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BONE ABSORPTIOMETRY IN METABOLIC BONE DISEASE: BASELINE VALUES AND LONG-TERM TREATMENT WITH CALCITRIOL (POST-MENOPAUSAL OSTEOPOROSIS VERSUS OSTEOMALACIA)

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Abstract

Total body bone absorptiometry reveals low mineral density in both postmenopausal osteoporosis and osteomalacia patients. The method was used to investigate the effect of calcitriol administration on patients suffering from one of these conditions. In osteomalacia, the administration of calcitriol resulted in a dramatic improvement in bone mineral density (sometimes up to 50% in 12 months), indicating the rapid mineralization of previously uncalcified bone tissue as a result of the normalization of the Ca x P product. In osteoporosis a similar treatment was seen to halt the progressive decrease in bone mineral levels and sometimes resulted in minor increases in density (up to 5%). This is likely to be due to a normalization of intestinal calcium malabsorption which halts secondary homeostatic bone resorption.

Key Words: Total body bone mineral density, postmenopausal osteoporosis, osteomalacia, calcitriol treatment.

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Introduction

Osteomalacia and postmenopausal osteoporosis are two pathological conditions that are very different in terms of their etiology, physiopathology and morbid anatomy. In osteomalacia, the bone mass normally produced by osteoblasts remains incompletely calcified mainly because of hypophosphatemia (due to insufficient intestinal absorption and/or the excessive renal loss of phosphate), which lowers the Ca x P product to below the minimum limit necessary for the formation of hydroxyapatite and the nucleation of its crystals in the organic matrix of newly formed bone. In postmenopausal osteoporosis, bone mass decreases mainly as a result of the increase in bone resorption, which occurs to maintain calcium homeostasis.

The possibility of measuring bone mineral content *in vivo* has always been a primary objective in the study of calcium and phosphate metabolism, but traditional radiology provides approximate indications concerning mineralization only when the skeleton has lost at least 30-40% of its mineral content. The introduction of absorptiometry (bone densitometry) has given a considerable boost to mineralometric research and the spread of such measurements to practical diagnostics.

Single photon absorptiometry [2] of the wrist has been very useful in screening large numbers of people at risk for osteoporosis, but it is difficult to use in longitudinal studies because of serious problems in positioning and repositioning the explored bone segment, which may surreptitiously modify bone mineral density measurements. Dual-photon absorptiometry [37] offers important methodological advantages: (a) dual-photon absorptiometry (DPA) uses gadolinium 153, a radioisotope that emits two photons with two different energy levels (44 and 100 KeV); (b) dual-energy X-ray absorptiometry (DPX or DEXA) uses an X-ray source with a cathode tube alternately emitting X-rays of 70 and 140 keV [23]. X-ray mineral measurements provide a higher photon flux which allows greater precision, a reduction in the duration of the examination, and a cheaper and longer lasting source.

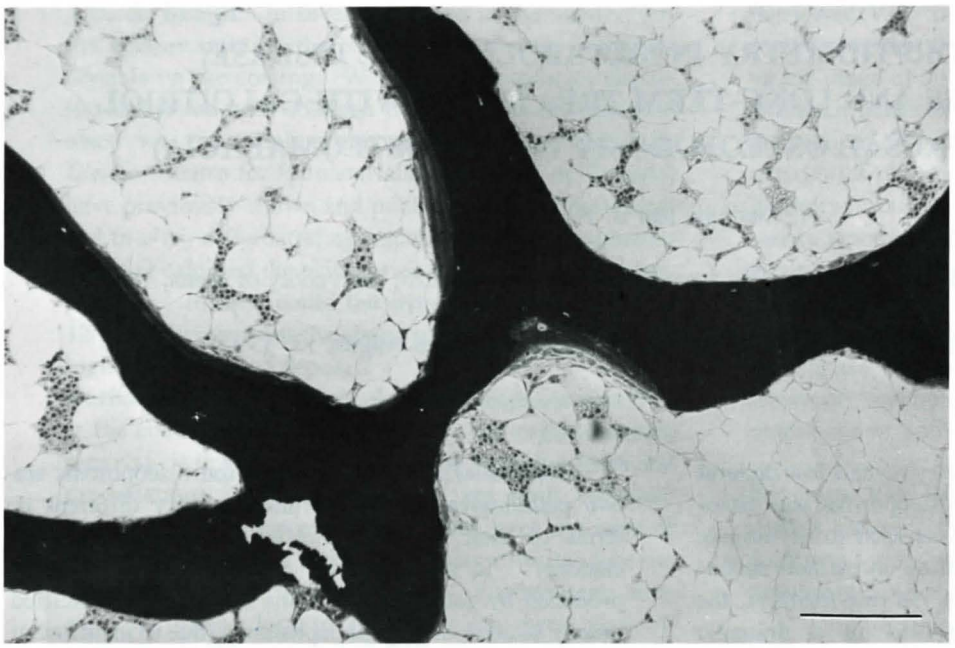


Figure 1. Biopsy of the iliac crest in a case of postmenopausal osteoporosis (von Kossa stain on non-decalcified bone). The bone trabeculae are extremely thin with a widening of the medullary spaces; hardly any osteoblasts or osteoclasts can be seen. The black colour of the trabeculae show that these are completely calcified. Bar = 200 μm.

Table 1. Total body densitometry (DEXA) g/cm^2 in Italians (normal values by decade).

Age →	21-30	31-40	41-50	51-60	61-70	71-80
Females						
Maximum	1.17	1.17	1.18	1.13	1.09	1.08
Minimum	0.98	1.03	1.01	0.99	0.97	0.95
Males						
Maximum	1.28	1.18	1.26	1.19	1.24	1.13
Minimum	1.07	1.01	1.04	1.06	1.08	1.05

In our opinion, dual-photon lumbar absorptiometry suffers from a number of drawbacks associated with anomalies in the anatomy of the explored region: problems in positioning and repositioning the lumbar spine when this is deformed by kyphosis or scoliosis; the uncertain visualization of intervertebral spaces; vertebral crushing; the presence of osteophytes or bone bridges, etc., all of which are frequently encountered in the elderly for whom this technique otherwise would be particularly appropriate [29].

Consequently, although lumbar vertebrae mineral measurements are extremely useful for evaluating mineral content under normal conditions, or in diseases involving osteopenia or demineralization, the prevailing tendency today is to use total body scans because they allow the drawbacks of the technique to be overcome and ensure impartial measurements. The prevalence of postmenopausal osteoporosis, which has been progressively increasing in white women throughout the world, has made bone absorptiometry very popular in the diagnostics of this metabolic disease of the skeleton [4, 24, 25].

The aim of the present study was to compare total body bone densitometry in postmenopausal osteoporosis and nutritional osteomalacia, two pathological conditions in which the positive therapeutic effect of calcitriol has been widely demonstrated. No consideration was given to other types of osteopenia.

Materials and Methods

The study included patients with osteomalacia or postmenopausal osteoporosis. All patients included in the study gave informed consent. The diagnoses of postmenopausal osteoporosis and nutritional osteomalacia for this study were made on the basis of traditional clinical and radiological criteria: bone fractures and deformations; laboratory data, such as plasma calcium, phosphate and alkaline phosphatase levels, 24-hour urinary calcium, phosphate and hydroxyproline; radio-calcium

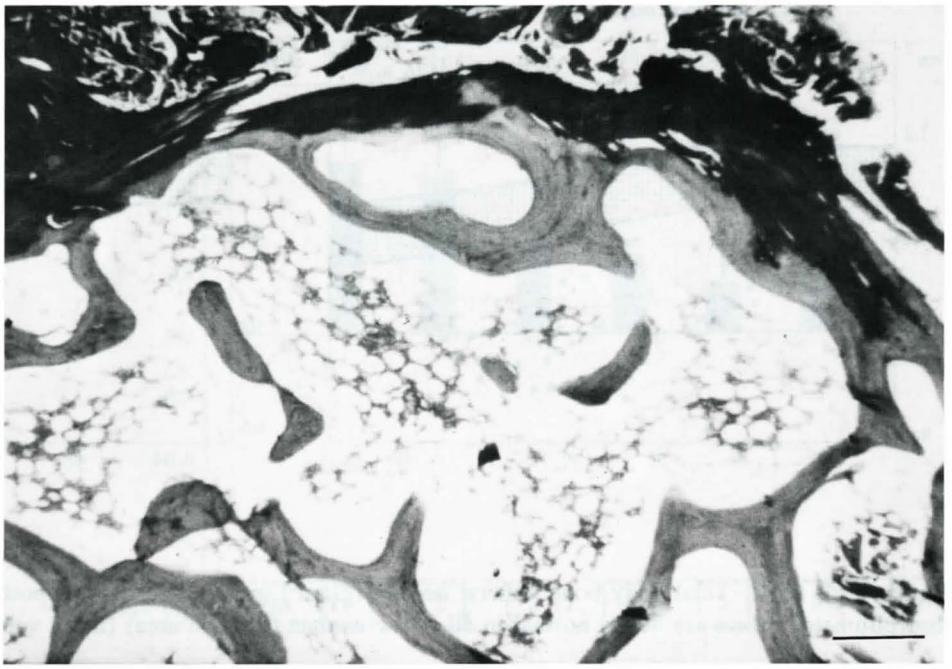


Figure 2. Biopsy of the iliac crest in a case of postmenopausal osteoporosis. The resorption of the cortex leads to a "spongy transformation" of cortical bone: no Haversian channels can be seen under the periosteum. Bar = 200 μm.

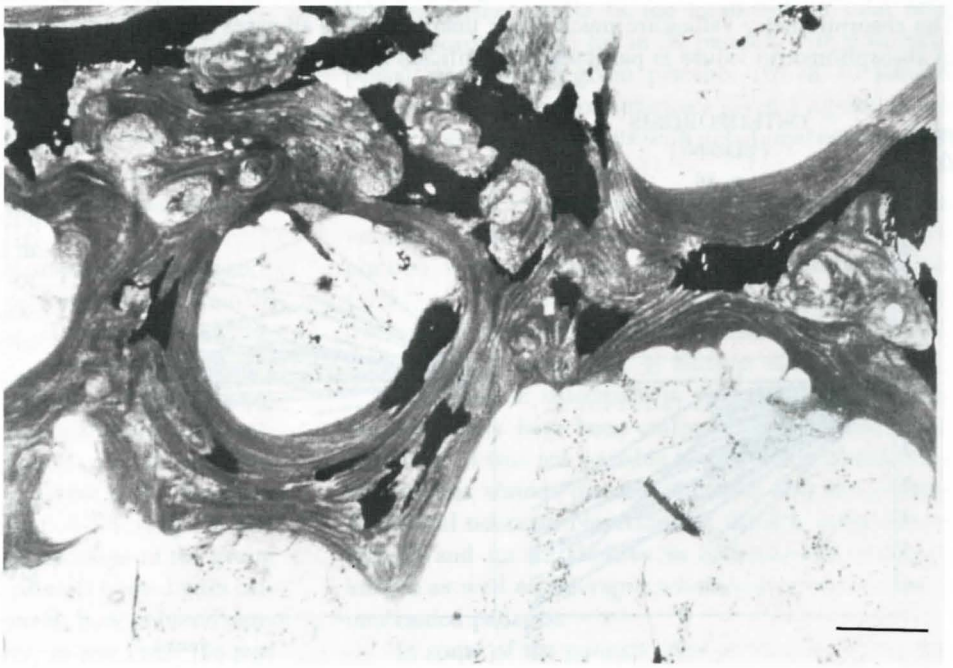


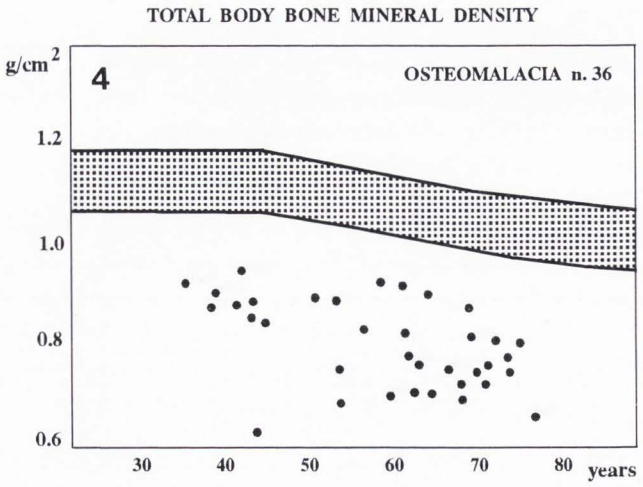
Figure 3. Biopsy of the iliac crest in a case of nutritional osteomalacia (von Kossa stain on non-decalcified bone). The thickness of the bone trabeculae is normal. Trabeculae show areas of completely calcified bone (black) alternating with large red areas of non-calcified osteoid tissue, which appear grey in the black and white photograph. Bar = 200 μm.

oral tests to assess intestinal calcium transport. In most of the patients, the diagnosis was confirmed by a biopsy of the iliac crest.

The mean age of the postmenopausal osteoporotic women at the start of treatment was 66 $\pm$ 9.5 years (range 41 to 81); that of the osteomalacic women was 61 $\pm$ 12.6 years (range 34 to 78).

No particular diet was prescribed. Our postmenopausal osteoporotic patients were ambulatory and their diet was that of average elderly Italian women: bread, pasta or rice, vegetables, fruit, and very small quantities of meat, cheese and milk. In brief, a diet that is much poorer in calcium than that of the populations of Northern Europe and the USA (500-700 mg/day Ca).

The skeleton of the patients was analyzed by total body absorptiometry, which allows an accurate and precise analysis of the mineral content of the whole skeleton, as well as of some regions of interest. The Lunar DEXA densitometer used by us scans at a speed of 8 or 16 cm/sec with longitudinal step intervals of 1 cm; the pixel size is 4.8 x 9.6 mm and, of the total number of 22,000 pixels, 4500 correspond to bone. The radiation



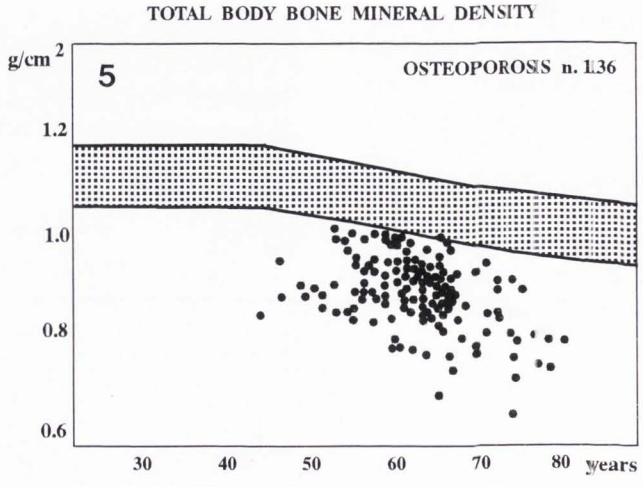


Figure 4 (at left). Total body bone mineral density (g/cm^2) in 136 women with postmenopausal osteoporosis. The absorptiometry values are below normal in all of the women (hatched area) (mean value 0.911).

Figure 5 (at right). Total body bone mineral density (g/cm^2) in 36 subjects with histologically proven osteomalacia. The absorptiometry values are much lower than normal in all cases (hatched area) (mean value 0.804). The reduction in absorptiometric values is particularly significant in the younger subjects

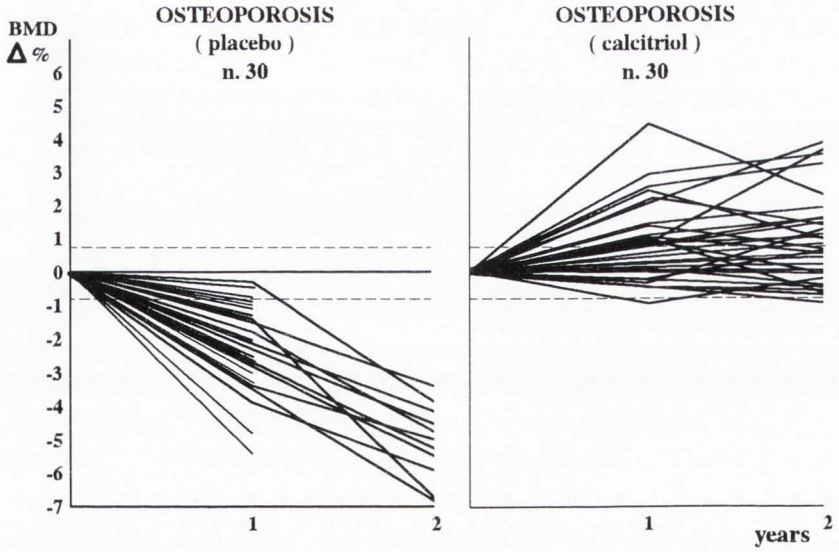


Figure 6. The behaviour of total body bone mineral density in 30 women with postmenopausal osteoporosis treated for two years with an inert placebo (left panel) and in 30 women with postmenopausal osteoporosis continuously treated with calcitriol (1 μg/day) for two years (right panel). The progressive reduction in bone mineral density (-5% $\pm$ 1.7 after two years) corresponding to progressive bone loss is clear in the placebo group and it is halted in the calcitriol group (+1.2% $\pm$ 1.6).

dose is about 1 mRem. The data supplied include: total body bone mineral content (TBBM), of which calcium represents 38%, the total bone density (TBD), and the bone density of the areas of major interest (the spinal column for spongy bone; the limbs for compact bone). The coefficient of variation (precision) of total bone density is 0.34% in normal subjects and 0.70% in osteoporotic patients [30].

The range of correlation between bone mineral density and age has been constructed for normal subjects of both sexes (see Table 1) [22, 26].

Results

Figures 1-3 describe the histology of postmenopausal osteoporosis and osteomalacia. Postmenopausal osteoporosis is defined as bone loss, with normal mineralization of the remaining bone. The bone trabeculae become increasingly thinner, fracture and many of them disappear (Fig. 1). The resorption of the cortex leads to a progressive "spongy transformation" of cortical bone (Fig. 2). In osteomalacia, on the other hand, the osteoblasts regularly produce the bone collagen that structures

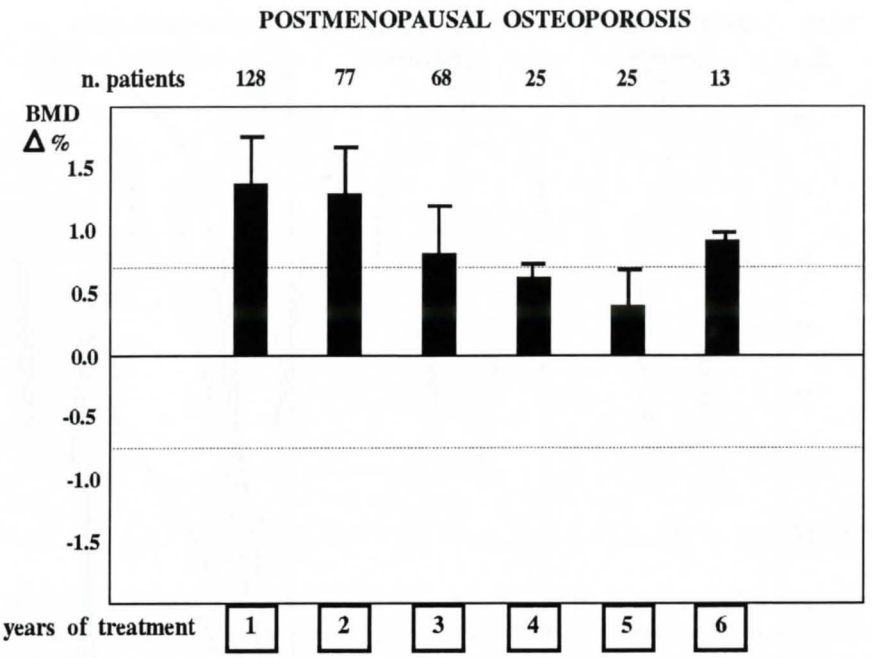


Figure 7. The behaviour of total body bone mineral density in a group of women with postmenopausal osteoporosis continuously treated with calcitriol (1 μg/day) for periods ranging from one to six years. The columns show the mean percentage modifications and standard deviation in the individual groups. The majority of the patients remained within the precision limits of the method. In other words, calcitriol impeded the progressive bone loss which would have occurred if the patients had not been treated (or if they had been treated with placebo).

the osteoid layers, but these remain incompletely calcified (Fig. 3).

In the study summarized in Figure 4, a total of 136 postmenopausal osteoporotic women were involved. The values of total body absorptiometry were lower than in age-matched non-osteoporotic women (Fig. 4). The total body absorptiometry values of 36 patients with nutritional osteomalacia were also lower than those of age-matched normal subjects (Fig. 5).

In a double-blind study, we compared 30 postmenopausal osteoporotic women given 1 μg/day of calcitriol with 30 age-matched postmenopausal osteoporotic women given an inert placebo. In the "untreated" placebo group, bone mineral density decreased, and a significant number of these patients voluntarily stopped the treatment after one year probably because of its poor efficacy; in those who completed the two-year study, the average decrease in density was about 4-5% (Fig. 6, left panel). The bone density did not decrease in the group of postmenopausal osteoporotic patients treated with calcitriol. In some, but not all, women, bone mineral density actually increased. However, in any case, the loss of bone mineral density was halted (Fig. 6, right panel). This was also seen in a study ranging over 6 years including 336 patients with postmenopausal osteoporosis (Fig. 7). Since the patients experienced a positive effect from the treatment, compliance was better than in the placebo group.

In a group of patients with nutritional osteomalacia and total body densitometry values that were lower than normal, two years' treatment with calcitriol resulted in a dramatic increase in these values (Fig. 8), which sometimes increased by more than 50% after a period of 12-24 months. The three different panels of Figure 8 summarize the effects of the treatment on total body bone absorptiometry: (a) in 30 patients with postmenopausal osteoporosis given placebo; (b) in 30 patients with postmenopausal osteoporosis given 1 μg/day of calcitriol; and (c) in 7 patients with nutritional osteomalacia given 1 μg/day of calcitriol.

Statistical comparisons of the densitometric percent variations after two years has been performed: (1) in placebo versus calcitriol treated osteoporotic patients ($-5\% \pm 1.7$ versus $1.2\% \pm 1.6$; $p < 0.01$); and (2) in osteoporotic versus osteomalacic patients given calcitriol ($1.2\% \pm 1.6$ versus $26\% \pm 10.6$; $p < 0.01$).

The data on osteomalacia patients included in the present papers have been collected over several years; therefore, it was not possible to perform a double blind trial of this serious disease; this was also not possible for ethical reasons. Nevertheless, the efficiency of vitamin D and its metabolites in osteomalacia is largely known as well as the rapid worsening of the disease in unattended patients.

In some of the patients with osteomalacia, the subsequent visual display images of the densitometer were very impressive (Fig. 9), and it was possible to directly follow the progressive increase in bone mineral density throughout the course of treatment.

Discussion

With regard to bone mineral density, patients with osteomalacia have a different response to calcitriol treatment, compared to patients with postmenopausal osteoporosis. In patients with nutritional osteomalacia,

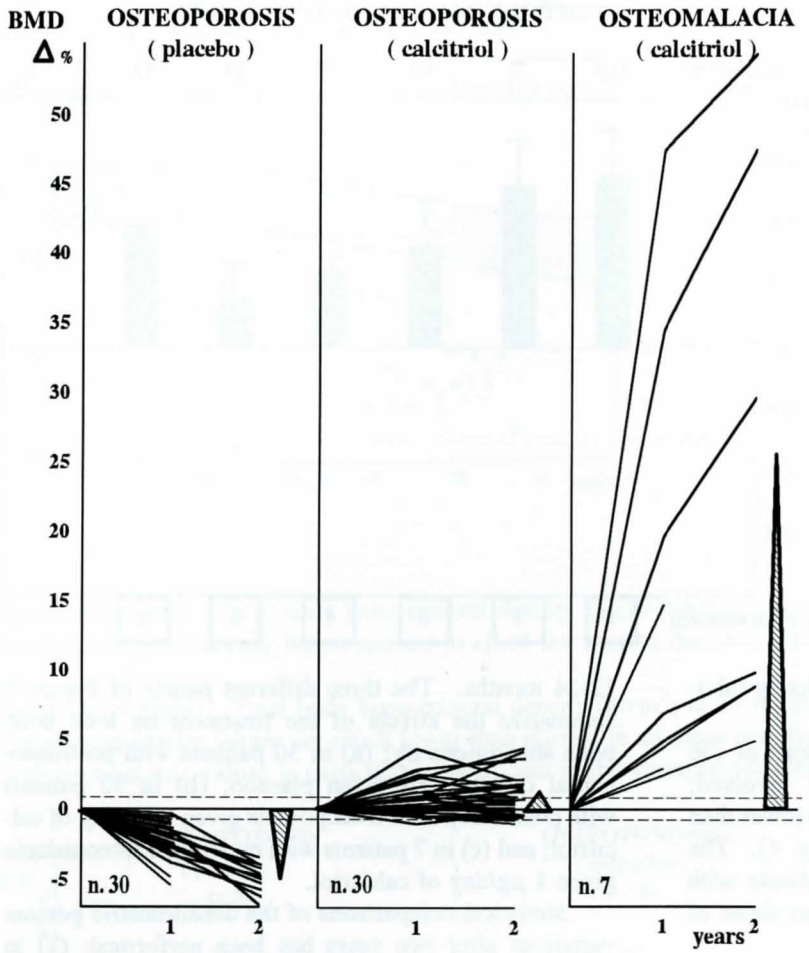


Figure 8. The behaviour of total body bone mineral density in a number of subjects with nutritional osteomalacia given long-term calcitriol 1 μg/day treatment (right panel). The increase in absorptiometric values is constant and, in some case, has reached considerable percentages (mean: 26% ± 10.6 after two years). Response was greater in patients who had not previously received treatment with vitamin D or its metabolites, and was much more evident than in the osteoporotic patients treated with calcitriol (centre panel: 1.2% ± 1.6)) or placebo (left panel: -5% ± 1.7). The horizontal axis shows the number of years of treatment and the vertical axis the percent increases in bone mineral density; the triangles indicate the mean values.

calcitriol normalizes the intestinal absorption of calcium and phosphate, restores normal plasma calcium and phosphate levels and thus increases the Ca x P product. This restores the production and nucleation of hydroxyapatite crystals in newly formed bone and makes the transformation of osteoid tissue into normally calcified bone possible. Pain disappears, normal muscular activity is resumed, the Looser-Milkman pseudo-fractures recover, and X-rays reveal recalcification of the skeleton.

In women with postmenopausal osteoporosis, bone loss is due to a homeostatic mechanism with the purpose to maintain normal blood calcium levels. The need to make use of skeletal calcium may arise because the decrease in estrogen hormone levels negatively affects the renal hydroxylation of vitamin D to calcitriol (necessary to stimulate the physiological mechanism of intestinal calcium transport), and thus leads to a negative calcium balance.

It is generally known that in postmenopausal osteoporosis, as in other generalized osteoporoses, total body densitometry reveals a decrease in bone mineral density related to the real "bone loss" underlying osteoporosis. The similar decrease in bone mineral density observed in osteomalacia cannot be accounted for by a real decrease in "bone mass" and, in these patients, it is therefore incorrect to speak of "bone loss" because their bone mass is volumetrically normal, even though it is poorly mineralized. It is also generally known that the bone mineral density of untreated women with postmenopausal osteoporosis decreases by 4-5% every year.

Since the studies by Albright and Reifenstein [1], it has been generally accepted that the most important step in the pathophysiology of postmenopausal osteoporosis is estrogen deficiency. Albright and Reifenstein [1] demonstrated that women with postmenopausal osteoporosis presented a negative calcium balance mainly because of fecal calcium losses, which disappeared when estrogens were administered and reappeared upon the withdrawal of these hormones. Our own studies in postmenopausal osteoporotic women documented a decrease in the active intestinal transport of radioactive calcium [7]. These findings have since been confirmed by others [17, 33]. In a double-blind study comparing estrogens/gestogens and placebo, we demonstrated that this combination of hormones corrected intestinal radio-calcium malabsorption in postmenopausal osteoporotic women [8].

The results described in the present study show, that

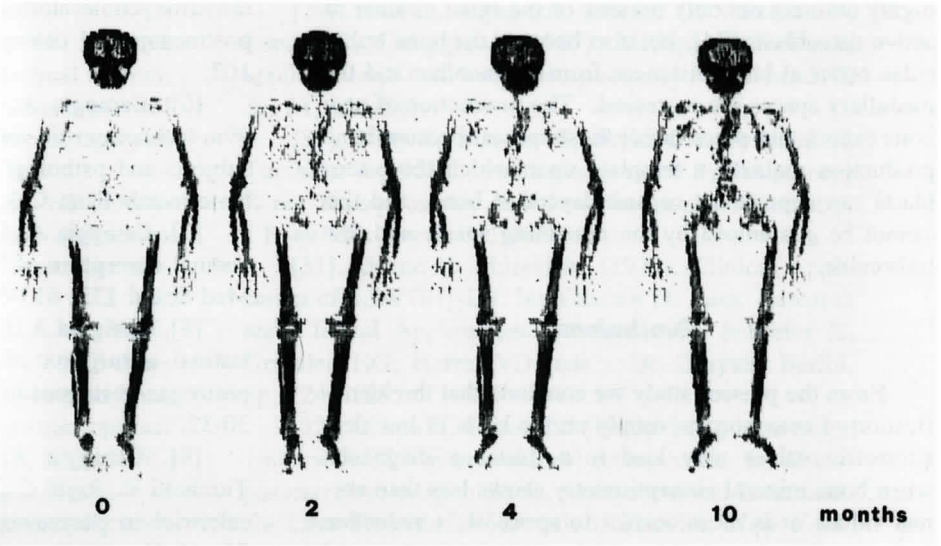


Figure 9. Successive visual displays of total body absorptiometry in a patient with nutritional osteomalacia treated with calcitriol 1 μg/day for 10 months. It can be seen that the skeleton "re-appears" as the treatment progresses.

by restoring calcium malabsorption, calcitriol opposes progressive bone resorption, and in a certain number of cases, it actually increases densitometric values.

Since the discovery of the hydroxylated metabolites of vitamin D [13, 16], a number of authors have found a decrease in 1,25(OH)2vitD levels in postmenopausal osteoporosis [17, 20, 21]. We have previously demonstrated that, in women with postmenopausal osteoporosis, the oral administration of calcitriol (1,25(OH)2vitD) at a physiological dose of 1 μg/day normalizes the intestinal transport of radio-calcium in a period of ten days; the result was different when an equivalent dose of 24,25(OH)2vitD was given [27]. At this dose, oral calcitriol rapidly corrects intestinal calcium malabsorption, reestablishes a positive calcium balance, rapidly eliminates bone pain, and prevents new pathological fractures [9, 10, 12, 19, 33, 35]. This effect continues without interruption provided calcitriol is taken every day, as can be seen from the results in many of our patients, some of whom have been under observation for a period of up to 14 years. We did not observe adverse effects provided the patients were not given oral calcium supplementation; the long-term compliance of the patients confirmed the efficacy of this treatment (relief of pain, well-being and no additional fractures).

In postmenopausal osteoporosis, calcitriol is a "replacement therapy". Treatment with calcitriol is fundamentally different from vitamin D treatment. Both parent vitamin D and calcidiol (25OHvitD) are useless in the therapy of postmenopausal osteoporosis because, in this particular condition, the presence of a hydroxyl group in position 1 is necessary in order to obtain a positive effect on intestinal calcium absorption. This is confirmed by the efficacy of other 1α-hydroxylated metabolites of vitamin D, such as 1,24(OH)2vitD [31] and 1α-OHvitD [10, 11, 32]. The hypothesis that estrogens act directly on renal 1α-hydroxylase has been supported by the studies of De Luca, Castillo and Tanaka [13, 14, 15], which had very appropriate experimental designs: e.g., hatching hens produce large quantities of estrogens and there is a parallel increase in the renal production of 1α-hydroxylase; this was not the case with chicks or adult chickens unless they were given estrogens. Studies of this kind are not possible in women; nevertheless, a number of authors have stressed the positive effect of estrogens on 1,25(OH)2vitD levels, which leads to a parallel improvement in radio-calcium absorption [5, 17, 18, 36], and the negative effects of ovariectomy in fertile women [28]. Hence, the possibility that the renal hydroxylation of 25OHvitD is the final step of this metabolic process, is a viable hypothesis.

In osteomalacia, the availability of calcium and phosphate normalizes the low Ca x P product responsible for the incomplete calcification of osteoid tissue, and allows the tissue to undertake the formation and nucleation of hydroxyapatite crystals: densitometry faithfully records its extreme avidity for bone mineral. Radio-calcium and 99mTc-methylene-diphosphonate kinetic studies have clearly shown the enlargement of the exchangeable calcium pool in osteomalacia [6] and the high affinity of osteoid-tissue for radioactive bone seeking tracers [3].

In osteoporosis, this does not occur. Under baseline conditions, there is a reduction in bone mass (hence the low densitometric values), but the bone is fully calcified and kinetic studies show that the uptake of tracers with affinity for bone is low. During calcitriol treatment, it is impossible to verify the mineralization of already completely calcified bone. Furthermore, a large production of bone (large enough to result in an obvious increase in absorptiometric values over baseline levels) is

highly unlikely not only because of the small number of active osteoblasts [34], but also because the bone trabeculae occur at large distances from one another and the medullary spaces are increased. The production of new bone cannot take place inside these spaces, because bone production requires a template upon which the osteoblasts can deposit the organic layers of bone, and this cannot be guaranteed by the remaining sparse and thin trabeculae.

Conclusions

From the present study we conclude that the identification of osteoporosis simply on the basis of low densitometric values may lead to a mistaken diagnosis: when bone mineral absorptiometry shows less than normal values, it is more correct to speak of "a reduction in bone mineral content", which may mean either real bone loss, or poor mineralization of a quantitatively normal bone mass. This distinction is anything but academic.

In osteomalacia, the rapid increase in bone densitometry values during calcitriol treatment indicates the rapid mineralization of a preexisting, quantitatively normal, but incompletely calcified bone mass, which quickly recalcifies once the necessary physical and chemical conditions are created. In osteoporosis, on the other hand, the loss of bone mineral density is halted, and a possible slight increase in densitometry values (1-5% over baseline values), are sufficient to indicate the satisfactory therapeutic activity of calcitriol. This activity does, however, not lead to the vigorous production of newly formed bone but mainly to the arrest of the homeostatic pathologic mechanism of bone hyper-resorption.

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Discussion with Reviewers

H.U. Bryant: The authors seem to be arguing that the entire basis for post-menopausal bone loss is due to vitamin D abnormalities associated with estrogen deficiency. While it may be true that a role for vitamin D deficiency may exist in some women, I think at best this is an overstatement, and fails to consider the wealth of data to the contrary. If true, the authors' statement here would suggest that vitamin D based therapy should be as efficacious as estrogen (or hormone) replacement therapy for postmenopausal osteoporosis, and there are numerous reports in the literature that this is not the case.

R.G. Erben: It should be mentioned that a dose of 1 μg calcitriol/day is already toxic in many patients with

a higher calcium intake. The usual and also more physiological treatment of nutritional osteomalacia is vitamin D and not calcitriol. Moreover, the risk of negative side effects is much lower with vitamin D treatment.

Authors: Our own studies of postmenopausal osteoporosis [5] have documented the fact that the administration of a physiological dose (1 μg) of 1,25(OH)2vitD3 corrects impaired intestinal transport of radio-calcium in ten days; this was not true for administration of 24,25(OH)2vitD3. Since then, we have been studying the possible therapeutic benefits of calcitriol in postmenopausal osteoporosis (more than 350 patients). We have found that: (a) the effective dose of calcitriol is 1 μg/day; (b) a dose of 0.5 μg/day is not always sufficient; and (c) a dose of 0.25 μg/day is absolutely ineffective. Calcitriol treatment of postmenopausal osteoporosis is not a "vitamin D based therapy": vitamin D as such is absolutely ineffective in postmenopausal osteoporotic patients, as is borne out by the thousands of physicians who have been trying it over the last 50 years or more. No major adverse effects have been observed in 350 women, a number of whom have been followed for up to 14 years. The long-term administration of calcitriol underlines patient compliance, which is a good indicator of treatment efficacy. These women have obtained relief from pain and have rarely presented additional fractures; there have been no negative effects on renal function, and there is no malignant hypercalcemia provided calcium supplementation is forbidden.

The medical treatment of osteomalacia can be performed with vitamin D as such (because, in this pathological condition, there is no defect in 1-alpha-hydroxilation of vit. D). Of course, the calcitriol treatment is particularly efficient.

R.G. Erben: The hypothesis that estrogens act directly on the 1α-hydroxylase in the kidney is not correct for mammals (see e.g., Ash and Goldin, Am J Clin Nutr **47**: 694, or Reichel *et al.*, N Engl J Med **320**: 980). Please comment.

Authors: As stated in the **Discussion**, the hypothesis that estrogens act directly on renal 1α-hydroxylase has been supported by the studies of De Luca, Castillo and Tanaka [13, 14, 15] in hens. Studies of this kind are obviously more difficult in women, although opinions on the subject vary: Ash and Goldin did not agree in rats, Reichel *et al.* did not agree with the direct effects of estrogens on renal 1α-hydroxylase. The positive effect of estrogens on intestinal radio-calcium absorption was demonstrated before the measurements of calcitriol levels [8]. The negative effects of ovariectomy have been documented by measurements of 1,25(OH)2vitD and the radio-calcium oral test [28]. Gallagher *et al.* [17] indicated a significant decrease in 1,25(OH)2vitD levels in postmenopausal osteoporotic women which paralleled calcium malabsorption. In a recent paper describing an experimental study in women, Van Hoof *et al.* [36] agree that estrogens stimulate 1α-hydroxylase in the kidney.

W.S.S. Jee: What is the reason why the Food and Drug Administration (FDA) has not approved the use of calcitriol in the treatment of osteoporosis?

Authors: Calcitriol has been approved since a number of years in Italy, Switzerland, and New Zealand, where it is currently on the market.

W.S.S. Jee: In Japan, and possibly Europe, analogs of calcitriol are used in the treatment of osteoporosis. Do they differ in action from calcitriol?

Authors: Calcitriol analogs can be used in the treatment of postmenopausal osteoporosis provided they are hydroxylated in position 1. We have studied the effects of 1-α(OH)vitD3 in postmenopausal osteoporosis (121 cases) [10]. It is less effective than 1,25(OH)2D3, probably because it needs previous hepatic hydroxylation in position 25.