Kidney International, Vol. 53 (1998), pp. 205–211

Diminished linear growth during intermittent calcitriol therapy in children undergoing CCPD

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Diminished linear growth during intermittent calcitriol therapy in children undergoing CCPD. Daily calcitriol therapy has been reported to improve linear growth in children with renal bone disease, and 1,25-dihydroxyvitamin D is a key regulator of chondrocyte proliferation and differentiation. Whereas large intermittent doses of calcitriol can lower serum parathyroid hormone (PTH) levels and reverse the skeletal changes of secondary hyperparathyroidism, the impact of intermittent calcitriol therapy on linear growth in children is not known. Thus, we studied 16 pre-pubertal patients with bone biopsy-proven secondary hyperparathyroidism who completed a 12-month prospective clinical trial of intermittent calcitriol therapy. Biochemical results and growth data obtained during intermittent calcitriol therapy were compared to values determined during the preceding 12 months of daily calcitriol therapy in each study subject; changes in bone histology were assessed after one year of intermittent calcitriol therapy. Z-scores for height did not change during 12 months of daily calcitriol therapy. Although the skeletal lesions of secondary hyperparathyroidism improved in most patients, Z-scores for height decreased from -1.8 ± 0.32 to -2.0 ± 0.33, $P < 0.01$, during intermittent calcitriol therapy. The largest reductions were seen in patients who developed adynamic bone lesions after 12 months of treatment. Delta Z-scores for height correlated with serum PTH, $r = 0.71$, $P < 0.01$, and alkaline phosphatase levels, $r = 0.67$, $P < 0.01$, during intermittent calcitriol therapy but not during daily calcitriol therapy. The data suggest that high dose intermittent calcitriol therapy adversely affects linear growth, particularly in patients with the adynamic lesion. The higher doses of calcitriol or the intermittent schedule of calcitriol administration may directly inhibit chondrocyte activity within growth plate cartilage of children with end-stage renal disease.

Treatment with daily doses of calcitriol, or 1,25-dihydroxyvitamin D, has been reported to improve linear growth and to prevent skeletal deformities in pediatric patients with renal bone disease [1, 2]. Such findings provide the rationale for the routine administration of calcitriol to nearly all children with chronic renal failure. Secondary hyperparathyroidism remains a persistent problem, however, in children with advanced renal disease, and osteitis fibrosa continues to be the most common skeletal lesion of renal osteodystrophy in those undergoing regular dialysis despite regular treatment with daily doses of oral calcitriol [3, 4]. Accordingly, alternative therapeutic regimens have been sought to provide better control of secondary hyperparathyroidism in pediatric patients with end-stage renal disease.

Large intermittent doses of calcitriol have recently been used to treat secondary hyperparathyroidism both in children and in adults [5–10]. Doses have generally been given thrice weekly by the oral, intravenous or intraperitoneal route of administration [6, 8, 11]. Available data indicate that approximately 40% of children currently undergoing regular hemodialysis are given calcitriol using an intermittent dosage regimen, but the impact of this therapeutic approach on linear growth has not been evaluated [12].

In this regard, intermittent calcitriol therapy has been shown to markedly reduce bone formation and to suppress osteoblastic activity both in adults and in children [6, 8]. Direct inhibitory effects of calcitriol on osteoblast function and/or proliferation may be partially responsible [8]. Whether calcitriol also diminishes chondrocyte activity within growth plate cartilage remains to be determined, but 1,25-dihydroxyvitamin D has potent antiproliferative actions *in vitro* in a variety of cell lines including chondrocytes [13]. The current study was undertaken, therefore, to measure linear growth during 12 months of intermittent calcitriol therapy and to compare the results with those obtained during the preceding year of daily oral calcitriol therapy in pre-pubertal children with secondary hyperparathyroidism undergoing maintenance peritoneal dialysis.

METHODS

Sixteen pre-pubertal subjects were selected from a total of 35 patients who had completed a 12-month prospective, randomized clinical trial of intermittent oral versus intermittent intraperitoneal calcitriol for the treatment of bone biopsy-proven secondary hyperparathyroidism. For the current study, only children who had not entered puberty after completing the 12-month clinical trial were included. Measurements of linear growth and monthly biochemical data obtained during intermittent calcitriol therapy were compared to values determined during the preceding 12 months of daily oral calcitriol therapy in each study subject. In addition, parameters of nutritional status and the number of peritonitis episodes, hospital admissions and total in-patient hospital days were evaluated during each 12 month period of observation.

Key words: calcitriol therapy, growth in children, end-stage renal disease, chondrocyte activity.

Received for publication March 19, 1997
and in revised form August 5, 1997
Accepted for publication August 6, 1997

Table 1. Indices of nutrition and morbidity during daily and intermittent calcitriol therapy

Variable	Daily	Intermittent
Hematocrit *%*	28.1 ± 0.8	31.2 ± 0.6[a]
Serum total CO_2 *mmol/liter*	23.3 ± 0.6	23.8 ± 0.6
Serum total protein *g/dl*	6.3 ± 0.2	6.4 ± 0.1
Serum albumin *g/dl*	3.7 ± 0.1	3.8 ± 0.1
Peritonitis *#/patient-year*	0.8 ± 0.3	0.8 ± 0.2
Hospital admissions *#/patient-year*	1.3 ± 0.3	1.6 ± 0.4
In-patient hospital days *#/patient-year*	8.1 ± 2.2	9.2 ± 4.0

Values are means ± SE. Individual values represent the average of 12 monthly determinations during each treatment period.
[a] $P < 0.01$

There were 9 female and 7 male patients, aged 10 ± 1.1 (SE) years. The average bone age was 9.5 ± 1.2 years, and the duration of maintenance dialysis prior to treatment with intermittent calcitriol was 20 ± 4.9 months. All patients received continuous cycling peritoneal dialysis (CCPD) throughout the 24 months of observation using standard peritoneal dialysate solutions containing 3.5 mEq/liter of calcium (Dianeal; Baxter, Deerfield, IL, USA) [3, 8]. Calcium carbonate was used as the primary phosphate-binding agent throughout the study, and the dose was adjusted according to monthly measurements of serum calcium and phosphorus levels as previously reported [8, 14]. The dietary intake of calcium and phosphorus was monitored each month during the 24 month period of observation using three-day diet histories [15]. All patients were treated with erythropoietin but none of the patients received recombinant human growth hormone (rhGH) during the 24 months of observation. All studies were approved by the UCLA Human Subjects Protection Committee, and written informed consent was obtained from all patients and their parents.

Intermittent calcitriol therapy

During intermittent calcitriol therapy, five patients received oral doses of calcitriol thrice weekly (Rocaltrol®; Hoffmann-LaRoche, Nutley, NJ, USA), whereas eleven patients were given intraperitoneal doses of calcitriol three times per week as previously described (Calcijex®; Abbott Laboratories, Abbott Park, IL, USA) [8]. The initial dose of calcitriol during intermittent therapy was 1.0 μg thrice weekly, and doses were adjusted monthly based on regular measurements of serum calcium and phosphorus levels. The dose of calcitriol was increased in increments of 0.5 μg if serum calcium levels remained less than 10 mg/dl and if serum phosphorus levels remained below 6.5 mg/dl. Treatment was temporarily withheld if hypercalcemia, defined as a serum calcium level above 11 mg/dl, or hyperphosphatemia, defined as a serum phosphorus level greater than 7 mg/dl developed. Calcitriol therapy was resumed after reducing the dose by 50% when serum calcium and phosphorus levels fell below 11 mg/dl and 7 mg/dl, respectively.

Iliac crest bone biopsies following double tetracycline labeling were obtained before and after 12 months of intermittent calcitriol therapy [3, 8]. As such, the bone biopsy done prior to starting intermittent calcitriol therapy reflected the histologic state of bone after 12 months of daily oral calcitriol therapy. The skeletal lesions of renal osteodystrophy were classified by histomorphometric criteria with reference to values established in children with normal renal function as described previously [3, 8]. The terminology established by the Nomenclature Committee of the American Society for Bone and Mineral Research was used to report all histomorphometric results [16].

Daily calcitriol therapy

All patients who entered the 12-month clinical trial of intermittent calcitriol therapy had previously been treated with daily oral doses of calcitriol for at least one year. Monthly measurements of height and monthly biochemical determinations obtained during daily oral calcitriol therapy were retrospectively evaluated, and the results compared to those obtained during intermittent calcitriol therapy. During daily calcitriol therapy, the initial dose of calcitriol was 0.25 to 0.5 μg, and doses were increased by 0.25 to 0.5 μg based upon regular measurements of serum calcium and phosphorus levels. The same biochemical criteria described previously for intermittent calcitriol therapy were used to guide dosage adjustments during daily therapy.

The average daily dose of calcitriol for each 12-month treatment interval was calculated by dividing the weekly cumulative dose by seven. Values were expressed in μg/day or in ng/kg body wt per day.

Assessments of growth and skeletal maturity

Standing heights were measured monthly by the same dietitian using a fixed, wall-mounted stadiometer. All height measurements were repeated until three consecutive values agreed within 0.2 cm. For statistical evaluation, height measurements were expressed as standard deviation (SD) scores, or Z-scores, relative to values corresponding to the 50th percentile of the population norm for children of the same age and gender according to tables provided by the National Center for Health Statistics, Hyattsville, Maryland [17]. Delta Z-scores for height were calculated from values obtained before and after each 12 month period of observation.

Skeletal maturity was determined using radiographs of the hand and wrist at the start of intermittent calcitriol therapy. Bone age was assessed by an independent observer using the method of Greulich and Pyle [18].

Hematological and biochemical determinations

Determinations of hematocrit and of total CO_2, total protein, albumin, calcium, phosphorus, alkaline phosphatase and PTH levels in serum were done as previously described [3, 8, 19]. Serum PTH levels were measured using an immunoradiometric assay for the intact hormone (Allegro PTH; Corning-Nichols, San Juan Capistrano, CA, USA) [19]. The reference range for subjects with normal renal function using this assay is 10 to 65 pg/ml.

Statistical analysis

All results are expressed as means ± standard error. Statistical analysis of the data were done using paired *t*-tests, one-way analysis of variance with contrasts, analysis of variance for repeated measures and chi-square analysis. Linear regression analysis was done by the method of least squares.

RESULTS

Biochemical and histologic results

All patients were clinically stable throughout the 24 months of observation, and none was withdrawn from study or lost to

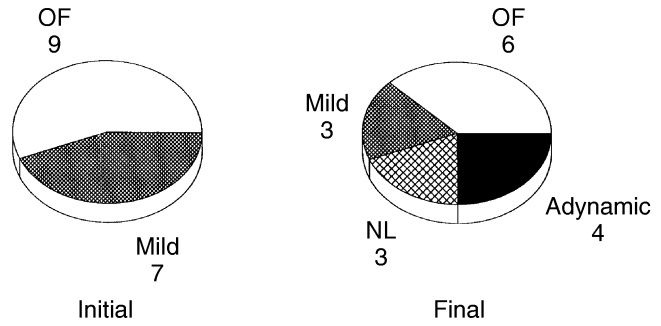

Fig. 1. Bone histology before and after 12 months of intermittent calcitriol therapy in 16 pre-pubertal children with secondary hyperparathyroidism. Abbreviations are: OF, osteitis fibrosa; mild, mild lesion of secondary hyperparathyroidism; NL, normal bone formation rate; and adynamic, adynamic renal osteodystrophy.

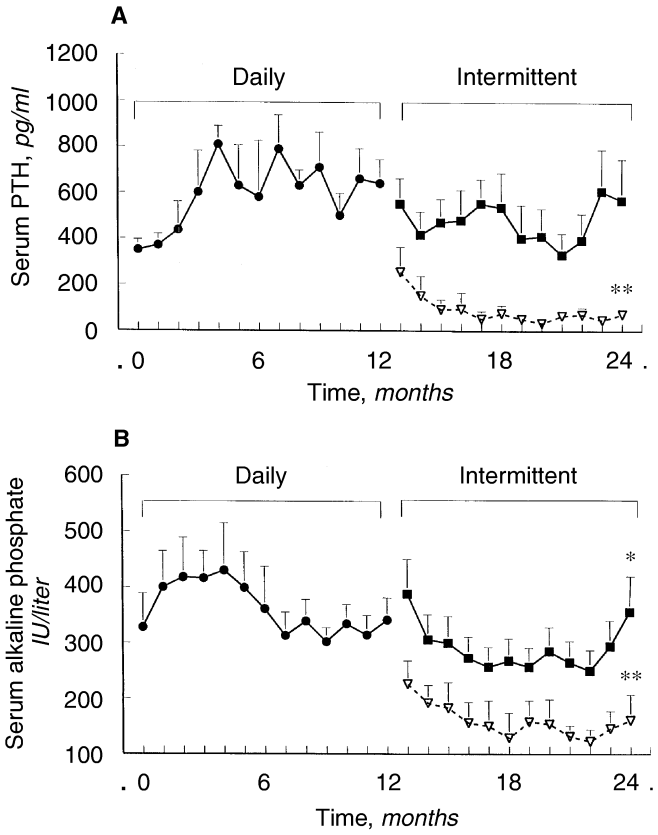

Fig. 2. Mean serum PTH (*A*) and alkaline phosphatase levels (*B*) during daily (●, $N = 16$) and intermittent (■, $N = 16$) calcitriol therapy. Values in four patients who developed adynamic skeletal lesions during intermittent calcitriol therapy are shown separately (▽). Values are means ± SE. Overall, serum alkaline phosphatase levels were lower during intermittent therapy than during daily therapy, $^{*}P < 0.01$ by analysis of variance for repeated measures. During intermittent calcitriol therapy, serum PTH and alkaline phosphatase values were lower in those who developed adynamic lesions than in subjects who did not have adynamic bone after 12 months of treatment, $^{**}P < 0.001$.

follow-up. The number of hospital admissions, total in-patient hospital days and peritonitis rates did not differ between the two treatment intervals (Table 1). In addition, there were no differences in the serum levels of total CO_2, total protein or albumin between daily and intermittent calcitriol therapy. Hematocrit values were slightly higher, however, during intermittent calcitriol therapy (Table 1).

Serum PTH levels were 550 ± 111 pg/ml at the start of intermittent calcitriol therapy, values consistent with the histologic severity of secondary hyperparathyroidism documented by bone biopsy. Accordingly, nine of 16 patients had osteitis fibrosa, whereas seven had mild lesions of secondary hyperparathyroidism (Fig. 1). After 12 months of intermittent calcitriol therapy, four patients had persistent changes of osteitis fibrosa, but the rate of bone formation and the extent of marrow and/or peri-trabecular fibrosis had decreased in each (Fig. 1). Three patients with initial lesions of overt osteitis fibrosa had mild lesions of secondary hyperparathyroidism on repeat bone biopsy, whereas two with mild secondary hyperparathyroidism developed osteitis fibrosa. Of the remaining patients, three had normal rates of bone formation on follow-up bone biopsy, whereas four patients, or 25% of subjects, developed adynamic lesions of renal osteodystrophy (Fig. 1). Overall, bone formation decreased from 1091 ± 132 to 548 ± 143 $\mu m^2/mm^2/day$ during intermittent calcitriol therapy ($P < 0.01$) and 9/16 patients had bone formation rates that fell within or below the range of normal for healthy subjects of the same age.

Despite histologic improvement, serum PTH levels remained elevated during treatment with intermittent doses of calcitriol, and values did not change from baseline levels during the subsequent 12 months (Fig. 2). Serum PTH levels were also persistently elevated during daily calcitriol therapy in all patients, and there was no overall difference in serum PTH levels between the two 12-month periods of observation (Fig. 2); monthly PTH values averaged 520 ± 109 pg/ml during intermittent calcitriol therapy and 553 ± 101 pg/liter during daily calcitriol therapy (P = NS).

Serum PTH levels were substantially lower, however, in subjects who developed adynamic lesions during intermittent calcitriol therapy (Fig. 2). In this subgroup of patients, serum PTH levels were 254 ± 108 pg/ml before treatment, but values decreased after the second month to levels that were often less that 100 pg/ml. In contrast, serum PTH levels at the beginning of treatment were 697 ± 134 pg/ml in patients who did not develop adynamic lesions of bone, and values generally remained above 400 pg/ml, ranging from 390 and 850 pg/ml. Serum PTH levels averaged over the full 12 months of treatment were 100 ± 30 pg/ml in those who developed adynamic lesions and 660 ± 120 pg/ml in those who did not have adynamic bone at the time of repeat bone biopsy ($P < 0.001$).

Serum alkaline phosphatase levels were moderately higher before starting intermittent calcitriol therapy, 388 ± 62 IU/liter, than before treatment with daily doses of calcitriol, 328 ± 61 IU/liter ($P < 0.001$; Fig. 2). Values averaged over the full 12 months of treatment were lower, however, during intermittent, 299 ± 35 IU/liter, than during daily calcitriol therapy, 334 ± 39 IU/liter ($P < 0.01$). Alkaline phosphatase levels decreased after the first month of intermittent therapy, and values at each monthly interval thereafter remained below baseline levels except during the final month of observation. These changes corresponded to marked reductions in bone formation documented by bone biopsy. In contrast, serum alkaline phosphatase levels were

persistently elevated throughout the 12 months of daily calcitriol therapy, results consistent with bone biopsy evidence of overt secondary hyperparathyroidism in all subjects at the time they were switched to intermittent calcitriol therapy (Fig. 2).

Baseline serum alkaline phosphatase levels were lower in patients who developed adynamic lesions, 226 ± 42 IU/liter, than in those who had normal or increased rates of bone formation, 442 ± 77 IU/liter, during intermittent calcitriol therapy (Fig. 2). Similarly, values averaged over the full 12 months of treatment were 157 ± 34 and 347 ± 35 IU/liter, respectively, in these two subgroups of patients ($P < 0.001$).

Serum calcium levels did not differ at the start of each treatment interval. Values were 9.6 ± 0.24 mg/dl before daily and 9.4 ± 0.33 mg/dl before intermittent therapy (P = NS). Serum calcium levels were greater, however, when values were averaged over the full 12 months of treatment with intermittent doses of calcitriol, 9.8 ± 0.24 versus 9.3 ± 0.28 mg/dl ($P < 0.05$), despite similar levels of dietary calcium intake. The average dietary calcium intake was 350 ± 41 mg/day during daily and 433 ± 26 mg/day during intermittent calcitriol therapy (P = NS). For each treatment interval of 192 patient-months, seventeen episodes of hypercalcemia were documented in eight patients given intermittent doses of calcitriol, whereas six episodes of hypercalcemia were observed in four patients receiving daily calcitriol ($\chi^2 = 5.6$, $P < 0.025$).

Baseline serum phosphorus levels also did not differ before treatment with intermittent or daily doses of calcitriol; values were 6.2 ± 0.44 and 6.2 ± 0.35 mg/dl, respectively. Despite equivalent levels of dietary phosphorus intake during intermittent, 740 ± 59 mg/day, and daily calcitriol therapy, 703 ± 60 mg/day (P = NS), serum phosphorus levels were greater during intermittent therapy, 6.4 ± 0.24 versus 6.1 ± 0.22 mg/dl ($P < 0.05$), when monthly values were averaged over each 12 months of observation. Overt hyperphosphatemia was more frequent during intermittent calcitriol therapy. There were 63 and 44 episodes of hyperphosphatemia during each 192 patient-months of treatment with intermittent and daily doses of calcitriol, respectively ($\chi^2 = 5.78$, $P < 0.025$).

The average daily dose of calcitriol was 1.18 ± 0.21 μg or 38.1 ± 5.4 ng/kg during intermittent calcitriol therapy and 0.45 ± 0.15 μg or 15.1 ± 3.5 ng/kg during daily therapy ($P < 0.01$). The dose of calcitriol did not differ, however, between patients who developed adynamic lesions and those who had normal or persistently elevated rates of bone formation after intermittent calcitriol therapy. Values were 1.01 ± 0.12 μg or 34.5 ± 2.9 ng/kg and 1.23 ± 0.27 μg or 39.2 ± 7.2 ng/kg, respectively, in these two subgroups (P = NS).

Assessments of growth

The mean Z-score for height at the start of each treatment interval did not differ, and values did not change during treatment with daily doses of calcitriol (Fig. 3). In contrast, Z-scores for height decreased from −1.8 ± 0.32 to −2.0 ± 0.33 ($P < 0.01$), after 12 months of intermittent calcitriol therapy (Fig. 3). The largest decline was seen in subjects who developed adynamic lesions of bone (Fig. 3). Individual delta Z-scores for height during intermittent calcitriol therapy correlated with the serum levels of PTH ($r = 0.71$, $P < 0.01$) and alkaline phosphatase ($r = 0.67$, $P < 0.01$) when the latter values were averaged over the full 12 months of treatment (Fig. 4). Similar relationships could not be documented, however, during daily calcitriol therapy; thus, delta Z-scores for height did not correspond to either serum PTH ($r = -0.38$, NS) or alkaline phosphatase levels ($r = 0.30$, NS) during daily calcitriol therapy.

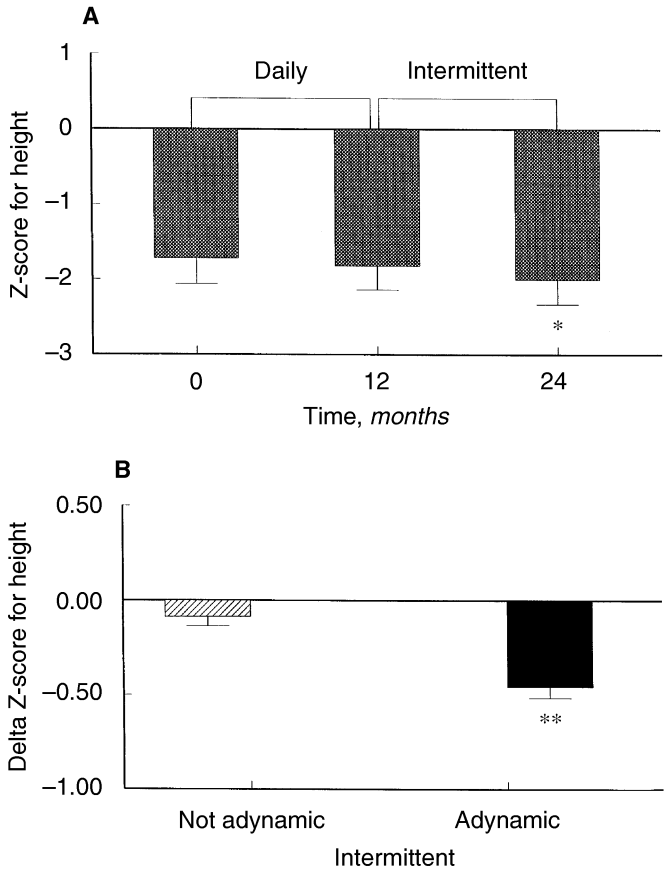

Fig. 3. Z-scores for height (*A*) in 16 pre-pubertal children with secondary hyperparathyroidism before and after each 12 months treatment interval, *P < 0.01 versus 12 months. The change in Z-scores for height during intermittent calcitriol (*B*) in patients who developed adynamic lesions of bone (■, $N = 4$) and in those with normal or persistently high bone formation rates (▨, $N = 12$) on follow-up evaluation, **$P < 0.001$.

DISCUSSION

The results of the current study indicate that high dose intermittent calcitriol therapy adversely affects linear growth in pre-pubertal children with chronic renal failure undergoing maintenance peritoneal dialysis. Linear growth during intermittent calcitriol therapy was less than during the preceding 12 months of daily calcitriol as judged by reductions in Z-scores for height in the same study subjects. Other factors which can adversely affect growth in children with advanced renal disease such as malnutrition, metabolic acidosis, anemia and intercurrent illnesses are unlikely to account for this finding. Thus, the serum levels of albumin, total protein and total CO_2 did not differ between treatment regimens, and hematocrit values were actually higher during intermittent calcitriol therapy. Also, the number of episodes of peritonitis, the number of hospital admissions and total number of in-patient hospital days during each treatment interval

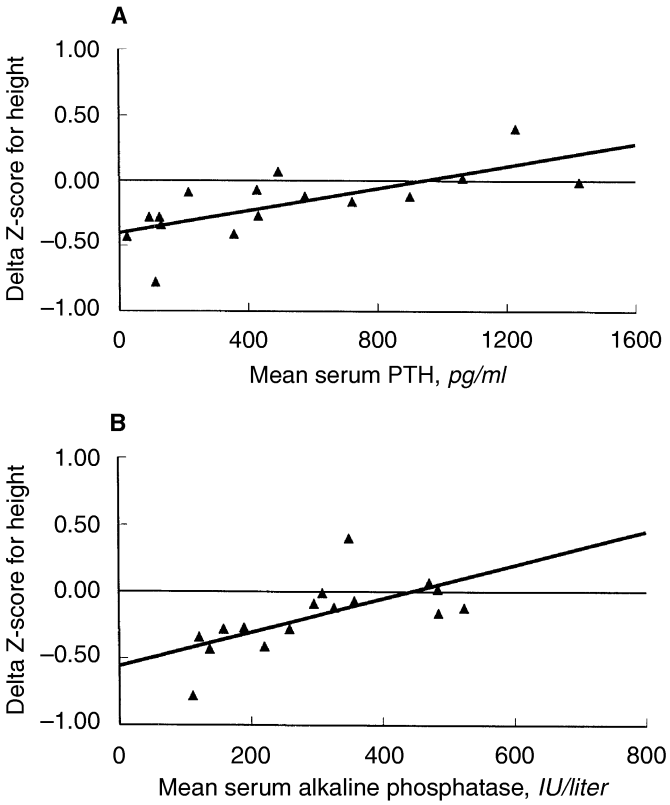

Fig. 4. Relationship between the change in Z-score for height and serum PTH (*A*; $r = 0.71$; $P < 0.01$) and alkaline phosphatase levels (*B*; $r = 0.67$; $P < 0.01$) during intermittent calcitriol therapy. Each data point represents the mean of 12 monthly determinations of PTH or alkaline phosphatase for an individual patient.

did not differ. The moderately higher serum calcium and phosphorus levels during intermittent therapy most probably reflect the larger average weekly dose of 1,25-dihydroxyvitamin D, but these changes were not associated with alterations in other nutritional indices. Such findings suggest that either the higher weekly dose of calcitriol delivered during intermittent therapy or the intermittent schedule of calcitriol administration adversely affects the chondrocyte activity within the growth plate of prepubertal children with end-stage renal disease.

The extent of growth retardation for subjects enrolled in the current study was characteristic of children undergoing regular peritoneal dialysis [12]. Z-scores for height were -1.72 ± 0.34 at the start of daily calcitriol therapy, and values did not change during the ensuing 12 months. In contrast, Z-scores for height decreased from -1.8 to -2.0, or by 10%, during intermittent calcitriol therapy, and the greatest reductions were seen in patients with adynamic lesions of renal osteodystrophy after 12 months of treatment. The results suggest that the risk of further growth retardation in children with chronic renal failure is greatest in patients who develop adynamic bone during intermittent calcitriol therapy.

Although calcitriol has been shown to enhance linear growth in rats with renal failure [20], clinical studies have not consistently demonstrated such a response [21–23]. Chesney et al [1] and Chan, Kodroff and Landwehr [2] reported increases in growth velocity during daily calcitriol therapy at doses ranging from 15 to 40 ng/kg/day in small numbers of children with stable chronic renal failure and in those undergoing regular dialysis. The severity of bone disease before treatment was quite advanced, however, in these early studies, and sustained increases in growth velocity could not be documented on long-term follow-up [24]. In subsequent studies, the administration of similar doses of daily oral calcitriol to children with renal failure failed to enhance linear growth [21–23]. The results for growth during the current 12 months study using equivalent doses of daily oral calcitriol agree, therefore, with several previous reports [21–23].

The reductions in growth observed during intermittent calcitriol therapy in the current clinical study are also consistent with the results of recent studies in experimental animals, which suggest that intermittent rather than continuous calcitriol administration adversely affects linear growth. Berger et al reported slower growth in rats given intermittent doses of calcitriol compared to animals given equivalent weekly doses of 1,25-dihydroxyvitamin D delivered continuously by mini-osmotic pump [25]. A similar disparity in linear growth was seen between intermittent and continuous calcitriol dosage regimens in animals receiving recombinant human growth hormone (rhGH) [25], and preliminary studies suggest that calcitriol blunts the expected increase in growth plate thickness during rhGH therapy in rats with renal failure [26]. Inhibitory effects of calcitriol on chondrocyte proliferation have been described in a variety of *in vitro* studies, and calcitriol plays an important role in regulating the rate of differentiation of proliferating chondrocytes within the growth plate [13, 27–30]. Overall, such findings suggest that the therapeutic administration of calcitriol can directly affect epiphyseal growth plate chondrocytes, thereby contributing to the reductions in linear growth documented in the current study.

Endochondral bone formation is a carefully controlled process in which PTHrP and the PTH/PTHrP receptor, together with the developmentally important hedgehog family of secreted proteins, interact through an autocrine/paracrine mechanism to regulate chondrocyte differentiation [31, 32]. Both PTHrP and Indian hedgehog (*Ihh*) act to delay the differentiation of proliferating chondrocytes into hypertrophic chondrocytes; as such, mice lacking both alleles of the gene for either PTHrP or the PTH/PTHrP receptor have disproportionately shortened limbs due to an acceleration of chondrocyte differentiation which leads to premature ossification of the cartilaginous templates of long bones [33]. In contrast, activating mutations of the PTH/PTHrP receptor such as the one found in Jansen's metaphyseal chondrodysplasia are associated with a delay in the transition of proliferating chondrocytes into hypertrophic chondrocytes within growth plate cartilage [34]. Similar changes occur in transgenic mice in which the expression of PTHrP is controlled by the type II collagen promoter [35]. Overall, these findings emphasize the critical role of PTHrP and the PTH/PTHrP receptor in the regulation of chondrocyte differentiation and bone elongation.

In chronic renal failure, PTH/PTHrP receptor expression is diminished in the epiphyseal growth plate of long bones [36], and 1,25-dihydroxyvitamin D lowers PTH/PTHrP receptor expression *in vitro* [37]. Whether the administration of exogenous calcitriol to children with renal failure disrupts the orderly transition of proliferating chondrocytes into hypertrophic chondrocytes or diminishes the rate of cell division within the zone of proliferation within the growth plate cartilage remains to be determined. Nevertheless, these *in vitro* and *in vivo* findings suggest that

alterations in the functional expression of the receptor for PTH/PTHrP in conjunction with either direct or indirect effects of 1,25-dihydroxyvitamin D on chondrocyte differentiation contribute to abnormalities in linear growth in children with chronic renal failure. Additional work will be required, however, to adequately characterize the role of calcitriol as a direct modifier of endochondral bone development.

The prevalence of adynamic renal osteodystrophy has increased substantially both in adults and in children [8, 38, 39], and previous work has demonstrated that this skeletal lesion can arise after intermittent calcitriol therapy, particularly when serum PTH and serum alkaline phosphatase levels fall substantially [8]. The long-term consequences of this disorder remain uncertain, but adynamic renal osteodystrophy often leads to recurrent episodes of hypercalcemia and it may be associated with an increase in fracture risk and with higher mortality rates in adult patients undergoing long-term dialysis [40, 41]. The results of the current study suggest that the adynamic lesion can also adversely affect linear growth in pre-pubertal children undergoing peritoneal dialysis if it develops during intermittent calcitriol therapy. As such, oversuppression of parathyroid gland function in pre-pubertal children undergoing regular dialysis should be avoided to diminish the risk of aggravating the growth retardation that characterizes this subgroup of patients.

ACKNOWLEDGMENTS

This study was supported in part by USPHS grants DK-35423, RR-00865 and the Casey Lee Ball Foundation. B.D.K. was supported by a fellowship from the National Kidney Foundation of Southern California. Portions of this work were presented at the 29th annual meeting of the American Society of Nephrology, November 3–6, 1996, New Orleans, LA, and published in abstract form (*J Am Soc Nephrol* 7:1792–1793, 1996).

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