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PROSPECTS

Role of the Vitamin D-Endocrine System in the Pathophysiology of Postmenopausal Osteoporosis

B. Lawrence Riggs*

Endocrine Research Unit, Mayo Clinic and Foundation, Rochester, Minnesota 55905

Abstract Impaired calcium absorption and impaired adaptation to a low calcium diet are common features of aging in women and these processes are even more severely impaired in patients with osteoporotic fractures. The calcium absorption defects are associated with several abnormalities of the vitamin D-endocrine system including secondary hyperparathyroidism, intestinal resistance to 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) action, decreased $1,25(OH)_2D$ production due to impaired 25(OH)D 1α-hydroxylase activity, and, in some elderly persons, nutritional deficiency of vitamin D. However, in postmenopausal women, most of these abnormalities are normalized by administration of physiologic replacement dosages of estrogen and, thus, appear to be secondary consequences of estrogen deficiency. Nonetheless, a minority of them, especially nutritional vitamin D deficiency and impaired 25(OH)D 1α-hydroxylase activity late in life, appear to be primary and are independent of estrogen deficiency. J. Cell. Biochem. 88: 209–215, 2003.

Key words: calcitriol; 1,25-dihydroxyvitamin D; 1α-hydroxyvitamin D; estrogen; calcium absorption

Osteoporosis is one of the most important medical problems facing the aging population. In order to prevent and treat osteoporosis effectively, it is important to define its pathophysiology rigorously. In the 1970s, the modern understanding of the vitamin D-endocrine system emerged and it was demonstrated that its two major effectors parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D (calcitriol; $1,25(OH)_2D$) play critical roles in maintaining bone and calcium homeostasis. This led to a series of studies attempting to define the role of this key system in the pathophysiology of osteoporosis.

In the limited space available here, I would like to summarize the considerable progress that has been made in this task and to provide my interpretation of the collective data. It is highly appropriate that I do so in this festschrift commemorating the distinguished career of Prof. Hector F. DeLuca. Although most of his prolific research has been devoted to basic studies on the structure and function of active vitamin D metabolites, Hector was one of the first to recognize the potential importance of the vitamin D-endocrine system in the pathophysiology of osteoporosis and the potential of active vitamin D metabolites in its treatment. Thus, I was both pleased and honored when he agreed to collaborate with me in a series of clinical investigative studies on osteoporosis. These continued over a span of almost two decades and have resulted in 11 publications. I would also like to acknowledge the contributions of Dr. S. Khosla and Dr. R. Kumar from the Mayo Staff and the postdoctoral fellows who participated in these previous studies, especially Dr. J.C. Gallagher, Dr. E. Seeman, Dr. K.S. Tsai, Dr. R. Eastell, Dr. P.R. Ebeling and Dr. S. Pattanaungkul from my laboratory, and Dr. J. Eisman from DeLuca's laboratory.

Here I will review the data obtained from our clinical investigative studies and those of others under the rubric of three critical issues—the evidence for abnormalities of the vitamin D-endocrine system with aging, the contribution

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*Correspondence to: B. Lawrence Riggs, MD, Mayo Clinic, 200 First Street SW, Rochester, MN 55905.
E-mail: Riggs.lawrence@mayo.edu

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of estrogen deficiency to the development of these abnormalities, and the contribution of these abnormalities to the bone loss that leads to postmenopausal and age-related osteoporosis.

ARE THERE AGE-RELATED ABNORMALITIES OF THE VITAMIN D-ENDOCRINE SYSTEM?

Many studies have consistently demonstrated that such age-related abnormalities exist and are even more severe in postmenopausal women with osteoporosis. For more details about and complete references on these abnormalities, I refer the reader to recent reviews [Eastell and Riggs, 1997; Bilezikian and Silverberg, 2001; Lips, 2001].

Impaired Calcium Absorption That is Corrected by Administration of $1,25(OH)_2D$

Many studies have shown that calcium absorption decreases with aging in women, and, probably, also in men [Eastell and Riggs, 1997]. The major exception to these reports was the study of Eastell et al. [1991], who found that true calcium absorption using stable calcium isotopes did not decreases with aging. However, these investigators also showed that serum $1,25(OH)_2D$ was increased with aging in their study subjects so that the failure of calcium absorption to increase in response to this was abnormal. In addition, the impairment in calcium absorption in elderly women is even greater in women with postmenopausal osteoporosis [Gallagher et al., 1979]. The most significant abnormalities have been found in elderly individuals with a low dietary calcium intake, indicating a failure of intestinal adaptation. Ireland and Fordtran [1973] using the small intestinal perfusion method directly demonstrated this impaired mal-adaptation with aging.

Moreover, the impairment in calcium absorption is correctable by the oral administration of as little as 0.5 μg/day of $1,25(OH)_2D_3$ [Riggs and Nelson, 1985] and (Fig. 1). Because this dosage is well below the endogenous production rate of $1,25(OH)_2D$, it suggests a causal relationship. One caveat, however, is that the intestinal vitamin D receptor (VDR) is exposed to a higher concentration of $1,25(OH)_2D$ in the intestinal lumen after oral administration than after endogenous production. However, administration of 0.5 μg/day to postmenopausal osteoporotic women restored calcium absorption to the normal mean (suggesting that it was a physiologic dosage), whereas the dosage of 0.75 μg/day increased it to slightly above normal mean [Riggs and Nelson, 1985] and (Fig. 1).

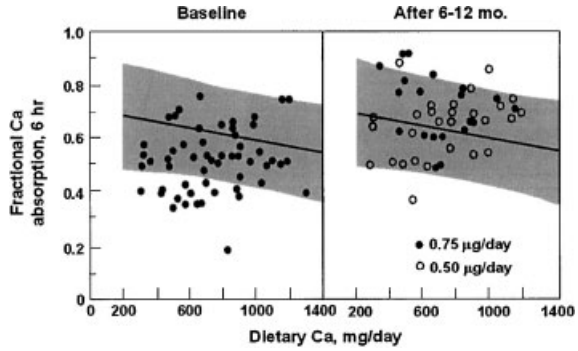

Fig. 1. Effect on fractional calcium absorption (assessed by double isotope method with 100 mg calcium carrier) at baseline and after 6–12 months of treatment with two dosages of $1,25(OH)_2D_3$ (calcitriol) in women with postmenopausal osteoporosis and vertebral fractures. Cross-hatched area represents normal values for age-comparable postmenopausal women. Placebo treatment of 26 osteoporotic women had no significant effect on calcium absorption. Data are plotted as function of habitual dietary calcium intake. Note that at baseline, three-quarters of the osteoporotic women were lower than the normal mean and one-quarter were below the normal range. Note also that treatment with 0.5 μg/day of $1,25(OH)_2D_3$ normalized calcium absorption whereas treatment with 0.75 μg/day increased it to slightly above the normal range. Data are from Riggs and Nelson [1985] with permission.

Progressive Secondary Hyperparathyroidism Leading to Increased Bone Resorption and Bone Loss

The impairment in calcium absorption could be either homeostatic (the decreased calcium absorption is the result of the bone loss) or non-homeostatic (the calcium absorption is the cause of the bone loss). These two possibilities can be distinguished by the level of serum PTH.

Our group has reported elsewhere [Riggs et al., 1998] that postmenopausal women have two phases of bone loss, each resulting from a separate process and each associated with a specific clinical type of osteoporosis. The first process begins at the menopause and leads to a rapid, transient phase of excessive loss of predominantly cancellous bone that subsides over 5–10 years period. In a small subset of postmenopausal women, an exaggeration of the rate of loss or an extension of its duration leads to what we have termed type I osteoporosis [Riggs et al., 1998]. This form of osteoporosis affects only early postmenopausal women and is characterized by rapid bone loss and Colles'

fracture and crush fractures of the vertebrae. It is associated with normal or partially suppressed PTH secretion due to increased skeletal calcium outflow and suppression of calcium absorption. Thus, this phase of bone loss is homeostatic.

This first rapid phase is replaced by a second, slow phase that continues indefinitely and results in losses of equal proportions of cortical and cancellous bone. A similar phase of bone loss also occurs in men. Many studies have shown that serum PTH increases with aging by 65–90% in both women and men [Khosla et al., 1998]. This increase is the likely cause of the concurrent increase in bone resorption, and, thus, of the increased bone loss. The increase in serum PTH correlated positively with the increase in bone resorption using age as a covariate [Khosla et al., 1998], and the gradient with higher bone resorption in elderly women than young adult women was abolished when serum PTH concentrations were equalized by calcium infusion. Moreover, as assessed by studies of PTH secretory dynamics, we showed that elderly women had findings suggestive of functional parathyroid hyperplasia [Ledger et al., 1994]. In some aging women and men, this slow phase leads to the fracture syndrome that we have called type II osteoporosis [Riggs et al., 1998]. It is characterized by hip fractures and vertebral wedging late in life and by decreased calcium absorption and even higher levels of serum PTH. Thus, the slow phase of bone loss and type II osteoporosis appear to be a non-homeostatic disease in which impaired calcium absorption and secondary hyperparathyroidism are the causes of the bone loss.

Abnormalities in Vitamin D Metabolism and Action

Because $1,25(OH)_2D$ is the major regulator of intestinal calcium absorption, a decrease in the production of $1,25(OH)_2D$ or an impairment in $1,25(OH)_2D$ action were the obvious prime suspects for causation of this abnormality. Serum values for $1,25(OH)_2D$, however, have been reported to increase, remain unchanged, or decrease with the age in women [Eastell and Riggs, 1997], reflecting differences in study design, age, sample size, subject selection, and measurement methods. However, our own data showed an overall increase with the age of about 22%, but by split point analysis, the serum levels were shown to plateau or decrease slightly after the age of 65 years [Eastell et al., 1991]. This pattern was also observed in a much larger study of 855 elderly persons (361 males and 494 females) [Epstein et al., 1986], and we believe it is the pattern that best reflects age-changes in the general population. This pattern suggests that there are two independent process affecting the serum $1,25(OH)_2D$ level, an earlier process that increases it and a subsequent one that decreases it. The initial increase in serum $1,25(OH)_2D$ is strong evidence for intestinal resistance to the action of $1,25(OH)_2D$ because intestinal absorption decreases with aging. Because we were unable to demonstrate resistance to $1,25(OH)_2D$ action using standard oral dosing, we reasoned that the resistance must be relatively subtle. Thus, we designed a study in which a wide range of serum $1,25(OH)_2D$ concentrations from low to high were produced experimentally and values then compared with concomitant measurements of fractional calcium absorption (FCA) in young adult and elderly women. We found a significant correlation between FCA and serum $1,25(OH)_2D$/vitamin D-binding protein ($r = 0.63$, $P = 0.003$), but no relationship in the elderly women, indicating that they had lost this adaptive response [Pattanaungkul et al., 2000] and (Fig. 2). The cause of the apparent intestinal resistance to $1,25(OH)_2D$ action is unclear. In rodents, however, this is associated with a decrease in intestinal VDR concentration [Horst et al., 1990]. Moreover, we have demonstrated a small (26%) but significant decrease in VDR concentration

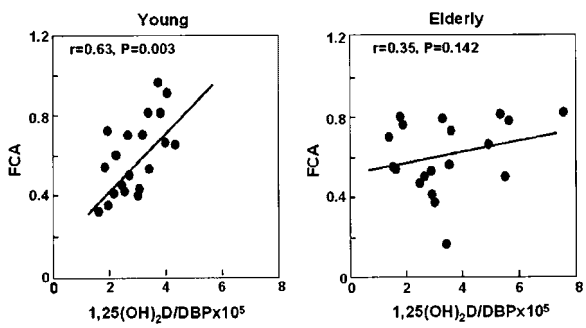

Fig. 2. Relationship between fractional calcium absorption (assessed by double isotope method with 100 mg calcium carrier) and the serum free $1,25(OH)_2D$ index ($1,25(OH)_2D$/vitamin D binding protein) in 20 young adult women and in 19 elderly normal women. Experimental protocol induced levels of serum free $1,25(OH)_2D$ index that ranged from below to above normal. Note that the significant correlations present in the young adult women were lost in the elderly women. Data are from Pattanaungkul et al. [2000], with permission.

with age in duodenal biopsy samples [Ebeling et al., 1992]. However, Barger-Lux et al. [1995] and Kinyamu et al. [1997] could not, so other mechanisms may be operative as well.

Impaired 25-Hydroxyvitamin D (25[OH]D) 1α-Hydroxylase Activity

Although the increase in serum $1,25(OH)_2D$ levels with age appear to be the consequence of resistance to its intestinal action, another mechanism must be found to explain the leveling off and subsequent decline of values after the age of 65 years. Tsai et al. [1984s] from our laboratory found that the rise in $1,25(OH)_2D$ in response to a 24 h PTH infusion decreased progressively with aging and was blunted even more in elderly women with hip fracture (Fig. 3). Slovik et al. [1981] and Kinyamu et al. [1996] reported similar results. This suggests an impairment in the activity of 25(OH)D 1α-hydroxylase late in life leads to reduced production of $1,25(OH)_2D$ in response to increasing levels of serum PTH and other physiologic stimulae. As is discussed in the next section, yet another potential contributor to this decrease late in life is a reduction in substrate due to nutritional deficiency of vitamin D.

Nutritional Deficiency of Vitamin D

Some members of the elderly population may be vitamin D deficient because of poor nutrition, limited sunlight exposure, and age-related decreases in vitamin D absorption and dermal synthesis [Eastell and Riggs, 1997; Lips et al., 2001]. The risk of vitamin D deficiency is greatest at more northernly latitudes, in populations in which the food supplies are not supplemented with vitamin D (as they are in the United States) and in-house-bound elderly persons. Most studies, including those in the United States, have shown that serum 25(OH)D, an index of the body stores of vitamin D, decreases with the age by about 50% in both women and men [Lips et al., 2000]. The data of Ooms et al. [1995], suggested that the threshold for vitamin D may be ~12 ng/ml since below, but not above, that level there are progressive decreases in serum $1,25(OH)_2D$ and bone density levels and increases in serum PTH. If so, ~30% of subjects above the age of 80 years, based on data from an age-stratified, random sample of women residing in Rochester, MN, would be vitamin D deficient, whereas only a few below that age would be [Tsai et al., 1987]. Indeed, about 10% of elderly American patients having a bone biopsy at the time of orthopedic surgery had histologic evidence of osteomalacia [Johnston et al., 1987]. In prospective studies, daily supplements of 800 U of vitamin D and 500 mg of calcium reduced hip fractures by 43% in elderly housebound subjects in Lyon, France [Chapuy et al., 1992], whereas a supplement of 400 U of vitamin D did not significantly reduce hip fractures in a comparable sample of elderly persons living in Amsterdam [Lips et al., 1996].

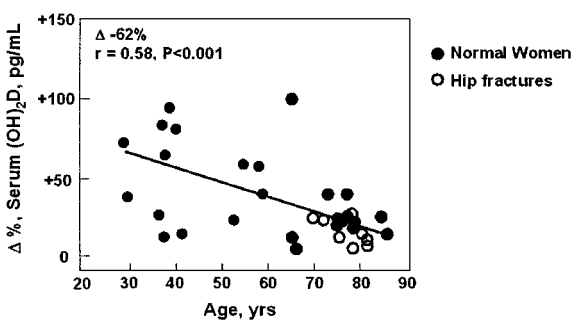

Fig. 3. Effect of age on 25(OH)D 1α-hydroxylase activity as assessed by rise in serum $1,25(OH)_2D$ levels after 24 h infusion with serum PTH(1–34) in 28 normal women and eight elderly women with hip fracture. Note the progressive diminution of activity with aging and that elderly women with hip fracture had even lower values. Data are from Tsai et al. [1984s], with permission.

ARE THE ABNORMALITIES OF THE VITAMIN D-ENDOCRINE SYSTEM PRIMARY OR ARE THEY SECONDARY TO ESTROGEN DEFICIENCY?

The rapid transient phase that begins with menopause is clearly due to estrogen deficiency since it can be prevented by estrogen replacement [Riggs et al., 1998].

Until recently, however, the general belief was that the late, slow phase of bone loss was due to age-related processes, such as secondary hyperparathyroidism and impaired osteoblast function, rather than estrogen deficiency. However, two recent studies have clearly shown that both the increase in bone resorption and serum PTH in elderly women can be completely reversed by physiologic doses of estrogen replacement [McKane et al., 1997; Khosla et al., 1998] (Table I). These clearly demonstrate that the abnormalities are mainly the result of estrogen deficiency rather than primary abnormalities in vitamin D metabolism. We suggest that the secondary hyperparathyroidism in elderly women is due to loss of the estrogen action on

TABLE I. Comparison of 30 Young Premenopausal Women (Pre M), 30 Untreated Postmenopausal Women (Post M), and 30 Post M Women Receiving Long-Term Estrogen Therapy

Variables	Pre M		Pre M		Post M
Number	30		30		30
Age (years)	32.0		73.8		73.8
Estrogen status	Replete		Untreated		ERT
		<0.01		<0.001	
Serum PTH	2.7		3.6		2.5
			NS		
		<0.01		<0.001	
Urine NTx	28.8		42.9		24.6
			NS		

The design allowed the effect of estrogen to be assessed independently of age. Note the increases in serum PTH and urine NH_2-terminal telopeptide (NTx), an index of bone resorption, were dependent on estrogen deficiency, but not on age.

extraskeletal calcium homeostasis. The intestine has been shown to contain functional estrogen receptors [Thomas et al., 1993] and estrogen increases intestinal calcium absorption both in rodents [Thomas et al., 1993] and in humans [Gennari et al., 1990; Gallagher et al., 2001]. Moreover, in women who had been ovariectomized 6 months earlier, the responsiveness of calcium absorption to short-term treatment with $1,25(OH)_2D$ was blunted and this was restored by estrogen replacement [Gennari et al., 1990]. Moreover, estrogen treatment in elderly postmenopausal women increases renal tubular reabsorption of calcium [McKane et al., 1995].

Thus, estrogen appears to have biphasic effects on bone—a direct effect via estrogen receptors in bone cells and an indirect effect via its actions on peripheral calcium homeostasis. We have suggested that the early rapid phase of bone loss is dominated by loss of the direct effects of estrogen on bone, whereas the late effects are dominated to loss of the effects on calcium absorption and renal calcium conservation [Riggs et al., 1998]. The first mechanism in the early rapid phase of bone loss leads to a primary increase in bone resorption, an outpouring of calcium from bone and to normal or suppressed PTH secretion and $1,25(OH)_2D$ production. The second mechanism in the subsequent slow continuous phase of bone loss leads to a primary decrease in calcium absorption due to loss of the intestinal estrogen effect, and, thus, to secondary hyperparathyroidism and increased bone resorption. The existence of both direct skeletal and direct intestinal actions of estrogen and the association of each process with a different phase of bone loss undoubtedly accounts for some of the conflicting data regarding age effects on vitamin D metabolism.

TO WHAT EXTENT DO ABNORMALITIES OF THE VITAMIN D-ENDOCRINE SYSTEM CONTRIBUTE TO AGE-RELATED BONE LOSS AND FRACTURES?

This issue can be best assessed by determining the effect of treatment with physiological dosages of $1,25(OH)_2D$ or other active vitamin D metabolites on bone loss and fractures. A number of clinical trials have now been conducted to address this issue and the reader is referred to recent reviews [Eastell and Riggs, 1997; Reid, 2001] for details and a complete account of published studies. To summarize previously reported data, the trials with $1,25(OH)_2D$ or 1α-OHD have given reasonably consistent results considering the wide divergence in experimental design, ages of subjects, dosages of active drug, and methods of measurement. Treatment for upto 3 years has resulted in most trials of modest to moderate (3% or less) increases in bone mineral density (BMD) at multiple skeletal measurement sites [Itami et al., 1982; Aloia et al., 1988; Gallagher and Goldgar, 1990; Menczel et al., 1994; Orimo et al., 1994; Chen et al., 1997]. The results that have been obtained have been critically dependent on the dosage. An excessive reduction in dosage may explain the negative findings in the trial of calcitriol therapy by Ott and Chesnut [1989]: on data reanalysis, they found that there were increases in BMD in those women who received at least $0.5\ \mu g$/day of $1,25(OH)_2D$, but no effect in women who received lower dosages (1990). Several groups [Orimo et al., 1987; Gallagher et al.,

1989; Tilyard et al., 1992; Gallagher et al., 2001] have reported impressive decreases in vertebral fracture rates of 30–60%, a response that seems larger than can be accounted for by the modest increases in BMD.

Gallagher et al. [2001] recently have reported the results of a 3-year double-blind prospective-controlled trial in 489 elderly women treated factorially with placebo, $1,25(OH)_2D$ (0.5 μg/day), estrogen replacement therapy (ERT) or ERT plus $1,25(OH)_2D$. In compliant subjects, they found that the $1,25(OH)_2D$ treatment group had a higher BMD ($\sim$2%, $P < 0.005$) at various scanning sites than the placebo group, although the group receiving ERT had a substantially higher BMD. However, the group receiving both $1,25(OH)_2D$ and ERT had the highest BMD. Interestingly, the two groups receiving $1,25(OH)_2D$ had 50% fewer fractures than the two groups who did not receive $1,25(OH)_2D$. Because of the factorial nature of the design, the relative effects of $1,25(OH)_2D$ and estrogen on BMD could be deconvoluted. Using this approach, the estimated proportion of the bone effect of estrogen that was mediated by $1,25(OH)_2D$ was 34.5% for the mean of four scanning sites, whereas the proportion of the bone effect of $1,25(OH)_2D$ that was independent of estrogen was estimated to be 18.3%. Although this study provides useful data, a major caveat is that subjects were excluded who had BMD values below the age-adjusted normal range. In previous studies, we have found that osteopenic and osteoporotic patients have the greatest abnormalities of calcium absorption and vitamin D metabolism [Gallagher et al., 1979; Riggs and Nelson, 1985]. Thus, these must be considered to be minimal estimates, and the true impact of primary abnormalities of vitamin D metabolism and action is likely to be larger.

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