MINIREVIEW

Vitamin D in the Treatment of Osteoporosis

(43371C)

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Osteoporosis is mainly treated with estrogen as the hormone replacement therapy in the United States and Europe. Intestinal calcium absorption is decreased in calcium deficiency in old age due to an impaired action of vitamin D and vitamin D derivatives that are capable of correcting these abnormalities (1, 2). Despite these facts, treatment with the metabolically active hormonal form of vitamin D has never been seriously considered as a candidate for an agent in hormone replacement therapy because of the conflicting results so far obtained on the effect of vitamin D derivatives on osteoporosis. In Japan, on the other hand, vitamin D has been most widely used for osteoporosis over the last 10 years, whereas scarcely any estrogen has been used. According to the 1990 Consensus Statement on Osteoporosis announced in Copenhagen, "The positive effect of 1,25-$(OH)_2$ vitamin D_3 and 1α-hydroxyvitamin D_3 on fracture incidence disclosed in some studies in osteoporotic subjects may reflect promotion of calcium absorption, especially in the elderly and those on low calcium intake." The discrepancy in the usefulness of vitamin D derivatives in different parts of the world may be explained, at least in part, by the various degrees of calcium and vitamin D deficiency in each area. As a step toward properly evaluating the usefulness of vitamin D derivatives in the treatment of osteoporosis, reports made so far on the effect of vitamin D derivatives in osteoporotics are reviewed for evaluation and analysis.

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P.S.E.B.M. 1992, Vol 199:394–399

0037-9727/92/1994-0394$3.00/0

Background: The Role of Vitamin D in the Pathogenesis of Osteoporosis

Intestinal Ca absorption decreases with advancing age, and such a decrease is especially pronounced in osteoporotics (3). The decrease in calcium absorption is associated with postmenopausal estrogen deficiency and may be corrected by estrogen administration (4). Decrease of 1,25-$(OH)_2$ vitamin D biosynthesis by the kidney on account of the aging of the kidney itself or estrogen deficiency may also contribute. Changes in the levels of vitamin D metabolites with age were also reported with controversy. Serum 1,25-$(OH)_2$ vitamin D was reported to decrease (5) or be unchanged (6) in aging. Serum 25-(OH) vitamin D was also reported to decrease or to show no change with aging, probably reflecting the level of vitamin D intake and solar exposure in the population. Aging of the intestine itself may be manifested by a decrease in the number of 1,25-$(OH)_2$ receptors in the intestinal mucosal cells.

Estrogen stimulates renal 1,25-$(OH)_2$ vitamin D synthesis (7) and is probably necessary to maintain this process. Estrogen administration increases 1,25-$(OH)_2$D in the blood of patients with postmenopausal osteoporosis (8). Early postmenopausal bone loss, however, was not associated with remarkable changes in vitamin D metabolites or vitamin D-binding protein in plasma (9). No significant changes in vitamin D metabolites were detected with reference to age and menopause up to the age of 75 years. In elderly patients with osteoporosis, 1,25-$(OH)_2$ vitamin D production from 25-(OH) vitamin D was impaired compared with young subjects (10).

The function of the kidney itself to produce 1,25-$(OH)_2$ vitamin D in response to exogenous stimuli, however, seems to be well preserved (11, 12). The administration of 25-(OH) vitamin D in osteoporotic subjects raised serum 1,25-$(OH)_2$ vitamin D and 24,25-$(OH)_2$ vitamin D effectively (13). According to another

group of investigators, however, the administration of vitamin D in elderly subjects was accompanied by a rise of 25-(OH) vitamin D, but not in 1,25-$(OH)_2$ vitamin D (14). The state of vitamin D deficiency in elderly postmenopausal subjects may be subclinical. According to Villareal *et al.* (15), 49 of 539 Midwestern women screened for osteoporosis showed low serum 25-(OH) vitamin D below 38 nmol/liter. Vertebral bone mineral content was low under a significant correlation with the serum 25-(OH) vitamin D level. Most of these women were also deficient in solar exposure. When serum 1,25-$(OH)_2$D was compared between pre- and postmenopausal women, it was lower in the latter than in the former (16).

According to Berlyne *et al.* (17), progressive renal failure in advancing age with a consequent fall in the production of 1,25-$(OH)_2$ vitamin D may be responsible for osteoporosis in aging, but bone changes in chronic renal failure is different from senile osteoporosis (18). The aging of the intestine itself with or without a decrease in receptors for 1,25-(OH) vitamin D also remains a possibility (19). According to Aksenes *et al.* (20), active elderly subjects between 70 and 96 years of age living at home exhibited a normal serum level of 1,25-(OH) vitamin D.

In order to define the role of vitamin D as a background factor for osteoporosis, it is essential to make a distinction between the immediate postmenopausal period and the later period with more advanced age. During a few years after menopause, the effect of estrogen withdrawal is so dramatic as to overshadow the participation of vitamin D or calcium deficiency in the development of osteoporosis. Since osteoporosis is also seen in men, factors other than estrogen deficiency must be playing some part. The participation of vitamin D deficiency in the development of osteoporosis, if any, would, therefore, be more clearly recognized in higher age, when the influence of estrogen withdrawal is wearing out and the impairment of renal production of 1,25-$(OH)_2$ vitamin D and calcium deficiency should be more pronounced.

Vitamin D deficiency and even osteomalacia may be prevalent in patients with hip fracture, the most serious complication of osteoporosis (21, 22). No difference in vitamin D metabolites, however, was found between subjects with and those without hip fracture, according to Weisman *et al.* (23). The nutritional status of the background population appears to be important to explain such a discrepancy.

Metabolic Effects of Vitamin D in Patients with Osteoporosis

From the earliest period of the clinical trial of vitamin D derivatives, an increase of intestinal calcium absorption was demonstrated. On daily administration of 0.5 μg of 1,25$(OH)_2$ vitamin D for 6 months, Haas *et al.* (24) found a marked increase of fractional calcium absorption from 21% to 45%, together with a doubling of urinary calcium excretion. The calcium balance became positive in three of the four subjects studied. Riggs and Gallagher's group and Caniggia's group (25–32) extensively studied the effect of 1,25-$(OH)_2$ vitamin D_3 on calcium metabolism, demonstrating a definite increase of intestinal calcium absorption, an increase of urinary calcium excretion, and an occasional rise of serum calcium. Similar metabolic effects were reported by Lips *et al.* (33). Urinary hydroxyproline excretion did not increase and the urinary calcium to hydroxyproline ratio even decreased, indicating that no augmentation of bone resorption is responsible for the increase of urinary calcium excretion.

Tjellesen *et al.* (34), on the other hand, failed to see any change of parameters of bone metabolism in response to 1,25-$(OH)_2$ vitamin D_3 in a group of immediate postmenopausal women and another group of 70-year-old women. Despite the increase of urinary calcium excretion inevitably accompanying administration of vitamin D derivatives, formation of kidney stones or development of nephrocalcinosis has been scarcely reported.

Effect of Vitamin D on Osteoporotic Bone. Since the first report on the use of vitamin D treatment of osteoporosis by Lund *et al.* (35), many groups of investigators have tested either 1α-(OH) vitamin D or 1,25-$(OH)_2$ vitamin D, but the evaluation of the effect has been controversial. Table I summarizes the reports of positive effects of vitamin D on osteoporosis (35–58), whereas Table II lists reports of negative effects.

Taking a glance at these two tables, there seems to be almost as many reports on the negative effects of vitamin D on osteoporosis as those on the positive effects, indicating controversial conclusions. The average dose employed appears to be slightly higher in reports on the positive effects, 0.6 ± 0.2 μg, than in those on the negative effect, 0.4 ± 0.1 μg, suggesting a threshold dose around 0.5 μg for the beneficial effect of 1,25-$(OH)_2$ vitamin D_3 on osteoporosis. Approximately twice as much as 1α-(OH) vitamin D_3 as 1,25-$(OH)_2$ vitamin D_3 seems to be required to achieve the same effect, so that the doses in Tables I and II were expressed as μg 1,25-$(OH)_2$ vitamin D_3 equivalent. Mean duration of administration appeared to be similar between the two groups of reports, 19 ± 12 (for positive effect) and 19 ± 11 (for negative effect) months. Several extensive and some careful studies on the fracture rate in osteoporotics under vitamin D treatment revealed a reduced rate of fracture occurrence, whereas evidence against it has not been convincingly presented (37, 39, 46, 47). Over the past 10 years, the method of bone measurement has evolved from radiogrammetry to single and dual photon absorptiometry and finally to dual energy x-ray absorptiometry. During this time, the classical

Table I. Reports on Positive Effects of Vitamin D on Osteoporosis[a]

Author (ref)	Year	Country	Dose (prep) (μg/day)	Duration (mos)	No. of patients	Age (yr)	Comments
Lund (35)	1975	Denmark	(1 α) 1	4	7	65–81	SPA forearm
Sørensen (36)	1977	Denmark	(1 α) 1	6	26	65–89	SPA forearm
Haas (24)	1979	Switzerland	(1,25) 0.5	6	4	52–67 (59 ± 3)	Biopsy
Krølner (37)	1980	Denmark	(1 α) 0.25–0.75	24	21	Postmenopausal	DPA spine
Itami (38)	1982	Japan	(1 α) 0.375	7	456	60–90	Metacarpal radiogram-metry
Recker (39)	1984	USA	(1,25) 0.5	24–26	30	Postmenopausal	Fracture rate
Caniggia (29)	1985	Italy	(1,25) 1.0	48	120	49–78 (64)	SPA forearm fracture rate
Shiraki (40)	1985	Japan	(1 α) 0.5	24	43	72 (mean)	SPA forearm
Orimo (41)	1987	Japan	(1 α) 0.5	20	47	69–73	Fracture rate
Fujita (42, 43)	1988	Japan	(1,25 & 1 α) 0.5	7	596	60–90	Metacarpalradiogram-metry
Aloia (44, 45, 46)	1988	USA	(1,25) 0.8	24	27	64 ± 2	DPA spine
Gallagher (47)	1990	USA	(1,25) 0.5	36	62	61–65	Fracture rate
Gallagher (48)	1990	USA	(1,25) 0.62	24	50	70 ± 6	Total body calcium
Tilyard (49)	1990	New Zealand	(1,25) 0.25	12	1055	64 (mean)	Fracture rate
Caniggia (32)	1990	Italy	(1,25) 1.0	12–96	270	49–78 (mean 63)	DPA total body calcium fracture rate

[a] Dose expressed as 1,25-$(OH)_2$ vitamin D_3 equivalent: dose of 1α-(OH) vitamin D_3 was divided by two.

Table II. Reports on Negative Effects of Vitamin D on Osteoporosis[a]

Author (ref)	Year	Country	Dose (prep) (μg/day)	Duration (mos)	No. of patients	Age (yr)	Comments
Hoikka (50)	1980	Finland	(1 α) 0.5	4	37	73–75	SPA forearm biopsy
Christiansen (51)	1981	Den-mark	(1,25) 0.25	12	46	45–55 (49)	SPA forearm
Lindholm (52)	1982	Sweden	(1 α) 0.25–1.0	36	10	54–64	DPA spine
Jensen (53)	1985	Den-mark	(1,25) 0.4	12	41	70	Vertebral height
Need (54)	1986	Australia	(1,25) 0.25		37	65 ± 1	SPA forearm
Felch (55)	1987	Norway	(1,25) 0.5	36	76	50–65 (60 ± 3)	SPA forearm
Ott (56, 57)	1989	USA	(1,25) 0.4	24	86	67 ± 1	DPA total body calcium
Arthur (58)	1990	USA	(1,25) 0.5	12	10	More than 60	Biopsy

[a] Dose expressed as 1,25-$(OH)_2$ vitamin D_3 equivalent: dose of 1α-(OH) vitamin D_3 was divided by two.

method of calculation of fracture rate has been used persistently. Changes in the method of evaluation so far have made a consistent long-term evaluation somewhat difficult. Because of government authorization, so far more reports have come from Europe and Japan than from the United States. Mean age of the patients studied was estimated to be 65 ± 4 years in the positive group and 60 ± 3 years in the negative group, i.e., slightly younger in the latter. It may be easier to obtain positive results in test subjects of higher age.

It is also tempting to speculate that the effect of vitamin D is related to the current and previous calcium and vitamin D intake, because replacement of any deficiency is easier than pharmacologic intervention in repletion. In Italy and Japan, the effect of vitamin D may be more apparent than in Scandinavian and other Northern European countries. The decisive factor may be the interest and persistence of the investigators in carrying out a long-term study, which might possibly detect the effects that would otherwise remain unnoticed.

The mechanism of action of low and high dose vitamin D may be different. In order to overcome calcium deficiency and secondary hyperparathyroidism, a low dose approximating the daily synthesis and secretion may be sufficient as a form of hormone replacement therapy, but higher doses will be required to utilize the pharmacologic effects of vitamin D, such as stimulation of differentiation and activation of bone cells for the treatment of osteoporosis. An increase of insulin-like growth factor-I receptor in osteoblasts by 1,25-$(OH)_2$ vitamin D_3 was also reported (59).

The problem of overdose cannot be avoided. A high enough dose of vitamin D will always cause hypercalcemia, hypercalciuria, and renal calcification accompanied by impairment of renal function. A high dietary intake of calcium would make administration of a higher dose of vitamin D more risky than would a low calcium intake diet. According to Gallagher, a calcium intake of 500 mg/day would make administration of 0.5 μg of 1,25-$(OH)_2$ vitamin D_3 safer than would a 1000-mg calcium intake (27). It is of interest that 500 mg is a common daily calcium intake among the elderly Japanese population, since this may explain a surprising safety of vitamin D among Japanese (43). Among 9987 patients treated with 1α-(OH) vitamin D_3, a rise in serum creatinine or blood urea nitrogen was seen in only eight patients and kidney stone was seen in one.

The side effects of vitamin D may be more frequent in countries where calcium and vitamin D intake is more abundant. Neither deterioration of kidney function nor renal stones developed during the 8-year clinical trial by Caniggia *et al.* (32). Schwartzman and Franck (60), on the other hand, described vitamin D intoxication in four patients with senile osteoporosis treated with vitamin D derivatives. According to Gallagher *et al.* (47), hypercalcemia and hypercalciuria may occur during the first few weeks of the dose titration procedure, but seldom after establishment of the safe maintenance dose.

Conclusion

Although the results of clinical trials of vitamin D on postmenopausal and senile osteoporosis are still controversial, higher doses, a longer duration of treatment, and more sensitive methods of measurement tend to give positive results, regardless of the location of the community. Nutritional background may also contribute to the achievement and possibly the appearance of side effects due to overdose. A decreased fracture rate in response to vitamin D treatment was pointed out by several reports and should be further looked into carefully. Side effects, especially hypercalcemia, hypercalciuria, and kidney stones with consequent decline of renal function, should be carefully weighed against the potential benefit of the treatment. Dietary calcium intake should be monitored with reference to the dose of vitamin D to avoid side effects.

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