Deficiency from The Lawson Wilkins Pediatric Endocrine Society and The European Society for Pediatric Endocrinology. J Clin Endocrinol Metab 2002; 87: 4048-4053 .

7. Speiser PW, White PC. Medical Progress-Congenital adrenal hyperplasia. N Engl J Med 2003; 349: 776-788.

8. Greulich WW, Pyle SI. Radiographic atlas of skeletal development of the hand and wrist. Stanford: Stanford University Press; 1996.

9. Kovacs.J, Votava F, Heize G, Solyom J, Lebl J, Pribilincova Z, *et al*. Lessons from 30 years of clinical diagnosis and treatment of congenital adrenal hyperplasia in five niddle european countries. J Clin Endocrinol Metab 2001; 86: 2958-2964.

10. Silva IN, Kater CE, Cunha CF, Viana MB. Randomised controlled trial of growth effect of hydrocortisone in congenital adrenal hyperplasia. Arch Dis Child 1997; 77: 214 - 218.

11. David M, Sempe M, Blanc MI. Final height in 69 patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Arch Pediatr 1994; 1: 363-367.

Bone Mineral Density in Response to Two Different Regimes in Rickets

Mustafa Akcam, Mustafa Yildiz*, Aygen Yilmaz and Reha Artan*****

*From the Department of Pediatrics and *Department of Nuclear Medicine, **Division of Pediatric Gastroenterology, Hepatology and Nutrition,***Faculty of Medicine, Süleyman Demirel University, Isparta, Turkey; and Hepatology and Nutrition. Faculty of Medicine, Akdeniz University, Antalya, Turkey.*

Correspondence to: Mustafa Akçam, Çelebiler Mh. 137. Cad. Hubanlar Apt. No. 10, Isparta, Turkey.
E-mail: makcam@sdu.edu.tr

Manuscript received: September 13, 2005, Initial review completed: December 12, 2005; Revision accepted: February 6, 2006.

The aim of this study was to compare the bone mineral density (BMD) of two different treatment regimens in infants with nutritional vitamin D deficient rickets (VDR). Ten patients (Group 1) were treated with a single dose of 600,000 IU of oral vitamin D_3 and another ten patients (Group 2) were treated with 20,000 IU/day of oral vitamin D_3 for 30 days. BMD was measured in the lumbar spine twice in all infants before the treatment and on the 31st day after initiating the treatment. The increases of BMD after treatment compared to pretreatment levels were statistically significant in both groups (P=0.005 in Group 1 and P=0.047 in Group 2). The increments of BMD were statistically similar between Group 1 and 2 (P=0.096). The present study suggests that these two different treatment regimens bring about similar healing in BMD.

Key words: *Bone mineral density, Nutritional rickets, Vitamin D.*

RICKETS signifies a failure in mineralization of growing bone or osteoid tissue. The predominant cause is nutritional vitamin D deficiency rickets (VDR) due either to inadequate direct exposure to ultraviolet rays in sunlight or inadequate intake of vitamin D, or both(1,2). There are various regimens of vitamin D replacement treatment(1-6). Two preferable regimens are daily administration of 20,000 IU/day of vitamin D for 2-4 wk or

administration of 600,000 IU of vitamin D in a single dose orally(1). High-single dose regimen may be advantageous because of rapid healing, possibly with earlier differential diagnosis from genetic vitamin D-resistant rickets and less dependence on parents for administration of vitamin D. However, this regimen has a disadvantage of the risk of hypercalcemia(1,2,4,5,7). These two regimes were compared with respect to clinical, biochemical and radiological findings in many reports(3-7). However, the literature regarding the increments of bone mineral density (BMD) with different therapy modalities is lacking. Although measurement of BMD is not necessary to diagnose VDR, it is useful to compare the responses to different therapy options. Dual Energy *X*-ray Absorptiometry (DEXA) scanner is the most widely used device to measure BMD values since it has high resolution and low radiation exposure(8,9).

The purpose of this study is to compare the increases of BMDs in two different therapy regimens of vitamin D (single dose of 600,000 IU, and 20,000 IU/day orally for 30 days) in infants with nutritional VDR.

Subjects and Methods

This study was conducted in Isparta Children's Hospital on 20 otherwise healthy infants, aged 5-13 months, who were diagnosed as nutritional rickets based on clinical, biochemical and radiological data. Age, body weight and height were recorded, and blood samples were obtained to determine serum calcium (Ca), phosphate (P), alkaline phosphatase (ALP), 25-hydroxycholecalciferol (25-HC) and blood count. The diagnosis of VDR was based on physical examination (Harrison's groove, enlargement of anterior fontanel, wrist flare, frontal bossing, and leg bowing in children who started walking), nutritional history, poor sunshine exposure, biochemical parameters of rickets (reduced Ca, P, 25-HC, and increased ALP) and radio-logic evidence of rickets (splaying and fraying at the distal metaphysis of radius and ulna or femur and at the proximal metaphysis of tibia, and increased zone of undermineralized osteoid). Diagnostic criteria were presence of all of positive findings of physical examination, radiology and biochemistry. All infants were born after full-term gestations and were breastfed; none had received any vitamin D supplementation. There was no history of vitamin D or calcium supplementation to mothers during pregnancy and lactation. None of the infants received anticonvulsant or corticosteroids or other drugs known to alter vitamin D or bone metabolism. All had normal renal, liver, and intestinal function. Infants were visited, and the values of Ca, P and ALP were tested once a week. The healing para-meters are described with Ca, P, and ALP levels, besides the clinical improvement.

The study population was divided into two groups. The alternative regimes were given to alternate patients. *Group 1* (six boys and four girls) received a high single dose of vitamin D (600,000 IU) per orally. *Group 2* (five boys and five girls) was administered 20,000 IU vitamin D per orally daily for 30 days. Patients in *Group 1*, received two vitamin D vials, each containing 300,000 IU vitamin D_3 (Devit-3 vial, Deva, Turkey) in a single dose, while patients of *Group 2* received daily 20.000 IU vitamin D_3 solution (50,000 IU/15 mL, Devit-3 oral solution, Deva, Turkey). No patient received calcium supplementation. In both groups lumbar BMDs were obtained before and one month after vitamin D therapy.

BMD (in grams per square centimeter) was measured in the lumbar spine from L2-L4, by dual-energy *X*-ray absorptiometry (Norland XR-46 bone densitometer, with dynamic filtration; Norland Corp, Fort Atkinson, WI).

The Norland XR-46 was calibrated daily; using a calibration standard and quality control phantom, 30 minutes after the apparatus was turned on.

Statistical analysis was conducted using the statistical software SPSS 11.00 (SPSS Inc, Chicago, IL). Results are given as the mean ± SD. Statistical significance was set at the 0.05 level. The groups were compared by Mann-Whitney U test. Differences within the same group were tested by Wilcoxon signed ranks test. The hospital ethics committee approved the study, and informed parental consent was obtained.

Results

The groups did not differ statistically in age, sex, weight, length, and pretreatment serum Ca, P, ALP, 25-HC and lumbar BMDs (*Table I*). The repeated levels of Ca, P, and ALP during the two treatments were not statistically different. Hypercalcemia did not develop in any infant. All patients showed healing of rickets following both treatments. Post treatment BMDs were 0.2776 ± 0.0384 and 0.2851 ± 0.0595 g/cm^2 in *Group* 1 and *2*, respectively. The increases in BMD from the pretreatment levels were statistically significant in both groups ($P = 0.005$ in *Group* 1 and $P = 0.047$ in *Group* 2). Although increments in BMDs were comparable between two groups, the increments of BMD were statistically indifferent between *Group 1* and *2* (P=0.096, power of the study = 0.70). Pre- and post-treatment BMDs, and biochemical values were given in *Table II*.

Discussion

This study suggests that BMD values increase significantly within one month by both treatment method. Although our sample size is small, comparison of daily dose of a 20,000 IU

TABLE I– *Characteristics of Patients before Treatment*

	Group 1 (600,000 IU single dose)	Group 2 20,000 IU/day (for 30 days)	p value
Age (mo)	7.6 ± 2.31	7.9 ± 1.96	0.616
Weight at exam (g)	7250 ± 2294	6740 ± 1161	0.970
Height at exam (cm)	64 ± 3	66 ± 3	0.286
Boys/girls	6/4	5/5	0.594
Gestation (wk)	39.5 ± 1.2	39.2 ± 1.0	0.666
Birth height (cm)	49.8 ± 1.5	50 ± 1.8	0.788
Birth weight (g)	3135 ± 409	3130 ± 391	0.879
Ca (N=2.2-2.70 mmol/L)	2.12 ± 0.15	2.08 ± 0.10	0.648
P (N=1.25-2.10 mmol/L)	0.92 ± 0.20	0.90 ± 0.12	0.939
ALP (N=145-420 U/L)	664 ± 81	669 ± 83	0.705
25-HC (N=14-42 ng/ml)	6.0 ± 2.4	5.7 ± 1.8	0.878
BMD (g/cm2)	0.2506 ± 0.0480	0.2731 ± 0.0662	0.597

Values are expressed as mean ± SD; Ca: Calcium, P: Phosphate, ALP: Alkaline phosphatase, 25-HC: 25-hydroxycholecalciferol, BMD: Bone mineral density.

Key Messages

- There is a significant increase in BMD of VDR patients within one month after oral vitamin D treatment.
- Increments of BMD values after a single high-dose (600,000 IU) and daily dose of 20,000 IU vitamin D (for 30 days) treatments were similar and not superior to each other.

TABLE II–*Comparison of Post-treatment BMD and Biochemical Values*

	Group 1 (high dose, n=10)	Group 2 (low-daily dose, n=10)	P value
BMD (g/cm^2)	0.2776 ± 0.0384	0.2851± 0.0595	0.940
Ca (N = 2.2-2.70 mmol/L)	2.4 ± 0.1	2.3 ± 0.1	0.445
P (N = 1.25-2.10 mmol/L)	1.33 ± 0.2	1.4 ± 0.2	0.595
ALP (N =145-420 U/L)	343 ± 43	350 ± 52	0.570

Values are expressed as mean±SD; Ca: Calcium, P: Phosphate, ALP: Alkaline phosphatase, BMD: Bone mineral density.

vitamin D for 30 days and a single high-dose (600,000 IU) treatment brings about similar healing in BMD.

We could find only one study that measured BMD in infants with rickets compared with healthy infants(10). However, pre- and post-treatment BMDs were not compared in that study. It is expected that BMD decreases in nutritional VDR. A previous study with a small number of subjects found lower but statistically insignificant BMD values compared to the controls(10). In a study, it was suggested that children with VDR had increased bone turnover, using bio-chemical markers of bone formation and bone resorption before and during the first 2-4 weeks of vitamin D treatment (3000-4000 IU per day)(11).

This is the first study that compares pre- and post-treatment BMDs in different treat-ment modes for nutritional VDR. Biochemical values 30 days after the treatment did not suggest vitamin D intoxication (*Table II*). BMDs increased significantly in both treat-ment groups. In contrast to previous studies based on clinical and biochemical findings, our study indicates that high dose therapy did not provide a more rapid healing in BMD than daily administration of 20,000 IU/day of vitamin D in infants with VDR. The small sample size, non-randomized and unblinded methods are the shortcomings of our study.

Contributors: All authors were involved in concept, design, collection of data, review of literature and drafting the manuscript. MA shall act as guarantor.

Funding: This study was supported by Akdeniz University Administration of Scientific Research Projects.

Competing interests: None stated.

REFERENCES

1. Heird WC. Vitamin deficiencies and excesses. In: Behrman ER, Kliegman MR, Jenson BH (eds). Nelson Textbook of Pediatrics, 17th edn. Philadelphia WB Saunders Co, 2004; 177-190.
2. Gertner JM. Metabolic bone disease. In: Lifshitz F (ed). Pediatric Endocrinology, 4th edn. New York; Marcel Dekker, Inc, 2003; 517-539.
3. Shah BR, Finberg L. Single-day therapy for

nutritional vitamin D-deficiency: A preferred method. J Pediatr 1994; 125: 487-490.

4. Zeghoud F, Ben Mekhbi H, Djeghri N, Garabedian M. Vitamin D prophylaxis during infancy: comparison of the long-term effects of three intermittent doses (15, 5, or 2.5 mg) on 25 hydroxyvitamin D concentrations. Am J Clin Nutr 1994; 60: 393-396.
5. Markestad T, Hesse V, Siebenhuner M, Jahreis G, Aksnes L, Plenert W, *et al*. Intermittent high-dose vitamin D prophylaxis during infancy: effect on vitamin D metabolites, calcium, and phosphorus. Am J Clin Nutr 1987; 46: 652-658.
6. Lubani MM, al-Shab TS, al-Saleh QA, Sharda DC, Quattawi SA, Ahmed SA, *et al*. Vitamin-D deficiency in Kuwait: The prevalence of a preventabl disease. Ann Trop Pediatr 1989; 3: 134-139.
7. Cesur Y, Caksen H, Gundem A, Kirimi E, Odabas D. Comparison of low and high dose of vitamin D treatment in nutritional vitamin D deficiency rickets. J Pediatr Endocrinol Metab 2003; 16: 1105-1109.
8. Theodorou DJ, Theodorou SJ. Dual-energy X-ray absorptiometry in clinical practice: Application and interpretation of scans beyond the numbers. Clin Imaging 2002; 26: 43-49.
9. Blake GM, Fogelman I. Technical Principles of Dual Energy *X*-ray Absorptiometry. Semin Nucl Med 1997; 27: 210-228.
10. Ergur AT, Erselcan T. Diagnostic value of bone mineral density measurements in infants with rickets. J Trop Pediatr 2000; 46:124-126.
11. Baroncelli GI, Bertelloni S, Ceccarelli C, Amato V, Saggese G. Bone turnover in children with vitamin D deficiency rickets before and during treatment. Acta Pediatr 2000; 89: 513-518.