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Osteoporosis and Vitamin D

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Abstract Bone "density" (bone mass/bone volume) declines with age from the menopause in women and from about age 55 in men. This fall in bone density (osteoporosis) weakens the bones and leads to a progressive rise in fracture rates, particularly in women. Many risk factors contribute to the bone-losing process, but one which attracts increasing attention is calcium absorption.

The main physiological regulator of calcium absorption is vitamin D. This is manufactured in the skin under the influence of UV-light and then converted to more potent metabolites in the liver and kidney. Although the serum levels of the most potent metabolite $1,25(OH)_2D_3$ (calcitriol) are generally normal in osteoporotic women, treatment with small doses of calcitriol (about 0.25 μg daily) has a remarkable effect on absorptive performance and slows down the rate of bone loss. Improved synthetic metabolites are under development.

There is likely also to be greatly increased scope for the use of vitamin D itself in osteoporosis. With advancing age, there is a tendency for men and women to be exposed to less and less sunlight, which is the main natural source of vitamin D. Vitamin D levels, therefore, decline with age, particularly in those who are housebound, and are found to be low in most reported series of hip fractures. It is likely that this form of vitamin D "insufficiency" has an adverse effect on calcium absorption in the elderly which accelerates bone loss and increases the risk of hip fracture and can be treated with small doses of vitamin D or its 25-hydroxy derivative. This offers a second important role for vitamin D in the prevention and management of osteoporosis.

Key words: calcitriol, fractures, osteomalcia, osteoporosis, vitamin D, bone density, menopause

In order to appreciate the connection between osteoporosis and vitamin D, which at first glance appears an unlikely conjunction, it is necessary to know something about the way in which research in these two areas has developed in the last twenty years. It will then become apparent that vitamin D and its derivatives are likely to play an important role in the future prevention and management of osteoporosis.

THE NATURE OF OSTEOPOROSIS

It has been known for a long time, perhaps 200 years or more, that fractures are increasingly common with advancing age—particularly in women. These fractures, commonly attributed to "brittle bones," are in fact due not so much to a change in the quality of bony tissue as to a decline in its mass with advancing age.

Bone is a living tissue composed of cells embedded in a mineralised collagenous matrix which is being continuously broken down and re-formed (half-life about 5 years). As and when it is being made, a form of calcium phosphate is deposited in the collagen to mature ultimately into a carbonate-containing apatite [Termine and Posner, 1967]. During growth, the rate of bone formation exceeds the rate of bone resorption (breakdown) but by the third decade, formation and resorption have come into equilibrium and the bone mass remains virtually stable until middle life.

At the time of the menopause in women, and at about the age of 55 in men, this bone equilibrium is disturbed, resulting in a progressive decline in bone mass which continues more or less to the end of life. In women, the initial change of state involves an increase in the rate of bone resorption, causing the removal of some 10–15% of skeletal tissue in the first five years after menopause. It then continues at a slower rate, accompanied perhaps by some age-related decline in the formation process. In men, the disequilibrium is largely due to a decline bone formation.

As this loss of bone progresses, the incidence of all fractures rises in both sexes, but because women start with less bone than men, lose it more rapidly and live longer, the increase in fracture prevalence with age is much greater

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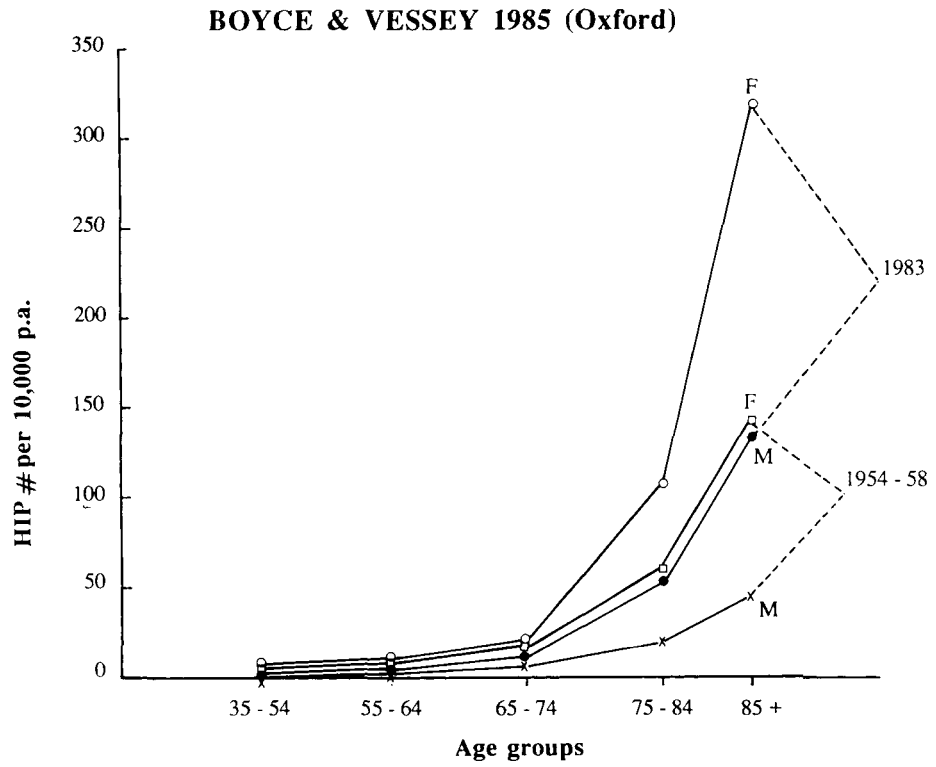

Fig. 1. Age-specific rates of hip fractures in men and women in 1954–58 and in 1983 [calculated from Boyce and Vessey, 1985].

and socially m(gnificant in them than in men. These age ted fractures appear to be more prevalent in whites than blacks and more prevalent in the developed than in the third world, where the fracture rates appear to be rising (Fig. 1).

Since there is no decline in bone size with age (if anything the reverse [Horsman, 1976]), the age-related loss of bony tissue represents a fall in "apparent" bone density, i.e., in the mass of bone relative to its external volume; there is no significant change in the density of the bony tissue itself. This reduction in apparent bone density is known as "osteoporosis" and is largely responsible for the age-related rise in fracture rates—though an increasing liability to falls from a variety of causes also makes a significant contribution in the very old. Some idea of the magnitude of the problem can be obtained from the estimate that hip fracture care in the United States alone costs some $10 billion a year [Kelsey and Hoffman, 1987]. It has been suggested that if present trends continue there will be 500,000 hip fractures a year in the United States by the end of this century.

PATHOGENESIS OF OSTEOPOROSIS

As indicated above, the age-related decline in bone density must be due to an imbalance between the rates of bone formation and bone resorption. In the early part of this century, before the socio-medical significance of osteoporosis had been appreciated, little attention was paid to the subject but it was inferred from animal experiments that the condition was due to calcium deficiency. In the 1930s, some confusion occurred in the collective scientific mind between the consequences of calcium deficiency and vitamin D deficiency, both of which were thought to cause rickets in children and osteomalacia in adults. These conditions represent a failure to mineralise new bone and a consequent reduction in the mineral content of bony tissue. To seek a way out of this confusion, Fuller Albright, the leading endocrine investigator of his time, proposed that osteoporosis was due to an insufficiency of bone collagen synthesis and quite distinct from calcium or vitamin D deficiency [Albright et al., 1941]. This view held sway for a generation until it was found to be an

unfruitful hypothesis and the earlier calcium deficiency model was revived [Nordin, 1960]. Since then, it has become apparent that high bone resorption, not low bone formation, is the main cause of osteoporosis, at least in women, and the idea is gaining ground that calcium deficiency may be at least in part responsible for the progressive loss of bone with advancing age.

Calcium deficiency in this context needs to be interpreted very broadly. Just as iron deficiency can occur from blood loss or malabsorption or low intake of iron, so calcium deficiency does not necessarily imply an absolute deficit in calcium intake. Calcium deficiency, like iron deficiency, is a state in which the obligatory loss of calcium in faeces, urine, and sweat exceeds the dietary intake, either because dietary intake is low or because the obligatory losses are high, or both. It is a striking feature of calcium metabolism that the human requirement for this element calculated from calcium balances, is relatively high—500 to 600 mg daily [Nordin et al., 1987] (though there are those who dispute this figure [Kanis and Passmore, 1989]). This arises on the one hand from the relatively low net fractional absorption of dietary calcium (only about 25%) and on the other from the relatively high obligatory calcium loss in the urine (100–150 mg daily), not to mention an obligatory loss through the skin (about 50 mg daily) [Charles et al., 1983]. If output exceeds intake, the deficit is made good by the skeleton, the removal of mineral to maintain the concentration of calcium in the plasma, being accompanied by the breakdown of bone and the development of osteoporosis. Because 99% of the body's calcium is stored in the skeleton, bone balance and calcium balance are in fact synonymous; a negative external calcium balance must cause a state of negative bone balance. Since calcium absorption varies inversely with calcium intake [Wilkinson, 1976; Bronner, 1988; Heaney et al., 1990], the capacity of an individual to adapt to different calcium intakes rests largely in the gastrointestinal tract. In calcium balance studies, absorbed calcium accounts for more of the variance in calcium balance than calcium intake and excretion together (Table I). Since vitamin D is the main regulator of calcium absorption, it is a very important determinant of calcium balance. This is not to deny that a primary imbalance between bone formation and resorption (negative bone balance) may be responsible for a secondary negative calcium balance, e.g., in hyperthyroidism (and, many would say, in oestrogen deficiency), but generally the osteoporotic process appears to be responsive to external manipulation of calcium balance.

TABLE I. Contributions of Calcium Intake, Absorption and Excretion to the Total Variance on Calcium Balance in 105 Balance Studies on Normal and Osteoporotic Postmenopausal Women

Variable	Proportion of balance variance accounted for (%)	*P*
Ca intake	1.6	ns
Ca absorption	57.5	<0.001
Ca urine	40.9	<0.001

VITAMIN D

Vitamin D_3 (cholecalciferol) is a secosterol, the existence of which was recognised in the 19th century, but the purification and identification of which was not completed until Mellanby reported it in 1921. Severe deficiency of this vitamin, now often classified as a hormone, is known to cause rickets in children and osteomalacia in adults. It is formed in the skin from 7-dehydroxycholesterol under the influence of ultraviolet light, transported to the liver, where it is hydroxylated in the 25 position. It then passes to the kidney where it is further hydroxylated in the 1 position to the most active form of vitamin D, or in the 24 position to a compound whose biological function is uncertain. The active forms of vitamin D are largely bound to vitamin D-binding protein in the plasma and exert their cellular effects by combining with a specific intracellular receptor [Reichel et al., 1989] which is found in the gastrointestinal tract, the bone, the kidneys, the parathyroids and in other tissues. Although the ratio of free $1,25(OH)_2D_3$ to free $25OHD_3$ in the plasma is only 1:100 [Bouillion et al., 1981] (Table II), the 1,25 derivative is the most important biologically because its affinity for the specific receptor is 1,000 times that of its 25 hydroxy precursor. The actions of vitamin D are therefore largely attributable to the action of the 1,25 dihydroxy compound produced in the kidney, but this is not to say that the precursor compounds cannot be active in their own right in the absence of the dihydroxy metabolite—as for instance in severe renal failure.

TABLE II. Production Rates and Normal Ranges in Plasma of the Principal Vitamin D Metabolites

Variable	Production rate	Serum level	
		Total	"Free" (%)
$25OHD_3$	10 nmol/day (4 μg)	100 nmol/L (40 μg/L)	0.1
$1,25(OH)_2D_3$	1 nmol/day (0.4 μg)	100 pmol/L (40 ng/L)	1

The best known action of vitamin D is to promote the absorption of calcium from the lumen of the gastrointestinal tract. Absorption occurs by active transport and by diffusion [Wilkinson, 1976; Bronner, 1988]; it is probably the former that is controlled by vitamin D, i.e., by calcitriol. This exerts its action by a rapid non-genomic action known as transcaltachia and a slower effect involving nucleo-protein synthesis [Nemere and Norman, 1987]. Less well recognised but equally important is the calcaemic action of vitamin D which facilitates the action of parathyroid hormone to maintain the plasma (ionized) calcium concentration in the narrow normal range that is vital for most cellular processes. This calcaemic action, first described by Carlsson and Lindqvist in 1955 can be demonstrated as bone resorption in tissue culture [Reynolds et al., 1973] and its loss is responsible for the hypocalcaemia and secondary hyperparathyroidism which are characteristic features of severe vitamin D deficiency [Peacock et al., 1985]. However, loss of this action seems to develop later in the process of vitamin D deficiency than impairment of calcium absorption. There is every reason to believe that a minor degree of vitamin D deficiency (what Peacock et al. [1985] has called "vitamin D insufficiency") may be associated with malabsorption of calcium before it is sufficiently severe to lower the plasma calcium concentration, stimulate the parathyroid hormone glands, and cause rickets or osteomalacia. This vitamin D insufficiency may occur with advancing age in people with intermediate levels of vitamin D in plasma and may contribute to the development of osteoporosis in the housebound and at latitudes where hours of sunlight are a limiting factor in the supply of vitamin D. This may be the significance of the low serum $25OHD_3$ levels reported in several series of hip fracture cases [e.g., Baker et al., 1979; Lips et al., 1982] although only a minority of them have histological evidence of osteomalacia [Aaron et al., 1974; Lips et al., 1982]. Many however have evidence of high bone resorption [Nagant de Deuxchaisnes and Devogelaer, 1986].

CALCIUM ABSORPTION IN OSTEOPOROSIS

There is of course every degree of osteoporosis. If the condition is defined as one in which bone density falls more than two standard deviations below the young normal mean in the same sex, then it affects virtually all women and most men sooner or later; at least 50% of women are osteoporotic on this definition by the age of 65. Some of these women develop more severe osteoporosis than others and go on to develop spontaneous fractures of the vertebral bodies in the spine. This condition, often referred to as spinal osteoporosis, is frequently the precursor of a later hip fracture but because it affects a rather younger population (mean age 65) it has been more extensively studied than the hip fracture and is the condition implied by most clinicians when they refer to "osteoporosis." There is every reason to believe that these women have reached their severely osteoporotic state by accelerated bone loss [Nordin, 1992]. A central question is, Why do they lose bone at an accelerated rate?

When osteoporotic women, defined in this way, are compared with age-matched controls, the variables in which they differ most significantly are calcium absorption (lower in the osteoporotics) and urinary calcium and hydroxyproline (higher in the osteoporotics) (Fig. 2). Their raised urinary hydroxyproline simply reflects their increased bone resorption, which is most easily explained as a response to the combination of decreased calcium absorption and increased calcium loss, though there are those who believe that both abnormalities are the result rather than the cause of the osteoporosis [Gallagher et al., 1979]. In a group of elderly, the urinary hydroxyproline is positively related to the urine calcium and negatively to the calcium absorption (Table III). When these two independent

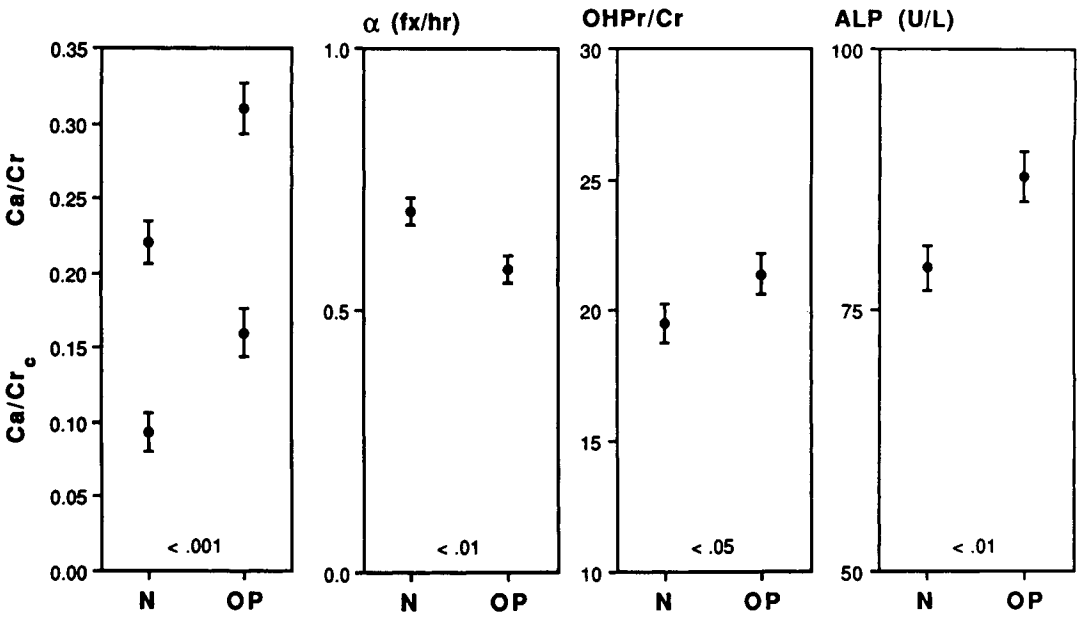

Fig. 2. Fasting urinary calcium (before and after correction for sodium), radiocalcium absorption urinary hydroxyproline and alkaline phosphatase in age-matched normal and osteoporotic postmenopausal women.

TABLE III. Regression of Fasting Urinary Hydroxyproline on Calcium Excretion and Calcium Absorption in Normal and Osteoporotic Postmenopausal Women

	P
OHPr/Cr = 15.4 Ca/Cr	<0.001
− 5.2 α	<0.005
+19.4	<0.001
Residuals: N −0.28: OP +0.18	ns

TABLE IV. Serum Calcitriol Concentration in Age-Matched Normal and Osteoporotic Postmenopausal Women

Group	n	Serum 1,25D (pmol/L) ± SE
Normal	72	93 ± 3.8
Osteoporotic	120	89 ± 3.7
P		ns

variables were allowed for, the difference in hydroxyproline between the normal and osteoporotic women lost its significance (Table III). There is therefore a strong presumption that impaired calcium absorption is in fact a significant risk factor for osteoporosis which has the same ultimate effect on the body's calcium economy as simple dietary deficiency. Some have argued that this malabsorption of calcium is due to secondary depression of the plasma calcitriol level [Riggs, 1985] but in our experience the calcitriol "deficiency" such as it is (Table IV) is not sufficient to account for the impairment in calcium absorption, which is more likely attributable to a receptor insufficiency in the gastrointestinal tract [Francis et al. 1984, Morris et al., 1991].

Whatever the true explanation of calcium malabsorption in postmenopausal osteoporosis may be (and it is also seen in other forms of osteoporosis such as that induced by corticosteroids [Morris et al., 1990]), it responds to calcitriol therapy in doses as small as 0.25 μg daily in a dose-related manner [Nordin et al., 1991a] (Fig. 3). Doses of 0.25 μg on alternate days have little effect; 0.25 μg daily has a very significant effect, and 0.5 μg daily an even greater effect. The administration of calcitriol is associated with a significant reduction in urinary hydroxyproline (Fig. 4) as would be expected if the high bone resorption were attributable—in part at least—to the impairment of calcium absorption. This malabsorption of calcium cannot be attributed to vitamin D deficiency, or even insufficiency, since the serum $25OHD_3$ is generally

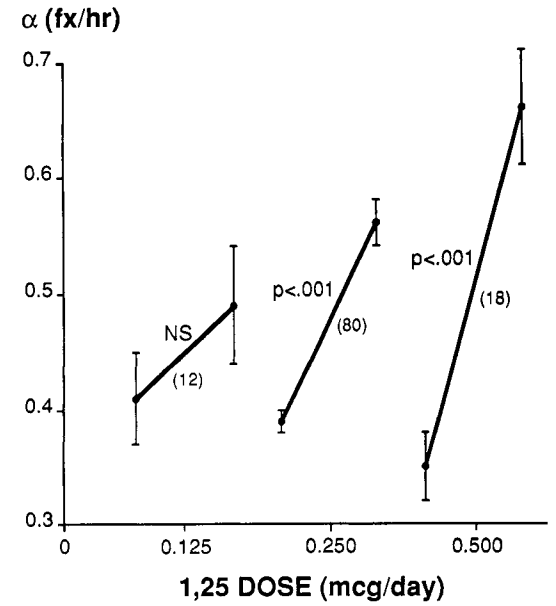

Fig. 3. Hourly fraction absorption and radiocalcium (α) in 33 osteoporotic postmenopausal women before and after treatment with 2 doses of calcitriol.

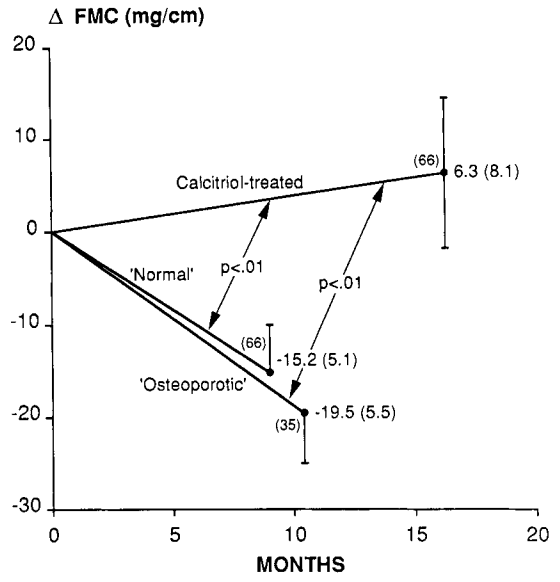

Fig. 5. Cumulative change in forearm mineral content in calcitriol-treated osteoporotic postmenopausal women compared with age-matched normal controls and untreated women with osteoporosis.

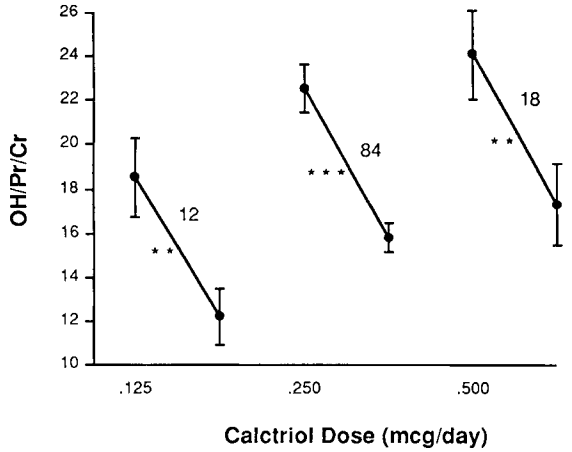

Fig. 4. Fasting urinary hydroxyproline in osteoporotic postmenopausal women before and after treatment with calcitriol.

normal in these patients and the malabsorption does not respond to treatment with $25OHD_3$ [Francis et al., 1984]. Moreover, there is no significant loss of bone in calcitriol-treated osteoporotic women compared with a significant loss in age-matched controls and untreated cases of osteoporosis (Fig. 5).

CONCLUSIONS

Proceeding along different paths for at least a generation, the stories of osteoporosis and vitamin D have converged and met. While the osteoporotic fracture rates rise from year to year in Western countries, and the total number of fracture cases increases even more rapidly owing to the ageing of the population, the underlying mechanisms are being gradually elucidated and point increasingly to a central role for calcium absorption—or more correctly malabsorption. The main interest at present attaches to the use of calcitriol in correcting the malabsorption of calcium in women with accelerated osteoporosis in doses which do not increase bone resorption by their calcaemic action but in fact reduce it. Many laboratories are now seeking to develop derivatives or analogues even more favourable in their relative effects on gut and bone than is calcitriol itself. Since there are vitamin D receptors in the kidney as well, it is not inconceivable that the renal calcium leak which follows the menopause [Nordin et al., 1991b] may also be amenable to one of these analogues. If bone formation could also be stimulated by some related compound, we could have an ideal treatment for this type of osteoporosis, which might also be preventive if the subjects at risk could be identified in advance.

There is also a second, more subtle potential role for vitamin D in the prevention and treatment of osteoporosis—namely, in those elderly individuals, particularly but not only the housebound, who develop vitamin D insufficiency. A

study of elderly apparently normal women in the north of England [Nordin et al., 1985] showed a significant positive effect on metacarpal bone mass of vitamin D treatment for 2 years in doses of 15,000 units weekly, which is essentially a replacement dose. This has far-reaching implications for the prevention of hip fractures, which may be occurring in women whose bone loss has been accelerated by impaired calcium absorption due to unrecognised vitamin D insufficiency.

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