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Effect of a vitamin D analog on leg bone mineral density in patients with chronic spinal cord injury

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Abstract—A randomized, placebo-controlled trial was performed to determine the effect of a vitamin D analog (1-alpha-hydroxyvitamin D_2 [1-alpha D_2]) on the bone mineral density (BMD) in patients with chronic spinal cord injury (SCI). Forty subjects with chronic complete motor SCI were enrolled. The mean plus or minus standard deviation age and duration of injury were 42 plus or minus 12 yr and 11 plus or minus 10 yr, respectively. Either 4 micrograms 1-alpha D_2 (n = 19) or placebo (n = 21) was administered daily for 24 mo. Metabolic markers of bone resorption and formation were obtained. Regional lower-limb dual-energy x-ray absorptiometry was performed at baseline and at 6, 12, 18, and 24 mo. Leg BMD and percent change from baseline significantly increased at 6 (percent change only), 12, 18, and 24 mo in the treatment group, but not in the placebo group. Urinary N-telopeptide, a marker of bone resorption, was significantly reduced during treatment with 1-alpha D_2, but markers of bone formation were not changed.

Key words: 1-alpha-hydroxyvitamin D_2, bone markers, bone metabolism in SCI, bone mineral density, cigarette smoking, disuse osteoporosis, Hectorol, N-telopeptide, paraplegia, spinal cord injury, tetraplegia, vitamin D analog.

INTRODUCTION

Persons with spinal cord injury (SCI) have severe loss of bone in the lower limbs and increased susceptibility to fractures [1–4]. An identical twin study, in which we were able to compute the difference between twin pairs, discordant for SCI, showed an increasing loss of bone mineral content and density in the pelvis and lower limbs with increasing duration of injury [5]. In a cross-sectional study of regional bone loss in women with SCI, increased age and menopause/estrogen withdrawal were associated with progressively lower bone mineral density (BMD) of the knee and Ward's triangle [6]. In persons with SCI who have had appreciable loss of bone after acute injury, additional loss of bone with longer duration

Abbreviations: 1α-D_2 = 1-alpha-hydroxyvitamin D_2, 1α-D_3 = 1-alpha-hydroxyvitamin D_3, $1,25(OH)_2D_3$ = 1,25-dihydroxyvitamin D_3, ANOVA = analysis of variance, BCE = bone collagen equivalent, BMD = bone mineral density, NTx = N-telopeptide of type 1 collagen, PINP = intact N-terminal propeptide of type 1 procollagen, SCI = spinal cord injury, SD = standard deviation.

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of injury or advancing age would be expected to increase the risk of fracture [3–4].

Vitamin D analogs are of clinical interest in the treatment of various forms of osteoporosis because of their action to increase bone mass while having a greatly reduced ability to stimulate gut absorption of calcium [7]. In postmenopausal osteoporosis, administration of 1,25-dihydroxyvitamin D_3 [1,25$(OH)_2D_3$] or a vitamin D analog reduced fracture incidence rates of both the axial and appendicular bones [8–9]. Shiraki et al. reported that a vitamin D_3 analog increased density in the radius in patients with senile osteoporosis compared with a progressive loss of density in the control group [10]. In persons immobilized for several years after suffering a stroke, the rate of bone loss was reduced on the hemiplegic side after treatment with a vitamin D analog [11]. The mechanism of action on bone of this class of agents presumably involves stimulation of osteoblast activity, but evidence also exists of a reduction in bone resorption as well [8–10]. The 1-alpha-hydroxyvitamin D_2 (1α-D_2) analog has been shown to be equipotent to the 1-alpha-hydroxyvitamin D_3 (1α-D_3) analog on bone, but the 1α-D_2 analog had markedly less hypercalcemic and hypercalciuric effects [12]. To date, vitamin D analogs have not been studied in persons with long-standing SCI. We performed this study to determine the effect of a vitamin D analog on lower-limb bone in subjects with chronic SCI.

Table 1.
Demographic data (values in mean ± standard deviation).

Variable	Treatment	Placebo
Subjects (*n*)	19	21
Age (yr)	43 ± 11	42 ± 14
DOI (yr)	14 ± 10	9 ± 9
Height (cm)	179 ± 117	175 ± 109
Weight (kg)	83.0 ± 15.8	84.1 ± 18.6
BMI (kg/m^2)	26.1 ± 4.9	27.3 ± 4.8
Sex (*n*)		
Male	19	20
Female	0	1
Level of Lesion (*n*)		
Tetraplegia	12	5
Paraplegia	7	16
Ethnicity (*n*)		
Caucasian	7	12
African American	8	1
Hispanic	3	5
Asian	0	1
Other	1	2
Smoking History (*n*)		
Never	11	12
Former	5	3
Current	3	6
Alcohol Intake History (*n*)		
None–Mild	17	21
Severe	1	0
Unknown	1	0

n = number, DOI = duration of injury, BMI = body mass index, never = smoked <100 cigarettes in lifetime, former = quit for longer than 1 year, current = current smoker.

METHODS

We enrolled 40 subjects with chronic complete motor SCI, 17 with tetraplegia and 23 with paraplegia (**Table 1**). (Continuous values are expressed as mean ± standard deviation (SDs) unless stated otherwise.) Metal prostheses were an exclusion criterion for participation in the study. The mean age was 43 ± 13 yr, and the mean duration of injury was 12 ± 10 yr (range: 1–34 yr); at time of enrollment, six subjects had a duration of injury of less than 2 years. Of the 40 subjects, 23 never smoked and 9 currently smoked. Long-bone fracture histories were not obtained on subjects. Either 1α-D_2 (4 µg/day) (Bone Care International, Madison, WI) (*n* = 19) or a placebo (*n* = 21) was administered daily for 24 months. Neither subject nor investigator had knowledge of randomization. Both groups received calcium (1.3 g/d) and vitamin D (800 IU/d; 20 µg/d) supplementation. Institutional review board approval was obtained and all subjects gave informed consent prior to enrollment in the study.

The presence of hypercalcemia (>10.5 mg/dL) and/or hypercalciuria (mild 250–350 or moderate/severe >350 mg/d) was determined by serum and urinary calcium measurements at baseline and at 1, 2, 6, 12, 18, and 24 months. A protocol for reduction of calcium intake and/or therapy (drug or placebo) was implemented in those who presented with or developed serum and/or urinary calcium elevations.

Regional dual-energy x-ray absorptiometry (Lunar Model DPX, version 3.6, Madison, WI) was performed at baseline and at 6, 12, 18 and 24 months after enrollment. Measurements were made of leg, pelvis, and spine (L2–L4) for BMD [13]. The operator applied software algorithms to obtain lower-limb values, and adjusted the final cut lines according to the Lunar instrumentation manual to

account for individual variation. A single, blinded investigator performed all cuts to avoid interrater variability.

Bone markers obtained at baseline and at 6, 12, 18, and 24 months provided a measure of bone metabolism. Morning spot urine samples and serum samples collected for N-telopeptide of type I collagen (NTx) (Osteomark™, Ostex International, Inc., Seattle, WA) were assayed for the evaluation of bone resorption; NTx values were corrected for urinary dilution and expressed in nanomoles bone collagen equivalents (nM BCE) per millimole creatinine (mM creatinine). Serum osteocalcin (Diagnostic Systems Laboratories, Inc., Webster, TX) and intact N-terminal propeptide of type 1 procollagen (PINP) (Orion Diagnostica, Espoo, Finland) were assayed for the evaluation of bone formation.

STATISTICAL ANALYSES

An unpaired *t*-test (continuous variables) or chi-square analysis (categorical variables) was performed between the treatment and placebo groups for the demographic variables. The main outcome variable was leg BMD (reported in the absolute value of grams per square centimeter and as a percent change from baseline); secondary outcome variables included pelvic and spine BMD, bone markers, and calcium values. Linear regression analysis was used to determine the relationship between baseline values for leg BMD with duration of injury and leg BMD with age. We used a two-factor (group, time) repeated measures analysis of variance (ANOVA) to determine the main and interaction effects for leg, pelvic, and spine BMD (grams per square centimeter). We used a one-sample *t*-test (with 0 as the hypothesized mean) to analyze change from baseline for leg BMD (percent change) within the groups. For variables expressed in their absolute values and with normal distribution, separate within-group analyses performed by a one-way ANOVA with a Fisher post hoc to determine significant differences from baseline at each time point. For variables expressed in their absolute values and without a normal distribution, a Mann-Whitney nonparametric analysis was performed. We used chi-square analysis to determine the differences in the frequency of occurrence between the treatment and placebo groups for mild or moderate/severe hypercalciuria. (Continuous values are expressed as mean ± SD, except where otherwise stated.)

RESULTS

No significant differences were found between the treatment and placebo groups for any of the demographic variables (**Table 1**). At baseline, an inverse relationship was found between leg BMD and duration of injury (r^2 = 0.35, $p < 0.0001$), whereas no such relationship was demonstrated for leg BMD and age (**Figure 1**). No differences were found for any time point for ethnicity, level of lesion, or smoking history for leg BMD. Leg BMD and percent change from baseline significantly increased at 6 (percent change only), 12, 18, and 24 months in the treatment group, but not in the placebo group (**Table 2**). A significant

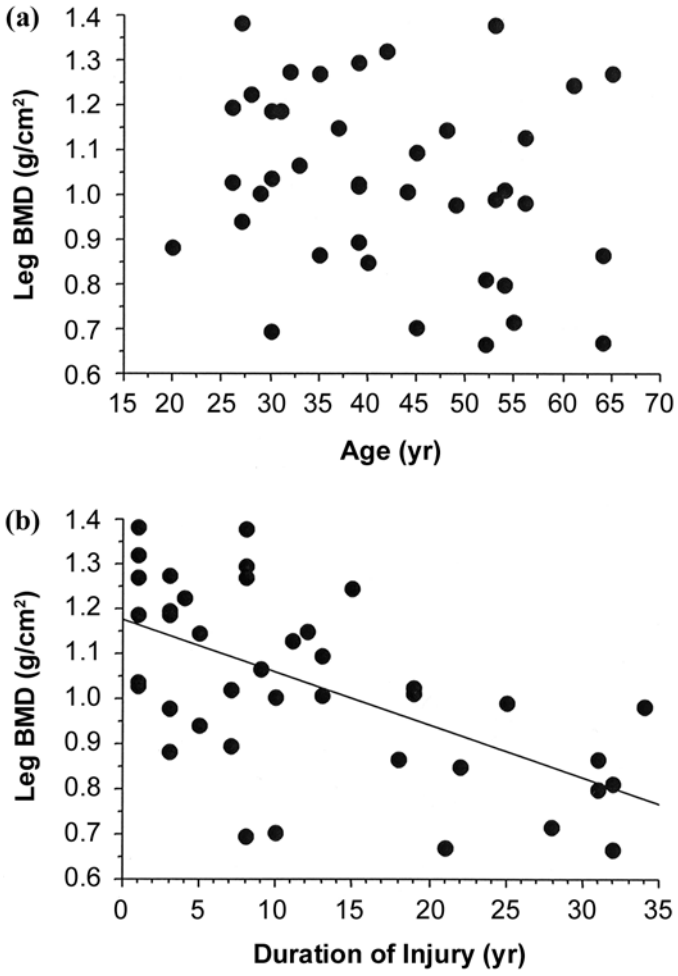

Figure 1.
Leg bone mineral density (BMD) compared with **(a)** age and **(b)** duration of injury. A correlation was found between leg BMD and duration of injury (r^2 = 0.35, $p < 0.0001$), whereas no significant correlation was noted with age (r^2 = 0.04, not significant).

Table 2.
Results of leg bone mineral density (BMD), bone markers, and calcium values (in mean ± standard deviations).

Condition	Normal Range	Intervention	Baseline	Month 6	Month 12	Month 18	Month 24
Leg BMD (g/cm^2)	—	Treatment	1.018 ± 0.240	1.031 ± 0.243	1.039 ± 0.244*	1.041 ± 0.247*	1.040 ± 0.244*
		Placebo	1.045 ± 0.166	1.040 ± 0.166	1.033 ± 0.158	1.033 ± 0.149	1.030 ± 0.144
Urine NTx/Cr (nM BCE/mM)	≤50	Treatment	30 ± 27	17 ± 8*	17 ± 15*	19 ± 9*	20 ± 13*
		Placebo	25 ± 16	25 ± 23	21 ± 10	22 ± 14	27 ± 18
Osteocalcin (ng/mL)	1.7–25.0	Treatment	5.1 ± 4.3	5.1 ± 3.9	4.5 ± 2.4	5.4 ± 4.1	5.4 ± 3.5
		Placebo	5.3 ± 3.2	5.5 ± 3.6	5.3 ± 3.1	4.9 ± 2.4	5.9 ± 3.0
PINP (ng/mL)	21–78	Treatment	25.3 ± 16.7	34.5 ± 29.3	26.0 ± 12.8	32.5 ± 21.9	32.2 ± 19.0
		Placebo	29.1 ± 20.3	29.0 ± 19.6	30.0 ± 18.8	26.8 ± 13.1	38.0 ± 19.6
Urine Calcium (mg/dL)	100–300	Treatment	166 ± 108	250 ± 147	220 ± 98	217 ± 114	221 ± 102
		Placebo	177 ± 109	183 ± 92	215 ± 88	203 ± 87	178 ± 78
Total Calcium (mg/dL)	8.5–10.5	Treatment	9.0 ± 0.5	9.4 ± 0.4	9.6 ± 0.4	9.4 ± 0.5	9.5 ± 0.5
		Placebo	9.3 ± 0.4	9.4 ± 0.4	9.4 ± 0.4	9.3 ± 0.4	9.5 ± 0.5
25 OH Vit D (ng/mL)	16–74	Treatment	11.2 ± 8.4	—	22.9 ± 7.1†	—	—
		Placebo	10.3 ± 5.9	—	22.1 ± 8.0†	—	—
TSH (μU/mL)	0.3–6.5	Treatment	1.9 ± 1.4	—	—	—	—
		Placebo	2.5 ± 2.0	—	—	—	—

*$p < 0.01$ significant difference from baseline.
†$p < 0.0001$ from baseline.
NTx = N-telopeptide of type I collagen, Cr = creatinine, BCE = bone collagen equivalent, PINP = intact N-terminal propeptide of type I collagen, 25 OH = 25-hydroxyvitamin D, TSH = thyroid stimulating hormone.

interaction effect for group by time ($p < 0.05$) was also noted. Additionally, at months 12 and 18, the treatment group had significantly greater increases in percent change for leg BMD than the placebo group (**Figure 2**). In the placebo group, vitamin D and calcium supplementation did not significantly affect leg BMD over the course of the study. At baseline and 24 months, no significant difference was found for pelvic BMD (0.966 ± 0.216 vs 0.944 ± 0.141 g/cm^2, not significant) or spine BMD (1.386 ± 0.248 vs 1.405 ± 0.189 g/cm^2, not significant).

In the treatment group, subjects who never smoked had a significant percent change in leg BMD from baseline at 12 and 24 months ($p < 0.05$ for both time points), whereas current smokers did not respond to the 1α-D_2 treatment (**Figure 3**). In the treatment group at month 24, those who never smoked had a significantly greater increase in percent change in leg BMD than the current smokers. In the placebo group, both those who never smoked and current smokers demonstrated no change from baseline leg BMD (**Figure 3**). In the total group and in the treatment group, baseline values between those who never smoked and current smokers for body mass index, serum 25 hydroxyvitamin D, and serum calcium were not significantly different.

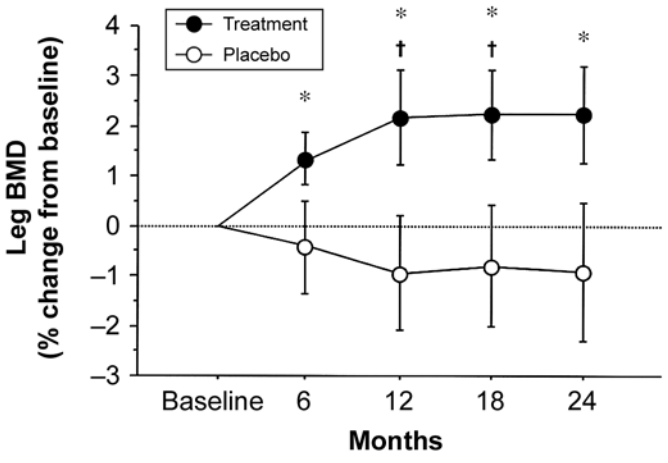

Figure 2.
Percent change in leg bone mineral density (BMD) in treatment (n = 19) and placebo (n = 21) groups. *$p < 0.05$ for percent change from baseline. †$p < 0.05$ for difference between groups.

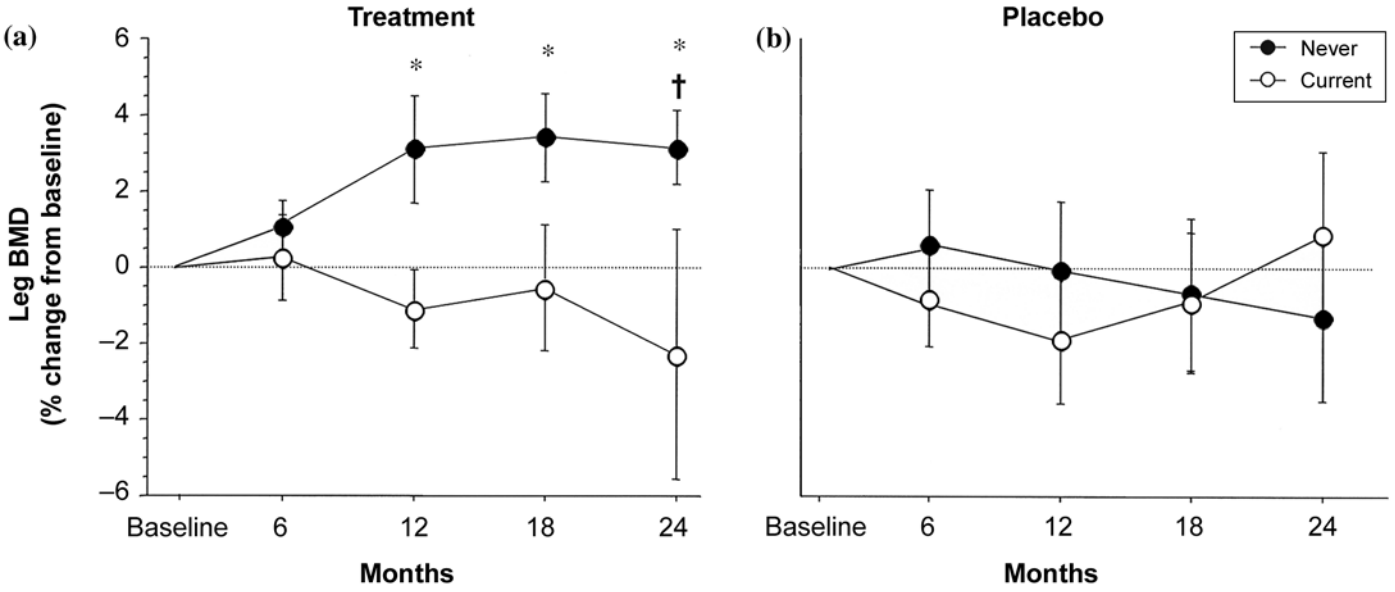

Figure 3.
Percent change in leg bone mineral density (BMD) in **(a)** treatment (n = 14) and **(b)** placebo groups (n = 18) comparing those who never smoked (n = 23, 11 treatment and 12 placebo) versus current smokers (n = 9, 3 treatment and 6 placebo). $^{*}p < 0.05$ for percent change from baseline in group who never smoked. $^{\dagger}p < 0.05$ for difference between groups at 24 months. Values are expressed as mean ± standard error of measurement.

Baseline values for urinary NTx were not significantly different between the treatment and placebo groups (**Table 2**, **Figure 4**). In the treatment group, significant reductions in urinary NTx from baseline occurred at 6, 12, 18, and 24 months (30 ± 27 vs 17 ± 8, 17 ± 15, 19 ± 9, 20 ± 13 nM BCE/mM, $p < 0.05$, respectively), whereas the placebo group had no change from baseline (**Figure 4**). In the treatment group, both those who never smoked and current smokers had reductions in urinary NTx from baseline at all time points; however, only in the group who never smoked at 6 and 12 months did statistically significant reductions occur (29 ± 26 vs 15 ± 4 and 14 ± 8 nM BCE/mM, $p < 0.05$, respectively). Serum osteocalcin and PINP were not significantly different at baseline or any time point between the treatment and placebo groups (**Table 2**), or in the subgroups of those who never smoked and current smokers.

Hypercalcemia did not develop in any subject during the study. At baseline, the average urinary calcium excretion was 167 ± 109 mg/d, and 12 of 40 (30%) subjects had mild or moderate to severe hypercalciuria. On average, the placebo and treatment groups had similar urinary calcium excretions (**Figure 5**). During the study no difference was noted for episodes of mild hypercalciuria between the treatment and placebo groups (**Table 3**). The occurrence of moderate to severe hypercalciuria was noted in both groups, and generally occurred by month 6 in the study protocol (**Table 3**). No statistical difference was found for the occurrence of moderate to severe hypercalciuria between the groups; however, at month 6, moderate to severe hypercalciuria was noted in four subjects in the treatment group versus none in the placebo

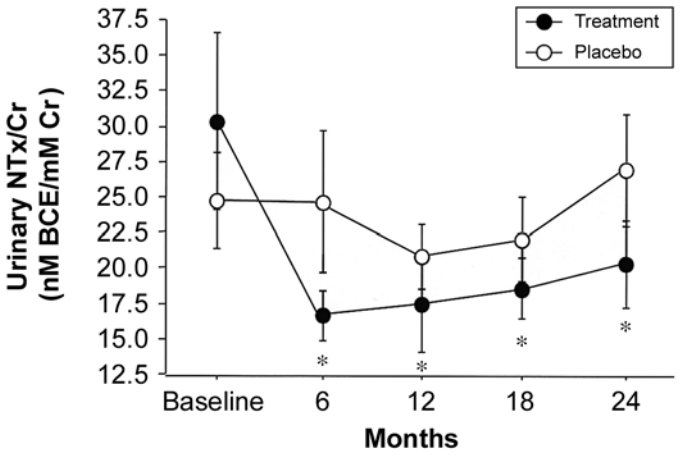

Figure 4.
Urinary N-telopeptide of type 1 collagen concentration (NTx/Cr) in treatment and placebo groups. Values are expressed in nanomoles bone collagen equivalents (nM BCE) per millimole (mM) creatinine (Cr). $^{*}p < 0.05$ for percent change from baseline in treatment group. Values are expressed as mean ± standard error of measurement.

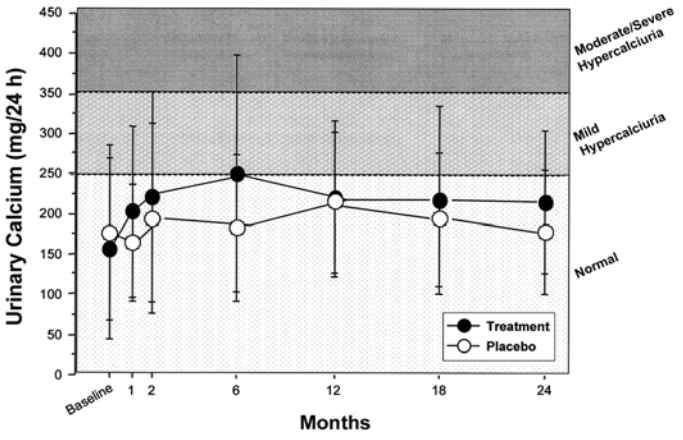

Figure 5.
Average daily urinary calcium excretion in treatment and placebo groups. No significant differences were found between groups for any time point. Values are expressed as mean ± standard deviation.

group. All subjects responded to appropriate calcium and/or 1α-D_2 reductions.

DISCUSSION

In this prospective, controlled trial, administration of a vitamin D analog, 1α-D2, resulted in a slight increase in leg BMD that occurred by 6 months, tended to increase by 12 months, and was maintained while the patient was on the drug over the ensuing 12-month period. This increase was minimal and may be of limited efficacy in restoring BMD loss of the lower limbs in persons with chronic SCI who are at increased risk of fracture. In contrast, in a study that mechanically stimulated the quadriceps in persons with SCI, regardless of muscle contraction against an isokinetic load or not, about a 30 percent recovery was reported of leg BMD lost compared with nondisabled controls [14]. In a study of functional electrical stimulation cycling training for 12 months, BMD of the proximal tibia increased by 10 percent, a modest benefit that was lost over the ensuing 6 months when training sessions were reduced from three times to once a week [15]. Thus, to date, success has been limited with either pharmacological or physical interventions in reversing the large losses of leg bone in persons with SCI [14–16]. In association with the small increase in leg BMD, urinary NTx levels significantly decreased in the treatment group. Interestingly, current smokers in the treatment group, albeit a small number of subjects, did not have a leg BMD response to 1α-D_2 administration, whereas those who never smoked had a significant increase. The lack of drug effect in current smokers cannot be explained by differences in 25 hydroxyvitamin D and serum calcium, because those who never smoked and current smokers had similar values. How smoking prevents the favorable bone effect from treatment with 1α-D_2 is unclear. The administration of 1α-D_2 and calcium was not associated with a significantly increased occurrence of hypercalciuria; moderate/severe hypercalciuria tended to occur more frequently than in the placebo group, which may have reached significance with additional subjects. Hypercalciuria may be assumed to be a consequence of calcium hyperabsorption because the increased calcium excretion responded to reduced supplemental calcium intake, and in one subject, drug dose reduction, with the ability to continue the study.

The rate of formation or degradation of bone matrix may be determined by a quantification of bone cell enzymatic activity or by a measurement of bone matrix components released into the circulation during the process of resorption [17–20]. In our study, the total group on 1α-D_2,

Table 3.
Distribution of occurrence of hypercalciuria.

Condition	Baseline	Month 1	Month 2	Month 6	Month 12	Month 18	Month 24
Normal, *n* (%)							
Treatment	14 (74)	12 (63)	12 (63)	11 (58)	12 (63)	12 (63)	14 (74)
Placebo	14 (67)	17 (81)	14 (67)	13 (62)	14 (67)	16 (76)	17 (80)
Mild Hypercalciuria, *n* (%)							
Treatment	4 (21)	5 (26)	3 (16)	4 (21)	5 (26)	5 (26)	3 (16)
Placebo	6 (29)	4 (19)	5 (24)	8 (38)	5 (24)	4 (19)	3 (14)
Moderate/Severe Hypercalciuria, *n* (%)							
Treatment	1 (5)	2 (11)	4 (21)	4 (21)	2 (11)	2 (11)	2 (11)
Placebo	1 (5)	0 (0)	2 (10)	0 (0)	2 (11)	1 (5)	1 (5)

as well as the subgroup of those who never smoked, had a decrease in urinary N-telopeptide excretion. No significant changes were found in markers of bone formation with treatment. However, in a study of 15 postmenopausal women after administration of 1α-D_2, a dose-dependent increase in serum osteocalcin was demonstrated [21]. The differential effect of 1α-D_2 on leg BMD in those who never smoked compared with current smokers may have been due to accelerated metabolism of 1α-D_2 associated with nicotine and the induction of the P450 hepatic microsomal fraction [22–23]. In addition, smoking has been demonstrated to have direct and indirect effects on the osteoblast. Smoking has been reported to reduce osteocalcin levels, suggesting inhibition of the osteoblast [24], albeit a finding not confirmed in this study. In rabbits in vivo, nicotine has been shown to inhibit expression of a wide range of cytokines, including those associated with osteoblast differentiation [25], and has been shown to reduce osteoblast differentiation in calvarial cells in vitro [26].

The results of our study with 1α-D_2 can be compared with those obtained with other vitamin D compounds in other conditions associated with osteoporosis. These include 1,25$(OH)_2D_3$ and 1α-D_3 in postmenopausal osteoporosis, senile osteoporosis, and stroke.

The therapeutic efficacy of 1,25$(OH)_2D_3$ has been demonstrated in the treatment of postmenopausal osteoporosis [8–9,27–29]. After 2 years of therapy with 1,25$(OH)_2D_3$ (mean dose of 0.62 μg/d) in 50 postmenopausal woman, spine BMD increased 1.94 percent compared with a decrease of 3.92 percent in the placebo group, and this therapy was associated with a significant reduction in vertebral fracture rates [8,28]. Of note, discontinuance of 1,25$(OH)_2D_3$ therapy after treatment for a year and a half resulted in a rapid decrease in spine density [29]. In a study of 622 women with postmenopausal osteoporosis and vertebral compression fractures, the subjects were randomly assigned to receive 1,25$(OH)_2D_3$ (0.25 μg twice a day) or supplemental calcium; the women who received 1,25$(OH)_2D_3$ had a significant reduction in the rate of new vertebral fractures, as well as peripheral fractures, during the second and third years of therapy compared with those who received calcium alone [9]. Despite the apparent therapeutic efficacy of using 1,25$(OH)_2D_3$ in the treatment of postmenopausal osteoporosis, the fairly narrow range of dosing to prevent possible complications associated with increased calcium absorption has led to the development of 1α derivatives of vitamin D.

Shiraki et al. retrospectively studied the effect of 5 years of treatment of 1α-D_3 in subjects with senile osteoporosis and found a 6 percent increase in radial mineral density at the peripheral cortical site compared with an 11 percent decrease in the untreated subjects [10]. In another report, 80 postmenopausal osteoporotic Japanese women received 1 μg of 1α-D_3 or a placebo for 1 year; lumbar BMD increased 0.65 percent in those treated and fell 1.14 percent in those untreated. Additionally, the vertebral fracture rate was significantly reduced in the treated compared with the placebo group [27]. A subsequent report by this group demonstrated a greater increase in BMD after 1 and 2 years of treatment with 1α-D_3, with increases in lumbar BMD of 1.81 and 2.32 percent, respectively [30].

Osteoporosis occurs on the hemiplegic side of stroke patients. In 64 chronic stroke patients randomized to receive drug or placebo therapy, the efficacy of 1α-D_3 (1.0 μg/d) and supplemental calcium (300 mg/d) was studied. Reductions in BMD on the hemiplegic side were attenuated in the treatment group compared with the placebo group (2.4% vs. 8.9%) [11]. Thus, in a form of neurologically induced immobilization, a vitamin D analog has reduced bone loss on the weak side, which may be expected to reduce the incidence of hip fractures.

CONCLUSIONS

A treatment of 1α-D_2 (4 μg daily) increased lower-limb BMD at 6 months, which continued to 24 months, compared with placebo administration. This favorable effect on bone was not evident in the subgroup of current smokers; additional investigation in a larger number of subjects is needed to confirm the apparent antagonistic effect of nicotine on 1α-D_2 treatment. Of note, reductions in a marker of bone resorption, urinary NTx, was demonstrated at several time points. The long-term effect of continued 1α-D_2 therapy in persons with chronic SCI requires further investigation. Combined therapy of an antiresorptive agent with 1α-D_2, as well as therapy with an antiresorptive agent after discontinuation of the vitamin D analog, should be investigated. Finally, the potential synergistic effects of pharmacological therapy and a physical intervention, possibly with a form of mechanical loading, may be considered.

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