of isotretinoin treatment at the recommended dose for severe acne has no clinically significant effect on lumbar spine and total hip BMD in the adolescent (12-17 years) population. (J Am Acad Dermatol 2004;51:709-17.)

For almost 2 decades, isotretinoin (13-*cis*-retinoic acid), has been available as a treatment for patients with severe, nodular acne that is unresponsive to conventional therapy. A single course of therapy has been sufficient for complete and prolonged remission of the disease in the majority of patients.[1-3] Accompanying the efficacy is a pattern of side effects, most of which are predictable from the general similarity of isotretinoin to vitamin A.

A contemporary review has described the clinical and radiographic features of hypervitaminosis A, including its effects on bone.[4] Bone-associated adverse effects may include periosteal thickening, premature closure of the epiphyses, and ossification similar to that seen in diffuse idiopathic skeletal hyperostosis. Reported musculoskeletal symptoms of hypervitaminosis A include backache, arthralgias, and severe bone pain. The clinical significance of the bony radiographic changes is not known because in many cases patients remain asymptomatic and the dose and duration of vitamin A are unknown.

A recent report has summarized the effects of isotretinoin and several synthetic retinoids on bone.[5] Although some bone abnormalities have been observed during long-term, high-dose therapy for disorders of cornification,[6-8] short courses of isotretinoin used in the treatment of acne in young adults have been reported to cause asymptomatic radiographic changes of hyperostosis of the anterior longitudinal and spinal ligaments.[9] Studies looking at changes in bone mineral density (BMD) with isotretinoin therapy have observed either no differences or minor decreases in BMD, the clinical significance of which remains unclear.[10-13] The current work reports the results obtained in a prospective study of the effect of a single course of isotretinoin therapy on BMD and on the incidence of skeletal hyperostosis in adolescents with severe, recalcitrant, nodular acne.

METHODS

This was an open-label, multicenter study without a separate control group. The study design included a screening baseline evaluation. The study protocol was approved by the institutional review boards of either the participating centers or by a central institutional review board (Schulman Associates, Cincinnati, Ohio). Before enrollment, written informed consent was obtained from each patient and his or her parent or guardian.

Study population

A total of 217 patients, recruited from hospital clinics and private practices, were enrolled at 19 centers. Each center enrolled from 2 to 33 patients. In all, 193 patients (88.9%) completed 16 weeks of treatment; 184 (84.8%) continued on to complete 20 weeks of treatment. A total of 36 patients were excluded from the per-protocol analysis because of: (1) protocol violations such as not having both a baseline and a final visit BMD measurement; (2) noncompliance, defined as returning greater than 20% of assigned medication; or (3) completing fewer than 16 weeks of isotretinoin therapy. Thus, the per-protocol analysis was performed on 181 patients. However, 217 patients received at least one dose of study medication and results for BMD data are presented for a subset of the intent-to-treat population who provided baseline and final visit dual energy radiograph absorptiometry (DXA) scans (N = 204 for lumbar spine, N = 201 for total hip). Final visit data contain the sum of the data from patients who had completed either 16 or 20 weeks of treatment.

Patients were treated with isotretinoin twice daily with food for a mean of 133 ± 26 days. Total cumulative dose was 8821 ± 2328 mg, which amounts to a mean daily dose of 66 mg (1 mg/kg/d).

Inclusion criteria

Eligible patients included boys or nonpregnant, nonlactating girls between the ages of 12 and 17 years, who required isotretinoin for the treatment of severe, recalcitrant, nodular acne. Girls of childbearing potential were required to use two separate and effective methods of birth control, unless abstinence was the chosen method, and to have had a negative serum pregnancy test 1 week before the start of isotretinoin therapy, which was begun on the second or third day of the menstrual cycle.

Exclusion criteria

Exclusion criteria included: use of vitamin A supplements in excess of the US recommended daily allowance; sensitivity or allergy to parabens; use of tetracyclines 14 days before, during, or 1 month after drug administration; current use of oral glucocorticoids or receipt of more than 12 cumulative weeks of inhalation glucocorticoid therapy within the previous year; use of thyroid hormone treatment; current use of anticonvulsant medication; recent history of drug or alcohol abuse; recent history of psychiatric disorders, mood or depressive disorders, significant depression, or a history of persistent symptoms of depression; previous therapy with oral retinoids, any metal implants, or bone disease that precluded successful DXA scans; weight less than 30 kg or more than 110 kg; uncontrolled type 1 diabetes mellitus; osteogenesis imperfecta (or other known disorders of collagen); HLA B27-related disease (ie, ankylosing spondylitis); juvenile rheumatoid arthritis; clinical rickets; any degree of vitamin D depletion as evidenced by a serum 25-hydroxyvitamin D level <10 ng/mL or any other type of metabolic bone disease; severe scoliosis (Cobb angle >15 degrees); a history of back operation, or current or history of severe lower back injuries; or presence of cervical hyperostosis at baseline.

Bone density measurements

BMD measurements of the posterior-anterior (PA) lumbar spine (L1-L4) and hip were obtained using DXA instruments (Lunar Corporation, Madison, Wis).

BMD of the lumbar spine (BMD_S) was calculated as follows using bone mineral content (BMC) and surface area (SA):

$$BMD_S = (BMC_{L1} + BMC_{L2} + BMC_{L3} + BMC_{L4})/(SA_{L1} + SA_{L2} + SA_{L3} + SA_{L4})$$

Similarly, the mean of total hip BMD (BMD_H) was calculated as follows:

$$BMD_H = (BMC_{shaft} + BMC_{neck} + BMC_{trochanter})/(SA_{shaft} + SA_{neck} + SA_{trochanter})$$

All DXA instruments (ie, each site) were cross-calibrated (Bio-imaging Technologies Inc, Newtown, Pa) using an appropriate calcium hydroxyapatite-based calibration phantom. All DXA scans were sent for analysis (Bio-imaging Technologies Inc). Triplicate DXA measurements of the PA lumbar spine and hip were taken at both baseline and final visit for each study participant. All BMD data are expressed in g/cm^2.

Lumbar *z* score

The BMD_S z score is the measurement of BMD_S relative to a normal, healthy, age-matched, sex-specific population. Explicitly, the difference is expressed as the number of SDs from the population normal, ie:

$$z\ \text{score} = (BMD - BMD_{normal})/SD_{normal}$$

Data for calculation of BMD_S z score were provided by the manufacturer of the DXA instrument (GE-Lunar, Madison, Wis). The z score for BMD_H was not calculated because a pediatric reference database was not available.

Radiographic assessment of the cervical spine

A single lateral radiograph of the cervical spine was also taken at these visits as a screen for the development of hyperostoses. Although it is not known which body location is the first to develop hyperostosis, the cervical spine may show some of the most clinically important hyperostosis. The radiograph taken at a patient's final visit was compared with that obtained at the baseline visit during centralized, blinded, independent assessments of films by the same pediatric bone radiologist. Reading of the radiographs was controlled as follows. The session consisted of the randomized display of the baseline and final visit images for each individual patient. The order in which patient images were displayed was determined by the sequential ordering of the randomization numbers. The reader was blinded to the time point of each radiograph represented.

Other study assessments

Acne severity was assessed according to the grading scale of Allen and Smith.[14] A complete safety profile was recorded which consisted of adverse events (AEs) and standardized laboratory tests including: complete blood cell count; serum chemistry; total calcium and phosphate; 25-hydroxyvitamin D; fasting serum lipids and liver function profile; creatine kinase; and urinalysis. At each visit patients completed a musculoskeletal events questionnaire that collected information on prior and current

Table I. Baseline demographic characteristics

Sex	
Male, N (%)	136 (63)
Female, N (%)	81 (37)
N	217
Race	
White, N (%)	173 (80)
Black, N (%)	6 (3)
Asian, N (%)	5 (2)
Other, N (%)	33 (15)
N	217
Age, y	
Mean ± SD	15.1 ± 1.47
Median	15.0
Range	12-17
N	217
Weight, kg	
Mean ± SD	65.8 ± 12.5
Median	64.0
Range	40.0-114.0
N	217
Height, cm	
Mean ± SD	169.8 ± 8.8
Median	170.0
Range	144.0-192.5
N	216

injuries and musculoskeletal pain events. AEs were defined as any adverse change from the patient's baseline condition, including intercurrent illness, that occurred during the course of the study after treatment was started, whether considered related to treatment or not. All adverse event terminologies were classified according to MedDRA (Medical Dictionary for Regulatory Activities) version 1.5. The investigator evaluated the intensity of each adverse event on a 3-point scale (mild, moderate, and severe). The number and percentage of patients reporting AEs was summarized by body system, intensity, and relationship to the study drug.

Statistical analysis

The differences between baseline and end of treatment were tested for significance by a paired *t* test. A 1-sample *t* test was used to test for significant differences from zero in the percent change from baseline in BMD_S and BMD_H.

RESULTS

A total of 217 patients were enrolled at 19 centers. Results for BMD data are presented for the intent-to-treat population. A total of 204 patients provided baseline and final visit DXA scans for lumbar spine, and 201 patients for total hip.

Table I summarizes the demographic characteristics of the study population. Approximately 80% of patients were Caucasian with the remainder distributed among black (3%), Asian (2%), and other (15%) ethnic groups. The distribution of patients according to age and sex in the total population (N = 217) was similar to that in the intent-to-treat population.

The clinical efficacy observed as resolution of acne was consistent with the excellent response typical of isotretinoin (unpublished data, available from Roche).

Changes in BMD from baseline to final visit

Values of BMD_S and BMD_H (the combined average of femoral neck, femoral shaft, and greater trochanter) at baseline and end of treatment are presented in Fig 1.

BMD_S increased from a baseline value of 1.108 ± 0.132 (range: 0.803-1.502) to 1.125 ± 0.127 (range: 0.843-1.502) at the end of treatment (Fig 1, *A*) ($P < .00001$). For BMD_H measurements, there was a slight decrease from baseline value of 1.088 ± 0.136 (range: 0.711-1.473) compared with end of treatment value of 1.086 ± 0.136 (range: 0.685-1.522) (Fig 1, *B*) that was not statistically significant ($P = .19$). Statistical analyses of data from all individual sites are shown in Table II.

Fig 2 depicts the data as percent change from baseline to end of treatment. Changes from baseline to end of treatment were statistically significantly different from zero for BMD_S (1.403 ± 2.5% [range: −4.9% to +12.3%], $P < .00001$), but not for BMD_H (−0.258 ± 3.0% [range: −11.3% to +15.0%], $P = .226$).

Change in *z* score

In the lumbar spine, the change from baseline at the final visit in *z* score was 0.090 ± 0.192 (range: −0.539 to 0.707) with a confidence interval of 0.064 to 0.117. The changes from baseline in *z* score parallel those percent change values for BMD_S previously discussed and presented in Fig 2.

Individual patient changes in BMD

There was considerable variation in BMD values at both baseline and the end of treatment, as would be expected in growing children of diverse ethnicity and size. More boys and girls gained than lost BMD_S; approximately equal numbers of both sexes gained or lost BMD_H.

Radiograph assessment of the cervical spine

Posttreatment hyperostosis was assessed by comparing the cervical spine radiograph at the baseline and final visit viewed in a randomized sequence, and blinded for time taken. At baseline, 216 patients provided images that were technically adequate; at the final visit, 203 images were of sufficient quality for an assessment to be made.

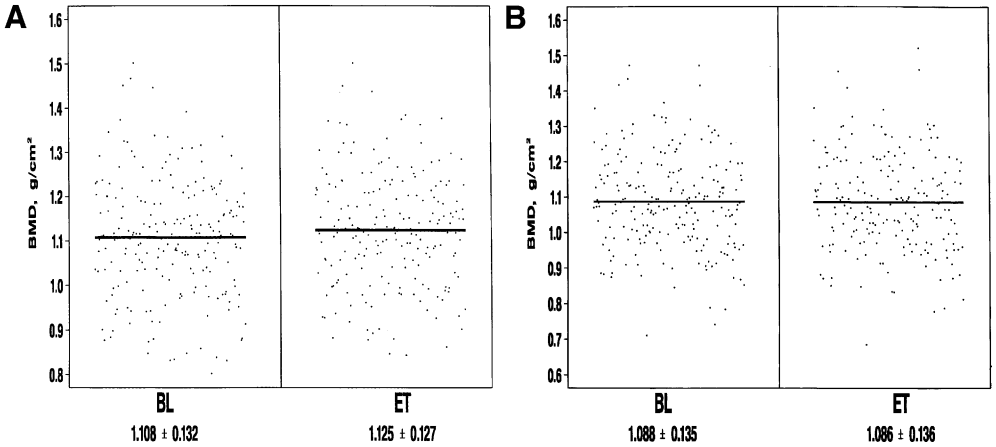

Fig 1. Scatterplot of lumbar spine (**A**) and total hip (**B**) bone mineral density (BMD) values, in g/cm^2, at baseline (BL) and end of treatment (ET). *Horizontal bars*, Mean values.

Table II. Bone mineral density changes in lumbar spine and hip

	BMD (g/cm^2)				
Anatomic site	**Baseline**	**End of treatment**	***P* value**	**Percent change**	***P* value**
Lumbar spine	1.108 ± 0.132	1.125 ± 0.127	<.00001	1.403 ± 2.479	<.00001
Total hip	1.088 ± 0.135	1.086 ± 0.136	.1913	−0.258 ± 3.009	.2262
Femoral neck	1.090 ± 0.135	1.084 ± 0.137	.0316	−0.521 ± 3.396	.0309
Greater trochanter	0.910 ± 0.137	0.910 ± 0.138	.7429	−0.049 ± 4.303	.8711
Ward's triangle	1.050 ± 0.165	1.034 ± 0.162	<.00001	−1.423 ± 4.212	<.00001

BMD, Bone mineral density.

Hyperostosis and other sclerotic change in the cervical spine were uniformly absent at both baseline and at the final visit. However, other pathologic changes were observed in 8 of 216 patients (3.7%) at baseline and in 9 of 203 patients (4.4%) at the final visit. In 7 patients the condition was present at both baseline and at final visit and, therefore, unrelated to the study. In one patient the condition observed at baseline was not observed at the final visit; and in two patients the condition was observed at the final visit but was not present at baseline. In the latter two patients changes observed were straightening or reversal of the cervical lordotic curve. One patient showed a decrease in disk height between C6 and C7 at both baseline and final visit, which was presumed to be a congenital defect. Other abnormalities were found in 19 patients both at baseline and at the final visit. These mainly took the form of minor anomalies in the spinous process of C2, or the presence of large adenoids.

Other study assessments

Mucocutaneous side effects were the most common AEs with 48% of patients reporting cheilitis. Next most common were back pain (41%), dry skin (32%), and arthralgia (31%). Laboratory test results were typical of other patients receiving isotretinoin for the treatment of severe, recalcitrant, nodular acne, including elevations over baseline in triglycerides (66.7%) and cholesterol (10.2%). No single value for cholesterol exceeded the reference range for abnormal whereas 25% of patients had transient elevations in triglycerides that reached 100% increase over baseline. Six patients had elevated serum phosphate (mean value: 1.74 mmol/L or >20% of upper limit of the normal range), but all had normal alkaline phosphatase.

Elevations in creatine kinase were observed, sometimes in association with reported musculoskeletal AEs, such as back pain, arthralgia, limb injury, and muscle sprain. In these patients, elevations quickly returned to normal. Two patients of 217 (0.92%) had creatine kinase levels of more than 10,000 U/L. In one case the value of 16,040 U/L decreased to 111 U/L 13 days after drug was discontinued; in the other case the value decreased from 12,630 U/L to 239 U/L after 9 days. No cases of rhabdomyolysis were reported.

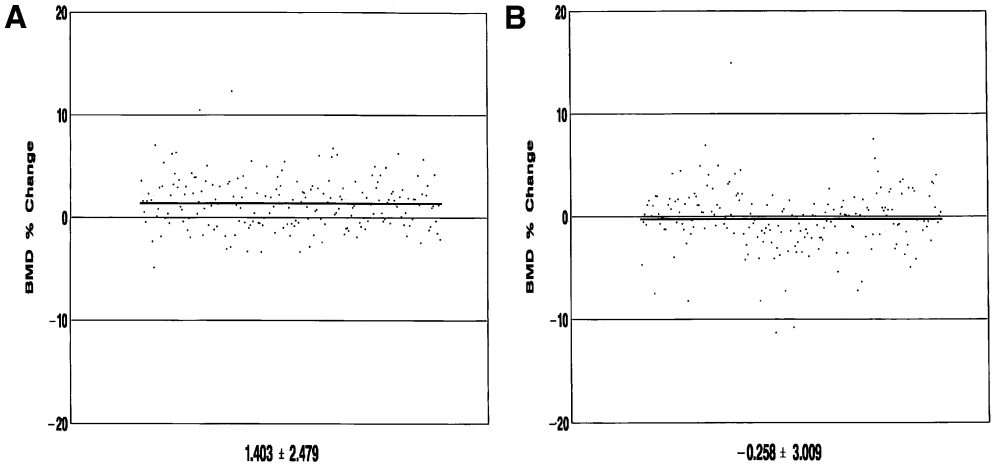

Fig 2. Scatterplot of percent change from baseline to end of treatment in lumbar spine (**A**) and total hip (**B**) bone mineral density (BMD). Horizontal bar shows mean value of individual percent changes.

DISCUSSION

One of the most important determinants of the bone mass lifeline is the magnitude of the gain in bone mass achieved during late adolescence. Accrual of bone mass throughout growth (birth through 18-20 years) determines a plateau from which a decline may start around the time of the menopause, or in older age.[15] It is believed that the higher the plateau achieved (peak bone mass), the longer the skeleton can delay potential decline to a fracture-susceptible level. Although genetic factors account for 30% to 70% of peak bone mass, environmental factors such as the use of nutrients required for bone building are also important. Environmental factors are potent during periods of active growth, and include general nutrition, threshold effects of mineral and vitamin D intakes, the positive effects of weight-bearing exercise, and the effects of chronic severe diseases and certain medications. However, standardized instruments to quantitate diet and exercise effects on bone mass are lacking, and there is disagreement on the optimal technique to measure bone mass in growing children. Thus, the exact timing of peak bone mass, and relationships between genetic influences and environmental factors, remain to be finalized.[16]

Although adolescence is the opportunity for accumulation of peak bone mass, it is also a time of vulnerability, because interruption of these normal processes can result in suboptimal peak bone mass, which may have subsequent lifelong effects by lowering the plateau. Examples of interruptions include periods of extended bed rest, inadequate dietary intake of mineral, or therapy with a drug that may affect bone modeling or remodeling.

Our study found no clinically significant effects on BMD levels in adolescents treated with isotretinoin for severe, recalcitrant, nodular acne. The data included a small difference observed at Ward's triangle, a problematic area of measurement that is considered to be unreliable for evaluation of BMD. The International Society for Clinical Densitometry is a nonprofit multidisciplinary society for which the mission is to promote quality in the performance and interpretation of bone density examination. They conducted a position development conference (July 20-21, 2001) addressing controversies that included: (1) which skeletal sites and regions of interest should be used for the diagnosis of osteoporosis; and (2) the role of serial BMD measurements.[17] The position statement recommends that the PA spine (first 4 lumbar vertebrae) should be measured as the preferred site, with the total hip used when the PA spine is technically invalid; furthermore, "Ward's region and lateral spine should not be used."[17] Measurement at Ward's area is imprecise and "would result in overdiagnosis of osteoporosis."[18] In addition, "the panel suggested that the manufacturers remove Ward's area from the default settings of their printouts."[18]

In addition to diagnosing osteoporosis, the panel addressed the capability of BMD to measure change over time (monitoring). Once again, they concluded that the PA spine is the preferred site for monitoring patients using DXA because it has the best precision. When PA spine is not measurable, the total hip region should be used for monitoring. "Ward's area should not be used for monitoring because of poorer precision."[19]

The effects on skeletal integrity of long-term, high-dose therapy with isotretinoin for diseases other than acne have been described. Radiographic hyperostosis is the most common observation in children treated for disorders of cornification.[5-7,20] Another study in patients undergoing long-term therapy for various dermatoses identified osteoporosis in patients treated with etretinate but not with isotretinoin.[13] Less clear are the effects on bone when the standard doses of isotretinoin are used in acne therapy. The limited data available demonstrate that minor changes in bone structure have been observed, but that they lacked clinical significance.[9,21,22] Taken together, the reports suggest that, for some skeletal toxicities, there may be a threshold exposure to isotretinoin required to produce a clinically significant effect on bone.

Three recent studies have focused on possible bone effects during an acne therapy regimen. Kocijancic[10] examined the effect of short-term isotretinoin on lumbar spine bone density in 15 patients undergoing a 6-month course (mean isotretinoin dose 0.4 mg/kg, range: 0.29-0.5 mg/kg). The mean increase in bone density observed was 3.0% in the adolescents and adults (mean age 19.8 years, range 13.7-30.1 years), comparable with normal bone gain. This study concluded that isotretinoin had no clinically important influence on lumbar bone density in boys with severe acne.

Margolis et al[11] studied 20 adult patients undergoing treatment for severe acne vulgaris. Patients, age 19 to 35 years, were treated for 20 weeks with a total dose of 122 mg/kg of isotretinoin (range: 108-137 mg/kg; mean daily dose 0.89 mg/kg). These patients had stopped growing an average of 10 years before the beginning of the study. DXA measurements of the lumbar spine and hip were used to assess bone mineralization before and after treatment. No significant changes in mineral density were noted in lumbar spine BMD or at the femoral neck, Ward's triangle, or the proximal femur.

Leachman et al[12] studied the effect of a 6-month course of isotretinoin (1 mg/kg) in 18 patients with cystic acne (range: 17-25 years) compared with healthy, age-matched untreated control subjects (N = 14, 19-26 years). These investigators found no significant change in lumbar spine BMD (+1.2%) or femoral neck BMD (+0.2%) when patients exposed to isotretinoin were compared with the control subjects. However, at Ward's triangle, in the isotretinoin group a 4.42% decrease was found (P = .04). In that study, no other concomitant changes occurred in biochemical markers of bone homeostasis. A subsequent letter reporting only results at Ward's triangle taken 5 to 9 years later showed a return to baseline in 3 of the 4 men who previously had the greatest percentage loss of density at that area.[23] Measurements of bone density at Ward's triangle, an area of trabecular bone with high turnover, are subject to great variability related to differences in positioning, and which are instrument-specific. Precision at this site is decreased because the standard error of measurement is around 2.5%.[24] Because of the unreliability of measurements at Ward's area, we would interpret the lack of change in the lumbar spine and femoral neck to indicate that isotretinoin had no effect on BMD.

A total of 1 SD is usually reserved for the minimum change in an age- and sex-matched normative population to denote adverse change (the World Health Organization definition of osteopenia is a T-score of greater than −1). The data in Fig 1 demonstrate that for both lumbar spine and total hip, the SD at both baseline and end of treatment is of the order of 12% of the mean value. This is similar to the normative data of the SDs supplied by the manufacturer of the DXA instrument (GE-Lunar, Madison, Wis) (lumbar spine values of approximately 13% and 16% for girls and boys, respectively, aged 13-17 years) and other published values (approximately 12%-14% for girls and 16% for boys age 13-17 years[16]). In the current study, the first powered to examine the effects of isotretinoin on bone in adolescents treated for acne, approximately half of the patients of both sexes gained bone mass. Of those who lost, no patient manifested a loss in BMD_S or BMD_H of even 1 SD and the vast majority of patients (>95%) had decreases of less than 30% to 40% of 1 SD. There is a well-known temporal delay between height acquisition and bone mineral accretion in rapidly growing children that leads, in some cases, to a transient state of lower bone mass.[15,25] This most likely explains the occurrence in two patients of decreases in BMD_H that exceeded 10% (Fig 2, *B*).

The wide range in BMD_H values in the study population as a whole is, at least in part, the result of an areal, as opposed to a volumetric, measurement being performed at an anatomic site where the geometry is changing during the course of the treatment because of normal growth of the study patients,[26] particularly at Ward's triangle.[24] Our observed values for BMD_H change are within the ranges observed for a population of growing, healthy adolescents.[27,28]

Our study showed that no hyperostosis occurred after 16 to 20 weeks of isotretinoin treatment, and only two adolescents had any pathologic changes noted at baseline and the end of the study, limited to straightening or reversal of the cervical lordotic curve. Such radiographic features are not clinically

significant, and the incidence reported here is not unusual in a population of growing adolescents. Effects on laboratory parameters in the adolescent population were minimal and as expected from the known effects of isotretinoin.[29-31] In this study, patients reported a high frequency of back pain (41%), which we attribute to a data collection phenomenon. At each visit patients completed a musculoskeletal events questionnaire and patients in this study were more likely to report AEs of a musculoskeletal nature. In this athletically active pediatric population, the self-reports were consistent with activity levels or injury reports. Back pain was usually mild or moderate and returned to baseline incidence by week 8.

Could this study have missed an isotretinoin-associated decrease in BMD? It is possible that longer exposures or higher doses might be associated with decreased BMD. One might speculate as to whether the development of calcification in ligaments around measurement areas could confound bone density measurements, and mask the measurement of early osteopenia. However, we did not observe hyperostosis in this study. In addition, some effects of isotretinoin persist after discontinuation of the drug, for example, acne continues to improve after therapy is discontinued; it is possible that effects on bone could continue as well.

The current report demonstrates that BMD_S and BMD_H accrual in a large, adolescent-age population was unaffected by a 16- to 20-week course of isotretinoin. We conclude that a short-term course of therapy for acne has no detrimental effects on adolescent bone mass. Perhaps longer-term therapy and lifelong dietary exposure to vitamin A[32] may influence bone mass in other ways.

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REFERENCES

1. Farrell LN, Strauss JS, Stranieri AM. The treatment of severe cystic acne with 13-*cis*-retinoic acid: evaluation of sebum production and the clinical response in a multiple-dose trial. J Am Acad Dermatol 1980;3:602-11.
2. Peck GL, Olsen TG, Yoder FW, Strauss JS, Downing DT, Pandya M, et al. Prolonged remissions of cystic and conglobate acne with 13-*cis*-retinoic acid. N Engl J Med 1979;300:329-33.
3. Jones H, Blanc D, Cunliffe WJ. 13-*cis*-retinoic acid and acne. Lancet 1980;2:1048-9.
4. Silverman AK, Ellis CN, Voorhees JJ. Hypervitaminosis A syndrome: a paradigm of retinoid side effects. J Am Acad Dermatol 1987;16:1027-39.
5. DiGiovanna JJ. Isotretinoin effects on bone. J Am Acad Dermatol 2001;45(Suppl):S176-82.
6. Pittsley RA, Yoder FW. Skeletal toxicity associated with long-term administration of 13-*cis*-retinoic acid for refractory ichthyosis. N Engl J Med 1983;308:1012-4.
7. Ellis CN, Madison KC, Pennes DR, Martel W, Voorhees JJ. Isotretinoin therapy is associated with early skeletal radiographic changes. J Am Acad Dermatol 1984;10:1024-9.
8. Pennes DR, Ellis CN, Madison KC, Voorhees JJ, Martel W. Early skeletal hyperostoses secondary to 13-*cis*-retinoic acid. Am J Radiol 1984;142:979-83.
9. Kilcoyne RF, Cope R, Cunningham W, Nardella FA, Denman D, Franz TJ, et al. Minimal spinal hyperostosis with low-dose isotretinoin therapy. Invest Radiol 1986;21:41-4.
10. Kocijancic M. 13-*cis*-Retinoic acid and bone density. Int J Dermatol 1995;34:733-4.
11. Margolis DJ, Attie M, Leyden JJ. Effects of isotretinoin on bone mineralization during routine therapy with isotretinoin for acne vulgaris. Arch Dermatol 1996;132:769-74.
12. Leachman SA, Insogna KL, Katz L, Ellison A, Milstone LM. Bone densities in patients receiving isotretinoin for cystic acne. Arch Dermatol 1999;135:961-5.
13. DiGiovanna JJ, Sollitto RB, Abangan DL, Steinberg SM, Reynolds JC. Osteoporosis is a toxic effect of long-tern etretinate therapy. Arch Dermatol 1995;131:1263-7.
14. Allen BS, Smith G. Various parameters for grading acne vulgaris. Arch Dermatol 1982;118:23-5.
15. Heaney RP, Abrams S, Dawson-Hughes B, Looker A, Marcus R, Matkovic V, et al. Peak bone mass. Osteoporos Int 2000;11: 985-1009.
16. Bachrach LK, Hastie T, Wang M-C, Narasimhan B, Marcus R. Bone mineral acquisition in healthy Asian, Hispanic, black, and Caucasian youth: a longitudinal study. J Clin Endocrinol Metab 1999;84:4702-12.
17. Lenchik L, Leib ES, Hamdy RC, Binkley NC, Miller PD, Watts NB. Executive summary, International Society for Clinical Densitometry position development conference, Denver, Colorado, July 20-22, 2001. J Clin Densitom 2002;5(Suppl):S1-3.
18. Hamdy RC, Petak SM, Lenchik L. Which central dual x-ray absorptiometry skeletal sites and regions of interest should be used to determine the diagnosis of osteoporosis? J Clin Densitom 2002;5(Suppl):S11-8.
19. Lenchik L, Kiebzak GM, Blunt BA. What is the role of serial bone mineral density measurements in patient management? J Clin Densitom 2002;5(Suppl):S29-38.
20. Pennes DR, Martel W, Ellis CN, Voorhees JJ. Evolution of skeletal hyperostoses caused by 13-*cis*-retinoic acid therapy. Am J Radiol 1988;151:967-73.
21. Carey BM, Parkin GJS, Cunliffe WJ, Pritlove J. Skeletal toxicity with isotretinoin therapy: a clinico-radiological evaluation. Br J Dermatol 1988;119:609-14.
22. Török L, Budai S, Kása M, Kádár L. Bone x-ray examinations in patients treated with isotretinoin: a prospective study. Br J Dermatol 1988;118:134-5.
23. Milstone AM, Milstone LM. Is retinoid induced osteopenia reversible? Arch Dermatol 2002;138:1516-7.
24. Takada M, Grampp S, Ouyang X, Engelke K, Genant HK. A new trabecular region of interest for femoral dual x-ray absorptiometry: short-term precision, age-related bone loss, and fracture discrimination compared with current femoral regions of interest. J Bone Miner Res 1997;12:832-8.
25. Fournier PE, Rizzoli R, Slosman DO, Theintz G, Bonjour JP. Asynchrony between the rates of standing height gain and bone mass accumulation during puberty. Osteoporos Int 1997;7:525-32.
26. Katzman DK, Bachrach LK, Carter DR, Marcus R. Clinical and anthropometric correlates of bone mineral acquisition in healthy adolescent girls. J Clin Endocrinol Metab 1991;73:1332-9.
27. Bachrach LK. Acquisition of optimal bone mass in childhood and adolescence. Trends Endocrinol Metab 2001;12:22-8.

28. Matkovic V, Jelic T, Wardlaw GM, Ilich JZ, Goel PK, Wright JK, et al. Timing of peak bone mass in Caucasian females and its implication for the prevention of osteoporosis. J Clin Invest 1994;93:799-808.
29. Strauss JS, Leyden JJ, Lucky AW, Lookingbill DP, Drake LA, Hanifin JM, et al. A randomized trial of the efficacy of a new micronized formulation versus a standard formulation of isotretinoin in patients with severe recalcitrant nodular acne. J Am Acad Dermatol 2001;45:187-95.
30. Strauss JS, Leyden JJ, Lucky AW, Lookingbill DP, Drake LA, Hanifin JM, et al. Safety of a new micronized formulation of isotretinoin in patients with severe recalcitrant nodular acne: a randomized trial comparing micronized isotretinoin with standard isotretinoin. J Am Acad Dermatol 2001;45: 196-207.
31. Strauss JS, Rapini RP, Shalita AR, Konecky E, Pochi PE, Comite H, et al. Isotretinoin therapy for acne: results of a multicenter dose-response study. J Am Acad Dermatol 1984;10:490-6.
32. Michaëlsson K, Lithell H, Vessby B, Melhus H. Serum retinol levels and the risk of fracture. N Engl J Med 2003;348: 287-94.

CORRECTIONS

Burgdorf WHC, Scholz A. Helen Ollendorf Curth and William Curth: From Breslau and Berlin to Bar Harbor. J Am Acad Dermatol 2004;51:84-9 (July).

Two factual errors in this article were recently brought to our attention. On page 87, A. Benson Cannon's tenure as Chairman of Dermatology at Columbia University (1947-1950) was not mentioned. He held the position after J. Gardner Hopkins and before Carl Truman Nelson.

On page 88, Urs W. Schnyder is identified as a trainee of Heinrich A. Gottron. Schnyder trained with Guido Miescher and Hans Storck in Zürich and was a colleague of Gottron's when they invited Helen Ollendorff Curth to write a chapter for the supplementary volumes to Jadassohn's Handbuch. We apologize to Professor Schnyder for the error.

Johr R, Braun R. Dermoscopy challenges (Self-Assessment examination of the American Academy of Dermatology). J Am Acad Dermatol 2004;51:156-64 (July).

In the section of the Self-Assessment examination titled Dermoscopy challenges, which begins on page 162, the answer to question 42 was given as "a. True." The answer should be "b. False."

Weary PE. Reply (to Look out, dermatology: Here comes Wal-Mart). J Am Acad Dermatol 2004;51:e2 (July; online only).

Several typographical errors appeared in Dr Weary's reply to the comments of Dr Robert A. Swerlick. In the first paragraph, second sentence, Dr Swerlick's name is misspelled. In the final paragraph, the sentence beginning "And finally. . ." should read as follows: "And finally, by clean I urge them [dermatologists] to remain professional and ethical and put the interests of their patients, both fiduciary and medical, above their own self interests as befit the role of the compassionate physician."