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Vitamin D Therapy of Osteoporosis: Plain Vitamin D Therapy Versus Active Vitamin D Analog (D-Hormone) Therapy

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Abstract. Normal intestinal calcium (Ca) absorption is an essential feature of bone homeostasis. As with many other organ systems, intestinal Ca absorption declines with aging, and this is one pathological factor that has been identified as a cause of senile osteoporosis in the elderly. This abnormality leads to secondary hyperparathyroidism, which is characterized by high serum parathyroid hormone (PTH) and an increase in bone resorption. Secondary hyperparathyroidism due to poor intestinal Ca absorption has been implicated not only in senile osteoporosis but also in age-related bone loss. Accordingly, in population-based studies, there is a gradual increase in serum PTH from about 20 years of age onward, which constitutes a maximum increase at 80 years of age of 50% of the basal value seen at 30 years of age. The cause of the increase in PTH is thought to be partly due to impaired intestinal Ca absorption that is associated with aging, a cause that is not entirely clear but at least in some instances is related to some form of vitamin D deficiency. There are three types of vitamin D deficiency: (1) primary vitamin D deficiency, which is due to a deficiency of vitamin D, the parent compound; (2) a deficiency of $1,25(OH)_2D_3$ resulting from decreased renal production of $1,25(OH)_2D_3$; and (3) resistance to $1,25(OH)_2D_3$ action owing to decreased responsiveness to $1,25(OH)_2D_3$ of target tissues. The cause for the resistance to $1,25(OH)_2D_3$ could be related to the finding that the vitamin D receptor level in the intestine tends to decrease with age. All three types of deficiencies can occur with aging, and each has been implicated as a potential cause of intestinal Ca malabsorption, secondary hyperparathyroidism, and senile osteoporosis. There are two forms of vitamin D replacement therapies: plain vitamin D therapy and active vitamin D analog (or D-hormone) therapy. Primary vitamin D deficiency can be corrected by vitamin supplements of 1000 U a day of plain vitamin D whereas $1,25(OH)_2D_3$ deficiency/resistance requires active vitamin D analog therapy [$1,25(OH)_2D_3$ or $1\alpha(OH)D_3$] to correct the high serum PTH and the Ca malabsorption. In addition, in the elderly, there are patients with decreased intestinal Ca absorption but with apparently normal vitamin D metabolism. Although the cause of poor intestinal Ca absorption in these patients is unclear, these patients, as well as all other patients with secondary hyperparathyroidism (not due to decreased renal function), show a decrease in serum PTH and an increase in Ca absorption in response to therapy with $1,25(OH)_2D_3$ or $1\alpha(OH)D_3$. In short, it is clear that some form of vitamin D therapy, either plain vitamin D or $1,25(OH)_2D_3$ or $1\alpha(OH)D_3$, can be used to correct all types of age-dependent impairments in intestinal Ca absorption and secondary hyperparathyroidism during aging. However, from a clinical standpoint, it is important to recognize the type of vitamin D deficiency in patients with senile osteoporosis so that primary vitamin D deficiency can be appropriately treated with plain vitamin D therapy, whereas $1,25(OH)_2D_3$ deficiency/resistance will be properly treated with $1,25(OH)_2D_3$ or $1\alpha(OH)D_3$ therapy. With respect to postmenopausal osteoporosis, there is strong evidence that active vitamin D analogs (but not plain vitamin D) may have bone-sparing actions. However, these effects appear to be results of their pharmacologic actions on bone formation and resorption rather than through replenishing a deficiency.

Key words: Osteoporosis — Vitamin D therapy — Calcitriol therapy — Alfacalcidol therapy (human).

Osteoporosis is characterized by the decrease in bone mass and the deterioration of microarchitectural integrity of bone tissues, leading to an impaired bone strength and an increased risk for nontraumatic bone fractures. The two forms of primary osteoporosis are postmenopausal (type I) and senile (type II). Although the pathogenesis of these two forms is different, there is evidence that in both types the efficiency of Ca absorption is impaired. Evidence of the latter is far more convincing in the senile than in postmenopausal osteoporosis [1–5]. This abnormality leads to secondary hyperparathyroidism, characterized by high serum PTH and an increase in bone resorption, which subsequently results in bone loss and osteoporosis [6, 7]. Thus, the aging-related Ca malabsorption has been implicated as one of the potential causes of osteoporosis in the elderly. The major physiologic regulator of intestinal Ca absorption is vitamin D. Accordingly, a potential cause of the aging-related Ca malabsorption is the vitamin D deficiency that frequently occurs with advancing age [8–10]. Moreover, vitamin D deficiency has often been associated with senile osteoporosis and fragility fractures [11]. Thus, the aging-related vitamin D deficiency[1] is a significant risk factor of age-related bone loss and senile osteoporosis [12].

There are currently two forms of vitamin D replacement therapy for osteoporosis: that which treats patients with vi-

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[1] *Classically, vitamin D deficiency is thought to cause osteomalacia. This is true for severe vitamin D deficiency, whereas mild vitamin D deficiency, where the serum calcium is usually in the normal range, causes osteoporosis and not osteomalacia.*

tamin D_2 or D_3, parent compounds of the active metabolite, $1,25(OH)_2D_3$ (we refer to this form as the plain vitamin D therapy); and that which uses the active vitamin D metabolite [i.e., $1,25(OH)_2D_3$ (calcitriol)] or an active analog [e.g., $1\alpha(OH)D_3$ (alfacalcidol)] as the therapeutic agent (we refer to this as the active vitamin D analog or D hormone therapy). Primary vitamin D therapy is effective in primary vitamin D deficiency, but not in patients who have Ca malabsorption as a consequence of a deficiency or a resistance to $1,25(OH)_2D_3$. The finding that both forms of therapy are effective in specific types of vitamin D deficiency has led to a disagreement over whether there are sufficient therapeutic differences between the two therapies to justify the need of the relatively more expensive active vitamin D analog therapy [13].

Types of Vitamin D Deficiency

Vitamin D deficiency collectively describes a number of pathophysiological conditions that are characterized by an inadequate amount or insufficient biological action of $1,25(OH)_2D_3$. Theoretically, vitamin D deficiency can be caused by (1) inadequate supplies of the precursors, vitamin D and/or $25(OH)D_3$, leading to insufficient production of $1,25(OH)_2D_3$ (primary vitamin D deficiency); (2) reduced abilities of the kidney to produce $1,25(OH)_2D_3$ [$1,25(OH)_2D_3$ deficiency]; and (3) reduced responsiveness of target organs to $1,25(OH)_2D_3$ actions [$1,25(OH)_2D_3$ resistance]. Thus, there can be three different subtypes of vitamin D deficiency.

Primary Vitamin D Deficiency

Primary vitamin D deficiency is caused by an inadequate supply of the precursors, i.e., vitamin D and/or $25(OH)D_3$, resulting in low serum levels of $1,25(OH)_2D_3$. Vitamin D is photosynthesized in the skin in response to the UVB light of sunlight or obtained through dietary sources. Inadequate sunlight exposure, which is regularly seen in countries of northern latitudes [14], or insufficient nutritional vitamin D intake, which is a common problem of the elderly [15], are frequent causes of primary vitamin D deficiency. The photosynthesized or absorbed vitamin D undergoes 25-hydroxylation to produce $25(OH)D_3$ in the liver. This hepatic hydroxylation is unregulated and solely substrate dependent. The $25(OH)D_3$ is converted to the physiologically active $1,25(OH)_2D_3$ in the kidney by the renal 25(OH)D-1α-hydroxylase. An inadequate vitamin D supply would lead to reduced levels of $25(OH)D_3$, which then limits the $1,25(OH)_2D_3$ production, resulting in low $1,25(OH)_2D_3$ levels,[2] i.e., vitamin D deficiency [16]. Thus, a low serum $25(OH)D_3$ level is a frequently used diagnostic hallmark for primary vitamin D deficiency. Primary vitamin D deficiency is not merely a biochemical abnormality, it is also regularly associated with secondary hyperparathyroidism, increased bone turnover, bone loss, osteoporosis [16, 17], and an increased risk of fractures [18, 19]. Consequently, the aging-associated primary vitamin D deficiency is a significant clinical problem for the elderly.

$1,25(OH)_2D_3$ Deficiency[3]

Primary $1,25(OH)_2D_3$ deficiency, unlike primary vitamin D deficiency, is not due to the limitation of precursors, e.g., vitamin D and/or $25(OH)D_3$, but rather, is caused by a defect in the synthesis of $1,25(OH)_2D_3$. $1,25(OH)_2D_3$ deficiency would then cause a decrease in intestinal Ca absorption, increased serum PTH, and increase bone resorption, bone loss, and osteoporosis. The pathogenesis of primary $1,25(OH)_2D_3$ deficiency is related to an impaired ability of the kidney to synthesize adequate amounts of $1,25(OH)_2D_3$ rather than an inadequate supply of the substrate $25(OH)D_3$. Thus, primary $1,25(OH)_2D_3$ deficiency is common in patients with renal insufficiency or renal failure, or other renal diseases. Accordingly, low serum levels of $25(OH)D_3$ would not be a characteristic of $1,25(OH)_2D_3$ deficiency. Conversely, typical diagnostic criteria of $1,25(OH)_2D_3$ deficiency are low serum $1,25(OH)_2D_3$, normal serum $25(OH)D_3$, Ca malabsorption, secondary hyperparathyroidism, increased bone turnover, and bone loss.

$1,25(OH)_2D_3$ Resistance

The aging-associated decline in functions of various tissues and organs in the elderly can produce resistance of target organs to $1,25(OH)_2D_3$, leading to reduced $1,25(OH)_2D_3$ biological actions. Accordingly, higher levels of $1,25(OH)_2D_3$ will be needed in patients with the $1,25(OH)_2D_3$ resistance to acquire the same levels of $1,25(OH)_2D_3$ biological actions as those seen in normal individuals. Thus, the "normal" $1,25(OH)_2D_3$ levels, which are adequate for normal subjects, would be insufficient to meet the physiological needs of resistant patients. Hence, $1,25(OH)_2D_3$ resistance may be considered as a form of secondary $1,25(OH)_2D_3$ deficiency. However, $1,25(OH)_2D_3$ resistance, unlike $1,25(OH)_2D_3$ deficiency which has a lower serum $1,25(OH)_2D_3$ level, would be expected to show normal or slightly elevated (due to feedback regulation) serum $1,25(OH)_2D_3$. On the other hand, in spite of elevated levels of serum $1,25(OH)_2D_3$, these patients would exhibit all the metabolic features of vitamin D deficiency; i.e., reduced intestinal Ca absorption, secondary hyperparathyroidism, increased bone turnover, and bone loss. Consequently, a typical patient with $1,25(OH)_2D_3$ resistance would have normal serum $25(OH)D_3$ levels, normal or slightly elevated serum $1,25(OH)_2D_3$ levels, but at the same time would exhibit reduced intestinal Ca absorption, sec-

[2] *During the development of a deficiency of $1,25(OH)_2D_3$, there is first a decrease in the level of $1,25(OH)_2D_3$, which results in an increase in serum PTH, which in turn raises the $1,25(OH)_2D_3$ level back to the normal level, though it may be a low normal level. Thus, one can have deficiency of $1,25(OH)_2D_3$ that is not always apparent. At the new equilibrium, there is a high serum PTH and a normal or low normal serum $1,25(OH)_2D_3$, changes that together result in increased bone resorption and thus bone loss.*

[3] *There is a progressive decrease in Ca absorption efficiency (i.e., percent of the oral load of Ca that is absorbed) as a function of aging, with a marked reduction in efficiency in the elderly. We assume that this reduction in Ca absorption efficiency is a consequence of a decreased action of $1,25(OH)_2D_3$. The basis for this assumption is that, invariably, the malabsorption of Ca in the elderly can be corrected by $1,25(OH)_2D_3$ therapy. This latter action of $1,25(OH)_2D_3$ constitutes presumptive, but not definitive, evidence for decreased $1,25(OH)_2D_3$ action as the cause of the Ca malabsorption in the elderly.*

ondary hyperparathyroidism, increased bone resorption, bone loss, and osteoporosis.

Vitamin D Deficiency and Aging

There is ample evidence that aging, even in apparently healthy individuals, is frequently associated with the primary vitamin D deficiency, as reflected by a progressive decline in serum $25(OH)D_3$ levels and a mild progressive increase in serum PTH [20, 21]. Primary vitamin D deficiency is an even more frequent problem for hospitalized or house-bound patients. For instance, a recent report indicated that 57% of patients in a large medical service showed low serum $25(OH)D_3$ levels, indicating just how widespread this deficiency may be [22]. Accordingly, primary vitamin D deficiency is prevalent in the elderly, especially those who live in institutions or are housebound and those who live in countries where sunlight is limited and/or where food is not fortified with vitamin D [23]. Therefore, primary vitamin D deficiency may be related to insufficient sunlight exposure and/or poor nutritional intake in the elderly population.

There is evidence that $1,25(OH)_2D_3$ deficiency is also a prevalent problem for the elderly. In this regard, there are reports that a significant number of elderly women, especially those over 65 years of age, had significantly lower levels of serum $1,25(OH)_2D_3$, even though their serum $25(OH)D_3$ levels were well within normal ranges [9,24–26]. There is also evidence for a progressive decline in renal function with age, leading to reduction in the renal 25(OH)D-1α-hydroxylase activity and a decrease in $1,25(OH)_2D_3$ production [9,27]. The response to a 24-hour PTH (a stimulator of renal 25(OH)D-1α-hydroxylase) infusion to produce $1,25(OH)_2D_3$ was also significantly lower in elderly women compared with that in younger women [9,26]. This reduction in response correlated inversely and significantly with age. The inability to produce $1,25(OH)_2D_3$ in response to the PTH challenge was more pronounced in the elderly women with hip fractures than in those without the fracture [27] and also, as shown in Figure 1, in patients with osteoporosis than in normal subjects [28]. In addition, a recent study indicated that dietary Ca deprivation (a potent activator of $1,25(OH)_2D_3$ synthesis) also failed to stimulate the $1,25(OH)_2D_3$ synthesis in patients with osteoporosis in contrast to the age-matched control subjects [29], further supporting the fact that a defect in renal 25(OH)D-1α-hydroxylase could be responsible for $1,25(OH)_2D_3$ deficiency in elderly patients with osteoporosis.

There is circumstantial evidence that $1,25(OH)_2D_3$ resistance may also be present in some elderly subjects. In this regard, it has been reported that serum $1,25(OH)_2D_3$ in a large number of elderly women either increased [24, 25, 30, 31] or remained unchanged [30–34] with age, notwithstanding that they all exhibited an aging-related decline in intestinal Ca absorption and increased serum PTH levels. These findings are consistent with the interpretation that these elderly women exhibited an intestinal resistance to the calcemic action of $1,25(OH)_2D_3$. A potential cause of the resistance may be due to defects in the regulation in the number of vitamin D receptors (VDR) which mediate genomic actions of vitamin D [35]. Figure 2, which shows a progressive decrease in the intestinal VDR level as a function of age, ranging from 20 to 90 years [31], supports the contention that $1,25(OH)_2D_3$ resistance is related to an age-associated reduction in VDR concentrations in target tissues. On the other hand, a recent study revealed that many

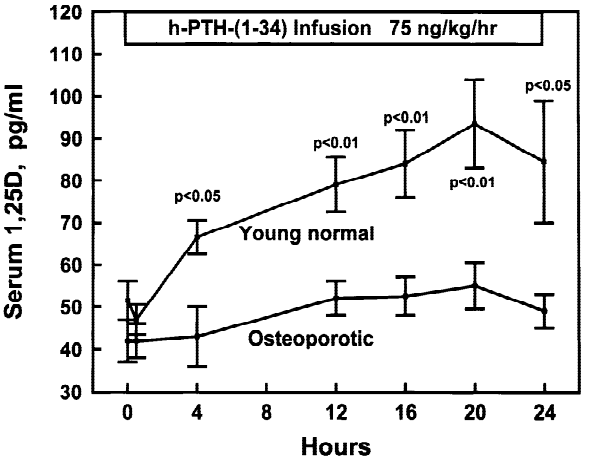

Fig. 1. Impaired serum $1,25(OH)_2D_3$ response to PTH infusion in osteoporotic patients. (Reproduced from Slovik *et al.,* 1981, with permission).

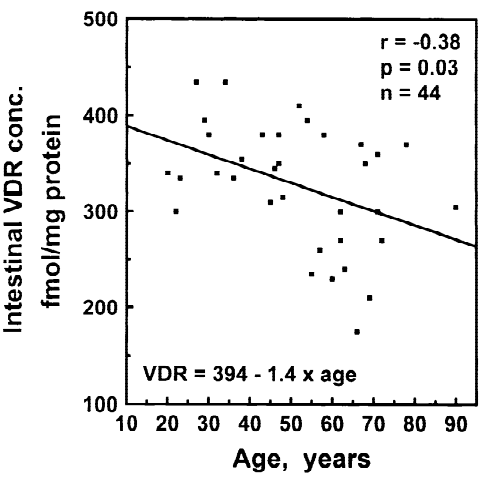

Fig. 2. Intestinal vitamin D receptor (VDR) concentration as a function of age in 44 healthy women of 20–87 years of age. (Reproduced from Ebeling *et al.,* 1992, with permission).

elderly women who had reduced intestinal Ca absorption in spite of normal levels of serum $1,25(OH)_2D_3$ (i.e., $1,25(OH)_2D_3$ resistance) had normal intestinal VDR levels [36]. Thus, we should also consider the alternative possibility that reduced $1,25(OH)_2D_3$ responsiveness may be due to a decrease in VDR affinity for $1,25(OH)_2D_3$ and/or to defects in other regulatory factors of $1,25(OH)_2D_3$ action and Ca absorption. Regardless of the cause of the resistance, there is now strong evidence that aging may also be attended by, in addition to primary vitamin D deficiency and $1,25(OH)_2D_3$ deficiency, $1,25(OH)_2D_3$ resistance [37]. Hence, the etiology of the aging-associated vitamin D deficiency may be multifactorial.

Vitamin D Deficiency and Osteoporosis

There is increasing evidence that vitamin D deficiency is involved in the pathogenesis of osteoporosis, particularly that of senile osteoporosis. Figure 3 illustrates a model of

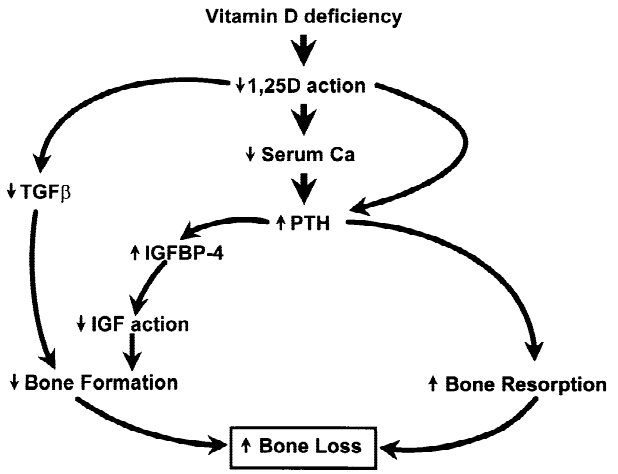

Fig. 3. A proposed model describing mechanisms by which vitamin D deficiency may lead to increased bone resorption and decreased bone formation (see text for details).

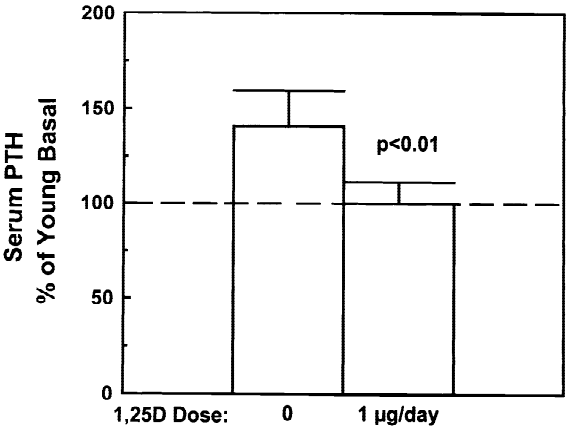

Fig. 4. Basal serum PTH and serum PTH after 1 week of calcitriol treatment in 10 elderly women (71–77 years of age). Serum PTH levels are expressed as percentage of premenopausal PTH level (adapted from Ledger *et al.*, 1994 with permission).

potential mechanisms whereby the age-associated vitamin D deficiency causes bone loss and, eventually, senile osteoporosis. Accordingly, the overall effect of the age-associated vitamin D deficiency, regardless of the etiology, is reduced effective concentrations and/or biological actions of $1,25(OH)_2D_3$, the biologically active form of vitamin D. A major action of $1,25(OH)_2D_3$ is to stimulate intestinal Ca absorption. Thus, vitamin D deficiency would lead to Ca malabsorption which subsequently results in a decline in serum Ca. In response to the reduced serum Ca level, PTH secretion increases, leading to secondary hyperparathyroidism, which in turn causes an increase in bone resorption. In addition to increasing intestinal Ca absorption, $1,25(OH)_2D_3$ also has a direct suppressive effect on PTH secretion [38]. Thus, reduction in $1,25(OH)_2D_3$ concentrations and/or actions would lessen the suppressive effect, causing further increases in PTH secretion and thereby increases in bone resorption. Vitamin D deficiency and the resulting secondary hyperparathyroidism not only could lead to an increased bone resorption, but could also cause an inhibition of bone formation [39].

Two findings raise the possibility that the inhibitory effect of high PTH on bone formation may be mediated through the reduction in overall bone growth factor activities: (1) *in vitro* studies of human bone cells suggest that the inhibition of PTH on bone formation could be mediated through increased production of the inhibitory insulin-like growth factor (IGF) binding protein, IGFBP-4 [40], which could lead to an inhibition of the IGF-mediated bone formation; (2) $1,25(OH)_2D_3$ deficiency caused a reduction in TGFβ secretion [41], resulting in decreases in bone formation rate. Consistent with this possibility, an age-dependent decrease in bone contents of growth factors, i.e., IGFs and TGFβ, was reported in femoral cortical and trabecular bone of both men and women [42, 43]. Conversely, $1,25(OH)_2D_3$ is a potent stimulator of osteoblast differentiation and bone collagen synthesis (an essential process of bone matrix formation). Hence, insufficient vitamin D activity could also lead to an inhibition of osteoblast maturation and bone matrix synthesis and thus bone formation. Consequently, the increase in bone resorption, along with the inhibition of bone formation, would result in significant bone loss in vitamin D deficiency and the age-associated vitamin D deficiency could contribute significantly to the pathogenesis of osteoporosis, especially that of senile osteoporosis.

There is an abundance of circumstantial evidence in support of this model. Accordingly, it has been well documented that aging is frequently associated with decreases in intestinal Ca absorption [1–5] and increases in serum PTH [25, 44]. These aging-associated changes in intestinal Ca absorption and serum PTH are closely related to the vitamin D deficiency, since the Ca malabsorption can be effectively corrected by treatments with vitamin D or active vitamin D analogs [6,45,46], and, as is shown in Figure 4, administration of $1,25(OH)_2D_3$ (1 μg/day for 1 week) to elderly women readily regressed their elevated serum PTH levels back to those of premenopausal women [47]. Aging is also associated with increases in bone resorption, as reflected by urinary cross-linked N-telopeptides (NTx) (Fig. 5) and by serum C-terminal telopeptide of type I collagen (ICTP) [48] in women between the ages of 30 to 80. Figure 5 also shows that the increase in NTx was accompanied by an age-dependent decrease in lumbar spine bone density [49]. Furthermore, it has been reported that the urine NTx level in women who were >20 years postmenopausal correlated significantly with serum PTH [50], indicating that the increased bone resorption in the elderly is associated with the increased PTH. Thus, the vitamin D deficiency and the associated secondary hyperparathyroidism are probably significant contributors to senile osteoporosis [50].

Rationale of Vitamin D Replacement Therapy

The most common approach to treating a deficiency is replacement therapy. However, an appropriate replacement therapy should address not only the symptoms but also the etiology of the disorder. Because there are three subtypes of vitamin D deficiency, and because each appears to have a different etiology, an appropriate treatment of each subtype of vitamin D deficiency may require a different type of vitamin D for replacement therapy. Accordingly, we will consider the theoretical basis of an appropriate replacement therapy for each subtype of vitamin D deficiency. Because the overall consequence of $1,25(OH)_2D_3$ deficiency and $1,25(OH)_2D_3$ resistance is essentially identical, i.e., insufficient biological actions of $1,25(OH)_2D_3$, we will consider

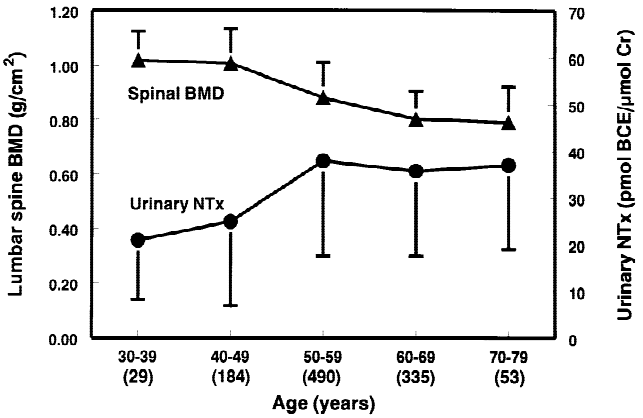

Fig. 5. Changes in bone resorption (reflected by urinary NTx level) and lumbar spinal bone mineral density as a function of age in Japanese women. The bracketed numbers under the age represent the number of subjects per group. This figure shows that there is an age-dependent increase in bone resorption and an age-dependent decrease in spinal bone density in these women. (Reproduced from Taguchi *et al.*, 1998, with permission).

these two subtypes of deficiency as a single form, i.e., $1,25(OH)_2D_3$ deficiency/resistance.

Primary Vitamin D Deficiency

Because primary vitamin D deficiency is caused by an insufficient supply of precursors of $1,25(OH)_2D_3$, it would seem logical to treat this subtype by replenishing the precursors with the vitamin D or 25(OH)D supplementation. Consequently, the plain vitamin D therapy would be an appropriate therapy for primary vitamin D deficiency. Indeed, there is ample evidence that the plain vitamin D therapy, in combination with Ca, effectively corrected the primary vitamin D deficiency and reduced hip fracture rate [51]. A vitamin D deficiency replacement protocol consists of daily oral supplementation of physiological doses (i.e., 400–1000 IU) of vitamin D_2 [or 15 μg/day $25(OH)D_3$] or administration of supraphysiological doses (>1000 IU) of vitamin D_2 for a short duration.

$1,25(OH)_2D_3$ Deficiency/Resistance

In contrast to primary vitamin D deficiency, $1,25(OH)_2D_3$ deficiency is caused by insufficient renal production of $1,25(OH)_2D_3$, and $1,25(OH)_2D_3$ resistance is the result of reduced responses of target tissues to $1,25(OH)_2D_3$. From theoretical standpoints, the defects associated with $1,25(OH)_2D_3$ deficiency/resistance could not be corrected by merely increasing the supply of vitamin D or 25(OH)D (i.e., plain vitamin D therapy). A successful replacement therapy would have to involve treatment with $1,25(OH)_2D_3$ (or an active analog, such as alfacalcidol) to raise effective concentrations of $1,25(OH)_2D_3$. Accordingly, the active vitamin D analog therapy, but not plain vitamin D, would be appropriate for $1,25(OH)_2D_3$ deficiency/resistance. In support of this contention, it has been shown that $1,25(OH)_2D_3$ therapy corrected the metabolic abnormalities associated with $1,25(OH)_2D_3$ deficiency [9]. Conversely, the plain vitamin D therapy, though it increased serum $25(OH)D_3$ levels, was unable to raise serum $1,25(OH)_2D_3$ levels or to correct the secondary hyperparathyroidism in patients with $1,25(OH)_2D_3$ deficiency [52].

However, it has been suggested that $25(OH)D_3$, at very high levels, could mimic $1,25(OH)_2D_3$ to act on VDR to exert biological effects [53, 54]. Accordingly, it is theoretically feasible that $1,25(OH)_2D_3$ deficiency/resistance may be treated with high doses of plain vitamin D or $25(OH)D_3$. However, in order to achieve sufficiently high levels of serum $25(OH)D_3$ to produce desirable clinical effects, patients are frequently required to be treated with extremely high doses of plain vitamin D at daily doses of 20,000–50,000 IU [55]. Therapies with such high doses of vitamin D or $25(OH)D_3$ would undoubtedly put patients at great risks of vitamin D toxicity [56–58], since chronic use of plain vitamin D at doses above 2000 IU/day can lead to toxic levels of vitamin D and elevated serum and urine Ca levels, resulting in extraskeletal calcifications and renal stones. Consequently, plain vitamin D therapy is not an optimal or safe therapy for $1,25(OH)_2D_3$ deficiency/resistance.

In light of these theoretical considerations, it is clear that although plain vitamin D replacement therapy is ideal for the primary vitamin D deficiency, a successful treatment of $1,25(OH)_2D_3$ deficiency/resistance would require therapy with effective doses of $1,25(OH)_2D_3$ or an active analog such as alfacalcidol. Thus, these considerations provide strong justification for the need of both the plain vitamin D and the active vitamin D analog therapy for vitamin D-deficient-related osteoporosis, depending on the cause of the vitamin D deficiency.

Vitamin D Therapies of Osteoporosis

Unfortunately, direct comparisons of plain vitamin D therapy and active vitamin D analog therapy in osteoporosis are scarce thus, the comparative efficacy of the two therapies has not been adequately assessed. However, a review and comparison of the results of past clinical studies that utilized either of these two vitamin D replacement therapies in primary osteoporosis should be informative. The ultimate goals of osteoporosis therapy are to increase bone mass (or reduce bone loss) and to reduce fracture risks, and the effects of these two vitamin D therapies on bone mass and fracture risks are discussed here.

The Plain Vitamin D Therapy

Table 1 summarizes the results of several prospective and retrospective clinical studies in which the plain vitamin D therapy was used to treat primary osteoporosis utilizing bone mass or fracture incidence as an end point. Most studies show that the plain vitamin D therapy reduced bone loss and decreased the risk of hip and nonvertebral fractures in vitamin D-deficient elderly patients. For instance, in a large study of 3270 institutionalized elderly women in France, 3-year daily treatment with plain vitamin D (800 IU plain vitamin D and 1.2 g Ca) significantly reduced hip fracture risk by 30% compared with the placebo group [59]. It has also been reported that the plain vitamin D therapy (700 IU vitamin D and 500 mg Ca per day) for 3 years produced a significant reduction in incidence of nonvertebral fractures in a group of 389 elderly American men and women [60]. Annual intramuscular injection of plain vitamin D in the elderly for up to 5 years also resulted in a significant de-

Table 1. Reported effects of the plain vitamin D therapy on bone mass and/or fractures in primary osteoporosis

Average dose (IU/day)	No. of subjects	Types of patient	Duration of treatment	Increase bone mass compared with control	Decrease fracture incidence	Comments	Reference
700	389	>65 yrs (men and women)	3 yrs	Yes	Yes	Decreased bone loss in femoral neck, spine, and reduced nonvertebral fracture incidence	[60]
800	3270	Elderly women	3 yrs	Yes	Yes	Decreased hip and nonvertebral fractures by 23%	[59]
150,000–300,000/yr (i.m. injection)	341	>75 yrs (women)	Up to 5 yrs	ND	Yes	Reduction in nonvertebral (especially upperlimb) fractures	[14]
400	2578	>70 yrs (men and women)	3.5 yrs	ND	No	No change in hip or other peripheral fracture incidence	[63]
400	348	>70 yrs (women)	2 yrs	Yes	ND	Decreased BMD at the femoral neck	[16]
15,000/week	109	65–74 yrs (women)	2 yrs	Yes	ND	Decreased metacarpal cortical bone loss	[62]
1000 (i.e., 25 μg)	77	30–87 yrs old (men)	3 yrs	No	ND	Not effective in preventing age-related bone loss	[64]

ND = not determined.

crease in nonvertebral fractures [14]. A daily dose of 400 IU of plain vitamin D also led to a decrease in bone loss from the lumbar spine compared with the control group, primarily during the winter months [61]. Several additional studies also showed beneficial effects with the plain vitamin D therapy on aging-associated bone loss and fracture incidence in elderly subjects [16, 62]. However, plain vitamin D treatment does not always produce beneficial effects on bone mass and fracture risks. In a study of 2578 elderly subjects in the Netherlands, daily treatment with 400 IU of plain vitamin D without Ca supplements for 3½ years did not reduce hip or peripheral fracture incidence [63]. Similarly, a 3-year, double-blind, placebo-controlled clinical trial in 77 men aged 30–87 years revealed that daily supplementation of 25 μg (~1000 IU) of plain vitamin D_2 and 1 g Ca was ineffective in preventing the aging-related bone loss [64].

The reason for the conflicting results may be partly due to differences in the dosage [55] and Ca supplementation [51]. However, a more probable explanation may be related to differences in the study population [65]. For instance, the French women who showed positive responses [51] had lower dietary Ca intakes, were more frail, and had lower serum 25(OH)D levels than the Dutch, who did not show a significant reduction in fracture risks [63]. Accordingly, it is possible that the plain vitamin D therapy may be effective only in subgroups of patients such as those who had primary vitamin D deficiency. Consistent with this notion, the MEDOS study of 1634 women showed that the plain vitamin D therapy effectively decreased relative hip fracture risks only in subgroups of women who were either older (>80 years of age) or more frail (with BMI <20 kg/m^2) [66]. The older and frail women are likely to be less active and may have less exposure to sunlight, thus are more likely to develop primary vitamin D deficiency. On the other hand, genetic differences may also contribute to the conflicting results since recent studies suggested that the response to plain vitamin D therapy may be influenced by the VDR genotype [67, 68].

With respect to the ability of the plain vitamin D therapy to correct the vitamin D deficiency and associated symptoms, most published data have demonstrated that daily oral supplementation with physiological doses of plain vitamin D or 25(OH)D_3 is sufficient to normalize serum 25(OH)D_3 and increase serum 1,25(OH)$_2D_3$ in elderly patients with primary vitamin D deficiency (i.e., those with low serum 25(OH)D_3). Accordingly, increasing serum 25(OH)D_3 and 1,25(OH)$_2D_3$ in response to the plain vitamin D therapy improves intestinal Ca absorption, decreases serum PTH, and reduces bone turnover in the elderly [10, 16, 51, 59, 69–71]. However, several studies show that in patients who did not seem to have primary vitamin D deficiency, the plain vitamin D therapy did not significantly increase serum 1,25(OH)$_2D_3$ or improve associated metabolic abnormalities [52, 64, 72]. Even in those studies that showed positive responses in the study population, there was a significant number of subjects who did not respond with an increase [10]. More importantly, the increase in serum 1,25(OH)$_2D_3$ was seen only in those whose basal serum 25(OH)D_3 was low (i.e., primary vitamin D deficiency) but not in those who had normal or elevated basal serum 25(OH)D_3 levels (i.e., 1,25(OH)$_2D_3$ deficiency/resistance) [10]. Thus, the efficacy of this therapy to increase serum 1,25(OH)$_2D_3$ levels (i.e., to correct vitamin D deficiency) may depend on the basal vitamin D status, and the therapy may be more effective in primary vitamin D deficiency.

Active Vitamin D Analog (D-Hormone) Therapy

Two forms of active vitamin D analog therapy are currently available: calcitriol [1,25(OH)$_2D_3$] therapy and alfacalcidol [1α(OH)D_3] therapy. An important difference between these two agents is their respective mode of action. 1,25(OH)$_2D_3$ is the physiologically active vitamin D metabolite. Accordingly, upon oral administration, calcitriol is already biologically active and immediately acts on target tissues to produce biological effects. Conversely, alfacalci-

Table 2. Reported effects of the active vitamin D analog therapy on bone mass and/or fractures in primary osteoporosis

Average daily dose	No. of subjects	Type of patients	Duration of treatment (months)	Increase spinal BMD compared with control	Decrease fracture incidence	Comments	Reference
0.5 μg 1,25D	622	Postmenopausal osteoporosis	36	ND	Yes	Three-fold reduction in new vertebral fractures after first year	[73]
0.8 μg 1,25D	27	Postmenopausal osteoporosis	24	Yes	Yes	Increased spinal BMD, and decreased vertebral fracture rates	[75]
0.43 μg 1,25D	86	Postmenopausal osteoporosis	24	No	No	No changes in BMD or new fractures compared with control	[77]
0.62 μg 1,25D	50	Postmenopausal osteoporosis	24	Yes	No	Increased spinal BMD but no difference in vertebral fracture rates	[76]
0.5 μg 1,25D	76	Postmenopausal osteoporosis	36	No	No	No significant effects on long bone BMD or new vertebral fracture rate	[78]
0.5 μg 1,25D	40	Postmenopausal osteoporosis	36	ND	Yes	Reduced vertebral fracture rate and improved Ca balance	[74]
1 μg 1αD	666	Postmenopausal osteoporosis	12	ND	Yes	Reduced vertebral fracture incidence	[81]
1 μg 1αD	86	Senile osteoporosis	20–26	ND	Yes	Reduced new vertebral fracture rates	[82]
1 μg 1αD	80	Postmenopausal osteoporosis	12	Yes	Yes	Decreased number of new vertebral fractures	[92]
0.75 μg 1αD	113	Postmenopausal osteoporosis	24	Yes	Yes	Increased spinal BMD and decreased new vertebral fractures	[85]
0.5 μg 1αD	31	Postmenopausal osteoporosis or osteopenia	12	Yes	ND	Prevented trabecular BMD loss	[86]

dol is a synthetic precursor of $1,25(OH)_2D_3$ and is biologically inert. It must be converted to $1,25(OH)_2D_3$, predominantly in the liver by the hepatic vitamin D-25-hydroxylase before it can act in target tissues to exert biological effects. Because of this difference, alfacalcidol produces a very different pharmacokinetic profile from calcitriol: after oral ingestion of calcitriol, the peak serum $1,25(OH)_2D_3$ level is reached within 2 hours whereas oral ingestion of alfacalcidol causes a slow rise in serum $1,25(OH)_2D_3$ levels with peak values after 8–18 hours. This is important with respect to their respective risks of side effects. Accordingly, calcitriol, upon ingestion, acts immediately and directly on the VDR in the intestinal mucosal cells to promote intestinal Ca absorption, leading to a rapid increase in serum Ca. In contrast, alfacalcidol has only very limited intestinal actions and thus does not produce an immediate stimulation of intestinal Ca absorption. Because of the direct action of calcitriol on the gut, the magnitude of immediate increase in Ca absorption is relatively larger than that seen with alfacalcidol therapy. The larger increase in Ca absorption potentially could pose a greater risk of hypercalcemia, which is a serious side effect. Accordingly, alfacalcidol therapy may be a safer therapy than calcitriol therapy. On the other hand, the side effect of hypercalcemia with calcitriol therapy can usually be avoided by limiting Ca intake to <800 mg/day [73, 74] and by adjusting the dosage (not more than 0.5 μg/day). Nonetheless, because of this potential side effect, patients must be closely monitored for hypercalcemia and hypercalciuria with the active analog therapy.

Table 2 summarizes the results of the major prospective and retrospective controlled studies on bone mass and fracture rates as end points using the active vitamin D analog therapy in primary osteoporosis. Earlier clinical trials using calcitriol in women with postmenopausal osteoporosis produced conflicting results. Aloia et al. [75] showed that calcitriol treatment reduced bone loss and vertebral fracture risks in women with postmenopausal osteoporosis by increasing Ca absorption and reducing bone resorption. Gallagher et al. [74, 76] reported that treatment with calcitriol resulted in significant increases in spinal BMD and total body Ca, reduction in vertebral fracture incidence, and improvement in Ca balance as compared with the placebo-treated control. In contrast, Ott and Chesnut [77] found the 2-year treatment with lower doses of calcitriol to be ineffective in the treatment of postmenopausal osteoporosis. Falch et al. [78] also failed to observe beneficial effects of calcitriol on new vertebral fracture incidence. The responses in bone mass to calcitriol therapy were also varied. Some studies reported very large increments (10–20%) in bone mass. Others have shown only modest increases which subsequently declined in magnitude [74–76, 79, 80], and some even reported no significant increases [77, 78]. However, in most cases, patients treated with calcitriol for 2 years usually showed an average of 1–2% increase in spinal BMD, whereas there would be a decrease of 2–3% in placebo-treated patients over the same period.

The controversy in these early studies may largely be related to factors such as the dosage, patient population, and

criteria used to assess efficacy. For example, demonstration of a benefit has usually required relatively high doses of calcitriol [75]; lower doses have shown no benefit [77]. In addition, a significant deficiency of the earlier studies was the small number of patients that were insufficient for a valid statistical analysis of fracture risks. Consequently, to appropriately assess the effect of the calcitriol therapy on fracture incidence, Tilyard et al. [73] performed a large randomized, prospective, fracture risk study in which 622 postmenopausal women with osteoporosis were treated with either 0.5 μg/day calcitriol or Ca for 3 years. A threefold reduction in the rate of new vertebral fractures was found after 2 years of calcitriol therapy, as compared with the Ca group. Similar benefits were noted in the incidence of nonvertebral fractures, including hip fractures.

The effects of alfacalcidol therapy on vertebral fracture incidence and spinal bone mass have been much more consistent and positive (Table 2) in that all reported studies showed significant decreases in new vertebral fracture incidence in patients treated with alfacalcidol, as compared with controls. The largest study undertaken with alfacalcidol thus far was on 666 Japanese patients, in which a daily dose of 1 μg was given without Ca supplements for 1 year [81]. A twofold reduction in new vertebral fracture incidence was observed compared with the placebo-treated control (76 versus 41/100 patient-years). Similar reduction of vertebral fracture incidence and stabilization of bone mass have been confirmed in many other clinical trials of postmenopausal osteoporosis, although the number of subjects was smaller [82–86]. Although the active analog therapy clearly benefits for the spine, there have not been any well-designed studies to evaluate whether active analog (calcitriol or alfacalcidol) therapy reduces the risk of hip fracture, which is a serious complication of osteoporosis.

Active vitamin D analog therapy can bypass the feedback regulation that controls renal $1,25(OH)_2D_3$ synthesis. Thus, in all published studies, active analog therapy effectively increases serum $1,25(OH)_2D_3$ and corrects the vitamin D deficiency and improves the Ca absorption that are often associated with osteoporosis. Accordingly, in each study, therapy with low doses of calcitriol or alfacalcidol rapidly and markedly stimulate Ca absorption, and the response is dose dependent [87]. This subsequently leads to rapid suppression of PTH secretion and a decrease in bone turnover [87–90]. Additionally, it appears that the active analog therapy may correct mild osteomalacia associated with aging-associated vitamin D deficiency and may promote micro-callus formation and bone fracture healing. This in turn may improve the bone quality, as has been demonstrated in animal models [91].

Although most available studies with active analog therapy, especially alfacalcidol, were performed on patients with postmenopausal osteoporosis, two studies showed that alfacalcidol therapy is also effective in reducing new vertebral fracture incidence in patients with senile osteoporosis [83, 92]. This is not unexpected, since active vitamin D analog therapy effectively corrects the vitamin D deficiency and improves metabolic abnormalities, including bone loss, that are frequently associated with senile osteoporosis. What is surprising, however, is that the active vitamin D analog therapy, especially alfacalcidol therapy, is effective in preventing spinal bone loss and reducing vertebral fracture risks in postmenopausal women. In this regard, there is no convincing evidence that bone loss in postmenopausal osteoporosis is associated with vitamin D deficiency. Therefore, the beneficial effect of active vitamin D analog therapy on spinal bone loss and on fracture risks may be related to the effect of this therapy to reduce bone turnover.

The pathogenesis of postmenopausal osteoporosis is multifactorial and is primarily mediated by the estrogen deficiency developed after menopause. Accordingly, estrogen deficiency increases production of resorptive cytokines, which stimulate bone resorption, resulting in a net Ca mobilization from the skeleton. Estrogen has also been shown *in vitro* to promote apoptosis of osteoclasts through stimulation of TGFβ production in osteoblasts [93]. In this regard, estrogen deficiency decreases production of TGFβ and reduces the TGFβ-mediated apoptosis of osteoclasts, leading to an increased life span of active osteoclasts, which results in a further stimulation in bone resorption. TGFβ is also a potent bone cell growth factor; therefore the decreased production of TGFβ in response to estrogen deficiency may also cause a reduction in bone formation. Thus, the combined effects, i.e., stimulation of bone resorption and inhibition of bone formation, are largely responsible for the bone loss and increased fracture risks in postmenopausal osteoporosis. On the other hand, $1,25(OH)_2D_3$, like TGFβ, is shown to promote apoptosis of human cells [94]. $1,25(OH)_2D_3$ treatment may also increase TGFβ production [41]. Accordingly, increased serum $1,25(OH)_2D_3$, in response to calcitriol (or alfacalcidol) therapy, could act directly on osteoclasts and/or through increased TGFβ production to promote apoptosis of osteoclasts. This would then limit the life span of active osteoclasts, resulting in an inhibition of osteoclastic resorption. In addition, increased serum $1,25(OH)_2D_3$ suppresses PTH secretion, which further reduces bone resorption. Moreover, the $1,25(OH)_2D_3$-mediated production of TGFβ [41] may also result in an increase in bone formation. Consequently, it may be speculated that this $1,25(OH)_2D_3$-induced inhibition of osteoclastic resorption, along with the TGFβ-mediated increase in bone formation, may serve to counteract the bone-wasting effects of estrogen deficiency and, thereby, may be responsible for the observed beneficial effects of active vitamin D analog therapy on bone mass and fracture risks in postmenopausal osteoporosis. Accordingly, the bone-sparing action of active vitamin D analogs in postmenopausal osteoporosis may be results of its pharmacological actions on bone formation and resorption rather than through replenishing a deficiency.

Comparison Between Plain Vitamin D Therapy and Active Vitamin D Analog (D-Hormone) Therapy

Direct comparisons between the plain vitamin D therapy and active vitamin D analog therapy under clinical settings have been very limited. There has only been one randomized, single-blinded, controlled study, which directly compared the effect of alfacalcidol and vitamin D_2 on Ca absorption, serum PTH, and bone turnover in 46 women with postmenopausal osteoporosis. It was found that the 6-month alfacalcidol (0.5 μg/day) treatment improved Ca absorption, suppressed secondary hyperparathyroidism, and reduced bone turnover. In contrast, daily treatment with 500–1000 IU vitamin D for the same time period had no significant effect on any of the measured parameters [45]. These findings need to be confirmed and extended to bone mass and fracture risk evaluations.

Conclusion

The discovery of vitamin D and its application as a vitamin to prevent rickets and osteomalacia has not led to the complete eradication of vitamin D deficiency. Accordingly, el-

derly folk, particularly those either house bound or living in northerly latitudes (with limited sunlight exposure) and those whose intake of dairy products is minimal, can develop vitamin D deficiency. Interestingly, severe vitamin D deficiency causes osteomalacia, whereas mild vitamin D deficiency results in osteoporosis. In this regard, we seldom see elderly patients with severe vitamin D deficiency and osteomalacia, even those living in northern latitudes. Instead, we see patients who appear to have osteoporosis in association with vitamin D deficiency, which leads to secondary hyperparathyroidism and bone loss.

The relatively high prevalence of vitamin D deficiency in the elderly has been recognized for more than two decades. The serum $25(OH)D_3$ assay was instrumental in identifying this problem because patients with vitamin D deficiency typically have a low serum $25(OH)D_3$ level. On the other hand, in the course of clinical investigations on osteoporosis, such patients were found with secondary hyperparathyroidism and poor Ca absorption but did not have a low serum $25(OH)D_3$ level. Further investigation into the cause of secondary hyperparathyroidism in these patients led to the discovery that the production of $1,25(OH)_2D_3$ in the kidney is impaired in these elderly subjects, raising the possible existence of another form of vitamin D deficiency in the elderly, namely, a deficiency of renal $1,25(OH)_2D_3$ production. However, not all patients who have secondary hyperparathyroidism and who do not have low serum $25(OH)D_3$ have a low serum $1,25(OH)_2D_3$ level. A possible explanation for their secondary hyperparathyroidism and not a low serum $1,25(OH)_2D_3$ level is that they have a resistance to $1,25(OH)_2D_3$. This possibility was heightened by the finding of an age-dependent decrease in intestinal VDR concentration. Accordingly, it is conceivable that, during aging, there can be secondary hyperparathyroidism due to an abnormality in vitamin D metabolism that is either due to a deficiency of the production of $1,25(OH)_2D_3$, or an inadequate action of $1,25(OH)_2D_3$, or a combination of both.

From a clinical standpoint, it is important to be able to recognize the difference between a deficiency of vitamin D and either a deficiency of or a resistance to $1,25(OH)_2D_3$. This is because, as outlined above, the treatment of these two types of vitamin D deficiencies is quite different. Accordingly, for primary vitamin D deficiency, 1000 IU of plain vitamin D daily is usually sufficient to correct this problem. In contrast, the use of plain vitamin D at this level will have no detectable impact on correcting the secondary hyperparathyroidism seen in those patients who have either $1,25(OH)_2D_3$ deficiency or resistance. On the other hand, these patients respond very well to either calcitriol or alfacalcidol, both of which can totally correct the secondary hyperparathyroidism seen in these patients. Consequently, it is important when evaluating patients with secondary hyperparathyroidism to measure the serum $25(OH)D_3$ level. If it is low, the patient requires plain vitamin D therapy; if it is normal or slightly elevated, the patient should be considered for calcitriol and alfacalcidol therapy. What is important to emphasize, however, is that irrespective of the correctness of the above postulations as to the cause of vitamin D deficiency, if the appropriate type of vitamin D therapy is applied, it is possible to totally correct all types of vitamin D deficiency with either plain vitamin D or active vitamin D metabolites. Inasmuch as there are many diseases associated with aging that are incurable and even lack rational therapy, it is all the more important to take advantage of the fact that, in the case of senile osteoporosis and secondary hyperparathyroidism, we now have the therapeutic armament to completely correct the secondary hyperparathyroidism associated with any type of vitamin D deficiency.

Finally, there is also evidence that active vitamin D analog therapy appears to have a bone-sparing action in postmenopausal osteoporosis. However, these effects are results of pharmacological actions of the active vitamin D metabolite (D-hormone) on bone formation and resorption rather than through replenishing a deficiency. Nonetheless, these apparent bone-sparing effects of active vitamin D analogs (i.e., $1,25(OH)_2D_3$ and $1\alpha(OH)D_3$) in postmenopausal osteoporosis provide an additional justification for the need of active vitamin D analog therapy in osteoporosis.

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