Metabolic Bone Diseases with Special Emphasis on Osteoporosis

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In their classic description of metabolic bone diseases, Albright and Reifenstein[1] considered them to consist of three principal forms, - osteoporosis, osteomalacia and osteitis fibrosa. They attributed specific metabolic disturbances for the pathogenesis of each form of bone disease: defective matrix synthesis for osteoporosis, vitamin D deficiency for osteomalacia and parathyroid hormone (PTH)-excess for osteitis fibrosa. Although still applicable in broad terms, it has become apparent that this concept needs to be refined and modified, to accommodate recent advances in the hormonal control of bone cell metabolism. Particularly noteworthy has been the observation that a disturbance in vitamin D metabolism may play a critical role in the pathogenesis of all three forms of bone disease. In previous medical grand rounds,[2,3] primary hyperparathyroidism and osteomalacia were discussed. During this grand round, modern concepts of metabolic bone disease will be presented, with a special emphasis on osteoporosis.

We shall first consider normal bone cell metabolism and its regulation, and specific disturbances leading to, or found in metabolic bone diseases. We shall then review in detail the clinical presentation, pathogenesis, diagnostic criteria and treatment of osteoporosis, particularly that which appears in the postmenopausal state.

Normal Bone Cell Metabolism

Bone tissue may be depicted schematically as a block, composed of osteoid (non-mineralized matrix) and calcified bone (Fig. 1).

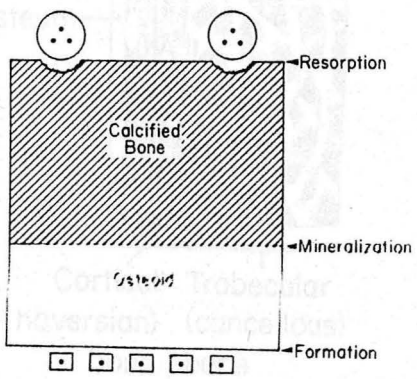


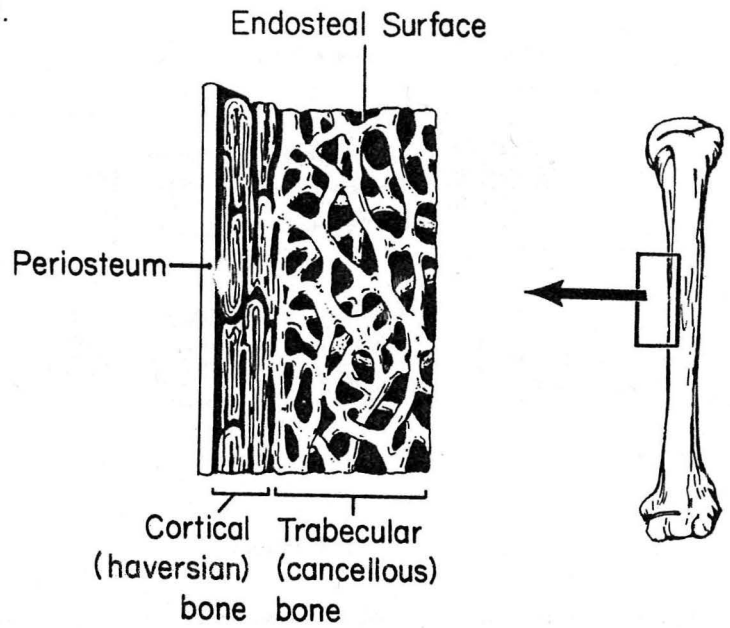
Figure 1.

It is a dynamic tissue undergoing continuous remodelling. The remodelling entails three processes: (a) matrix (collagen) synthesis by osteoblasts, (b) mineralization of collagen (or deposition principally of calcium phosphate) to form calcified bone, and (c) bone resorption, or destruction of calcified bone by osteoclasts. In its customary usage, bone formation refers to matrix synthesis. The formation of calcified bone is therefore the sum of bone formation and mineralization.

These processes occur principally at bone surfaces,—endosteal surface covering trabecular (cancellous) bone, periosteal surface, and haversian system within the cortical bone (Fig. 2).[4] Each surface, called cell envelope, is covered by mesenchymal cells, thought to be precursor cells for osteoclasts, osteoblasts and osteocytes.

At the cellular level, bone undergoes continual breakdown and repair in discrete areas called "bone remodelling units". In periosteum and in trabecular bone, these units are spread out over the surface, and are supplied by blood from the periosteal and medullary vessels. In cortical bone, the remodelling units are parallel to the long axis of the haversian system; they are supplied by haversian vessels.

Figure 2.



The remodelling unit for the cortical bone is called osteon. It is illustrated in Figure 3. Each unit has areas of resorption and formation.[4] Resorption is initiated (on the left of the figure) by osteoclasts

that resorb calcified bone, forming a cavity of about 250 μ in diameter, while advancing longitudinally (to the left in the figure) at a rate of 20 μ/day. The resorption is followed by osteoblasts which form osteoid. After the osteoid grows to a thickness of about 10-15μ, it becomes mineralized. Matrix synthesis and mineralization then proceeds together at a rate of approximately one μ/day. At the closing cone of the osteon, matrix synthesis slows down and eventually ceases; mineralization continues to complete calcified bone formation. This remodelling process takes approximately four months.

Under normal circumstances, there is a close "coupling" between bone resorption and bone formation; i.e. osteoclastic bone resorption is quickly followed by osteoblastic matrix synthesis. To explain coupling, Bordier and Rasmussen introduced the hypothesis of cellular continuity, where osteoclasts derive their origin from osteoprogenitor cells, and osteoblasts form by transformation of osteoclasts.[5]

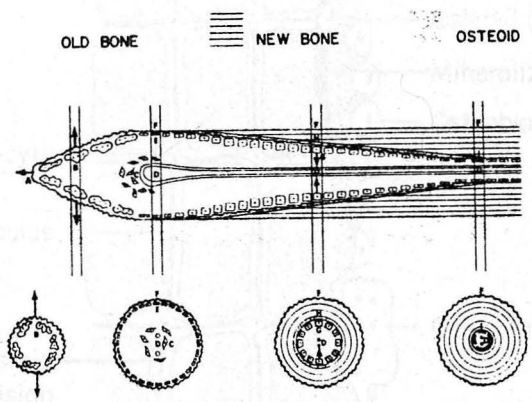


Figure 3

However, the validity of this hypothesis has been questioned by recent studies suggesting separate cellular origin for osteoclasts and osteoblasts. The close coupling that is generally observed may be consequent to certain hormonal influences acting on different cell populations.

There is internal remodelling as well. After osteoblasts form collagen, they become incorporated into matrix, and become osteoid osteocytes. These cells are believed to be responsible for the mineralization of the matrix by an elaboration of matrix vesicles. When mineralization is completed,

the cells become enclosed within calcified bone as mature osteocytes. These osteocytes are connected to each other and with surface osteocytes (cell envelope) by protoplasmic extensions passing through canaliculi (Fig. 4A). This system, comprising minicirculation of bone, provides a functional boundary between blood and bone. It is now recognized that mature osteocytes are capable of bone remodelling, involving a small amount of woven bone surrounding internal wall of lacunae and canaliculi. The woven bone, unlike the remaining lamellar bone, is more susceptible to metabolic turnover. Thus, osteocytic osteolysis and the system of minicirculation provide a readily mobilizable calcium pool which could be used for a rapid control of circulating calcium concentration.

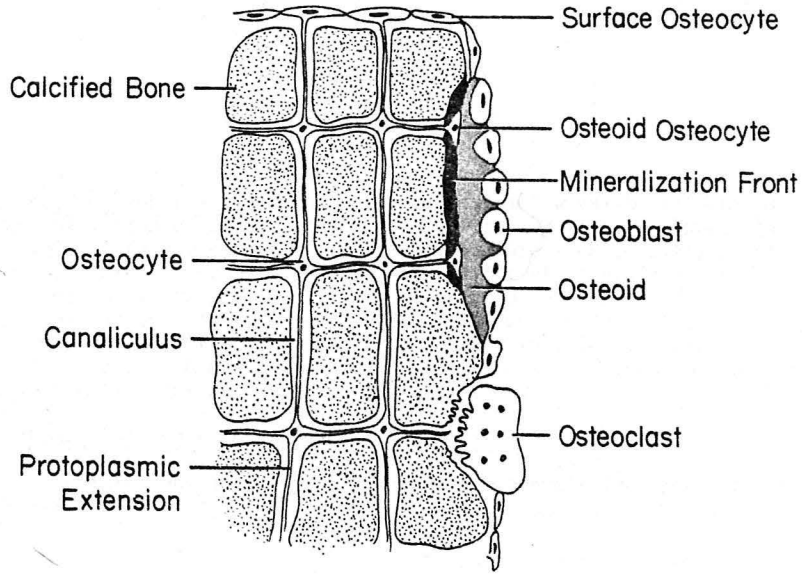


Figure 4A

In Fig. 4B, the functional role of four principal cell types are schematically presented.[6] As previously described, osteoclasts resorb calcified bone, and osteoblasts synthesize the matrix.

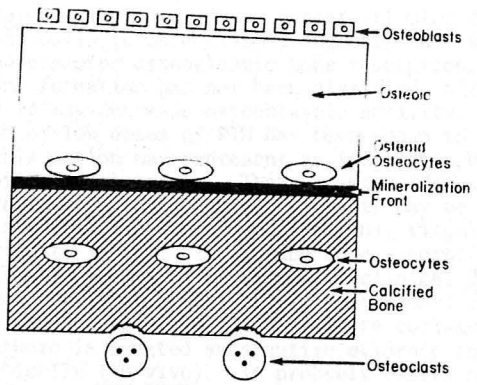


Figure 4B

Osteoid osteocytes, located over osteoid lamella may be responsible for the initiation of mineralization by elaborating membrane-bound extracellular matrix vesicles.[7] These vesicles are rich in alkaline phosphatase and are believed to be the initial site of mineralization. A sharp line of calcification separating the osteoid and calcified bone is called mineralization front. Osteoid width represents the thickness of non-mineralized matrix. Osteocytes located in calcified bone may play a crucial role in mediating rapid mobilization of calcium and phosphate into the circulation under appropriate stimuli.

Hormonal Influences on Bone Cell Metabolism

Certain substances directly exert a profound effect on bone cell metabolism (Fig. 5).

Figure 5. Hormonal Effects on Bone Cell Function

	PTH	Estrogen	Vitamin D
Osteoclastic resorption	↑	↓	↑
Osteocytic resorption	-	-	↑
Osteoblastic matrix synthesis	-	-	↓
Osteocytic matrix vesicle activity (Mineralization)	-	-	↓

Parathyroid hormone provides a potent stimulus to the conversion of osteoprogenitor cells to osteoclasts, augments the skeletal content of cyclic AMP and promotes osteoclastic bone resorption.[8] Whether PTH influences bone formation has not been clarified, although there is some evidence that it may decrease osteoblastic activity. Although a continuous administration of low doses of PTH has been shown to increase bone formation,[9] this action may represent an indirect response to the primary stimulation of bone resorption. There is no evidence that PTH directly affects mineralization. Osteocytic osteolysis may be stimulated in vitamin D-repleted state (via PTH-dependent 1,25-$(OH)_2$ vitamin D synthesis). Estrogen was reported to inhibit PTH-induced bone resorption by Atkins et al.[10] This observation is supported by extensive clinical data,[11,12] even though it could not be confirmed by Raisz et al. (personal communication). Although estrogen has been shown to stimulate collagen synthesis in vitro,[13-16] there is limited substantive evidence that it augments bone formation clinically (in vivo). It probably exerts no direct effect on mineralization.

The role of vitamin D will be discussed in overall context§ without consideration of separate actions of different metabolites. Vitamin D alone does not activate osteoprogenitor cells to form osteoclasts. In the presence of PTH, vitamin D enhances PTH-dependent formation of osteoclasts. Vitamin D and PTH act synergistically to augment osteoclastic bone resorption. Vitamin D alone is capable of stimulating resorptive capacity of osteocytes in calcified bone. It has been suggested that calcium ions released by osteocytic osteolysis become available locally and accentuates PTH-dependent activation of osteoprogenitor cells by serving as a second messenger. Moreover, vitamin D stimulates matrix synthesis. Following vitamin D administration, osteoblasts become more numerous and assume histological appearance indicative of an increased synthetic activity.

It has long been appreciated that vitamin D stimulates mineralization of matrix. This action has been commonly attributed to the increased circulating concentration of calcium and phosphate resulting from vitamin D treatment. The prevailing view implicates a more direct role for vitamin D. Treatment of an osteomalacic patient with vitamin D alone caused bone "healing", even though a rise in the circulating concentration product of Ca and P was prevented by placing the patient on a very low Ca diet (personal observation). The restoration of normal mineral ion product by infusions of calcium and phosphate may induce mineralization;[17] however mineralization is patchy and disorderly. It has been speculated that vitamin D may influence mineralization by affecting the matrix vesicle formation or the calcium uptake by vesicles which may be critical in the initiation of mineralization.[6] Finally, there is some evidence that vitamin D may be necessary for adequate matrix maturation that is essential for mineralization.[18,19]

The functional role of vitamin D on bone cell metabolism may be specific or unique for each vitamin D metabolite, as will be discussed later.

It is recognized that other substances may influence bone cell metabolism.[5,20] They include calcitonin, adrenocorticosteroid hormone, growth hormone, thyroid hormone and prostaglandins. Another factor, though non-hormonal, is circulating P concentration. Hypophosphatemia may inhibit osteoblastic matrix synthesis.[21]

The indirect effects of these agents may often differ from their direct actions enumerated above. A direct hormonal effect may elicit secondary responses which could alter bone cell metabolism.

Disturbed Bone Cell Metabolism in Metabolic Bone Diseases

The pathogenesis of metabolic bone diseases may be ascribed to disturbances in hormonal regulation of bone cell metabolism. As prescribed by the traditional view of metabolic bone diseases, PTH-excess, vitamin D deficiency, or estrogen lack could lead to the development of osteitis fibrosa, osteomalacia or osteoporosis, respectively.

The disturbances in bone cell metabolism found in the classic presentations of osteitis fibrosa, osteomalacia and osteoporosis are compared in Figure 6. They reflect direct and infirect consequences of hormonal derangements discussed previously.

Figure 6. Bone Cell Metabolism in Metabolic Bone Diseases

	Osteitis Fibrosa (PTH-Excess)	Osteomalacia (Vitamin D Deficiency)	Osteoporosis (Estrogen Lack)
Osteoclastic resorption surface	++	-/+	+/-
Osteoblastic formation surface	+	+	-/+
Mineralization front	-	++	-/+
Osteoid volume	+	+	-/+
Osteoid width	-	+	-/+
Mineral apposition rate	-	+	-
Mineralization lag time	-	+	-
Bone volume	+	-	+
Cell envelope affected	periosteal haversian endosteal	endosteal haversian	endosteal

The PTH-excess is characterized by a high turnover rate of bone (an increased number of active remodelling units). Osteoclastic resorption is primarily increased, but osteoblastic formation is also high (probably reflecting coupling). Thus, the percentage of bone surface showing either active resorption or formation is increased (high turnover). Since mineralization is not altered, the mineralization front and lag time are normal. Mineralization keeps pace with the accelerated matrix synthesis; the osteoid width is normal. Since bone formation generally lags behind resorption, the total amount of bone may become reduced. When PTH-excess is marked, marrow fibrosis may develop (osteitis fibrosa).

Enlarged osteocytic lacunae may be present, a finding attesting to stimulated osteocytic resorption. The hyperparathyroid state affects all three bone cell envelopes. Thus, subperiosteal resorption may develop, and the volume of cortical and trabecular bone is reduced. However, there is recent evidence that trabecular bone may be less affected (Alexandre, C., personal communication).

In osteomalacia of vitamin D deficiency,[4] bone matrix synthesis is impaired. Osteoblasts appear flat and show histological appearance which indicate reduced protein synthesis. The mineralization is even more markedly delayed. The lag time in mineralization (duration from matrix synthesis and mineral deposition) is considerably prolonged and the rate of mineral apposition is substantially reduced. Thus, the osteoid width and osteoid volume (indicative of non-mineralized matrix) are increased and the mineralization front is reduced. The resorption is only slightly increased; thus, the total volume of bone is normal, but the proportion of non-mineralized matrix is substantially elevated. Both cortical and trabecular bone are affected.

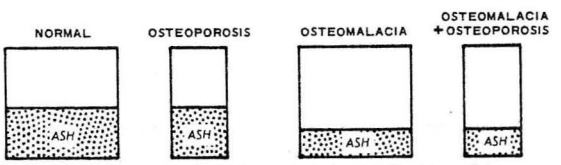
In osteoporosis, the total resorption surface is increased but the total formation surface is normal. The result suggested that the primary abnormality is a stimulation of osteoclastic resorption. However, the active resorption surface, obtained by histologic identification of active osteoclasts, has been reported to be normal, whereas the active formation surface is reduced. The latter finding suggested that the principle defect was an impairment in osteoblastic matrix synthesis. The current data do not allow resolution of this controversy. It is probable that both presentations may be found in osteoporosis, as characteristics of different subtypes (to be discussed under Postmenopausal Osteoporosis). Irrespective of the rate of resorption, the important consideration is the fact that the bone formation is less than resorption. Thus, there is an uncoupling between the two processes. However, the matrix synthesis and mineralization are generally intact. Osteoid volume, osteoid width and mineralization front are typically normal. (In some patients with osteoporosis, however, mineralization defect in the terminal phase of bone formation may be present and lead to an increased osteoid volume). The endosteal cell envelope is particularly affected by the osteoporotic process; this fact accounts for the reduced trabecular bone volume.

It is recognized that there are other hormonal and non-hormonal causes for metabolic bone diseases than those discussed above. For example, disordered vitamin D metabolism may be present in all three forms of bone disease, and not necessarily restricted to osteomalacia (see next section). Osteoporosis may be associated with either parathyroid stimulation or suppression. Accordingly, the derangement in bone cell metabolism may be modified from the classic presentations shown in Fig. 6.

However, irregardless of etiology, the following minimum criteria must be met: increased osteoclastic resorption, a high turnover rate, and marrow fibrosis for osteitis fibrosa; reduced mineralization front, low mineral apposition rate and increased osteoid width for osteomalacia; inappropriately high osteoclastic resorption relative to formation for osteoporosis.

The composition of bone serves to differentiate the three forms of metabolic bone disease, as shown schematically in Fig. 7. The amount of

bone is normal in osteomalacia, but is reduced in osteitis fibrosa and osteoporosis. The proportion of non-mineralized matrix is substantially increased in osteomalacia, but normal in other two.



Diagrammatic representation of the principal metabolic abnormalities of the skeleton.

Figure 7

Functional Specificity of Vitamin D Metabolites

Although the traditional concept of metabolic bone disease ascribed pathophysiologic significance of vitamin D only in osteomalacia, it is becoming increasingly evident that disturbances in vitamin D metabolism may be present in all three forms of bone disease. In primary hyperparathyroidism, the renal production of 1,25-dihydroxycholecalciferol (1,25-$(OH)_2$ D) may be stimulated, since the circulating concentration of this metabolite is significantly increased.[22-24] Osteomalacia has been shown to develop in states of defective 1,25-$(OH)_2$ D synthesis, such as chronic renal failure,[25] hypoparathyroidism[26] and vitamin D dependency rickets.[27] Osteomalacia has also been reported in 25-hydroxycholecalciferol (25-OHD) deficiency even when 1,25-$(OH)_2$ D production is normal or accelerated.[28] In osteoporosis of estrogen lack,[29] hyperthyroidism[30] or hyperadrenocorticosteroidism,[31] a reduced circulating concentration of 1,25-$(OH)_2$ D has been found. However, a high circulating concentration of 1,25-$(OH)_2$ D is characteristic of "osteoporosis" of primary hyperparathyroidism (a high turnover state).[22-24]

These findings raise intriguing questions. How do a high and low production of 1,25-$(OH)_2D$ contribute to the development of osteoporosis? When the synthesis of 1,25-$(OH)_2D$ is impaired, what determines whether osteoporosis or osteomalacia develops? Is the osteomalacia developing following 1,25-$(OH)_2D$ deficiency different from that occurring after 25-OHD lack? Although definitive answers are lacking, these questions may be better clarified if the functional heterogeneity of vitamin D metabolites is recognized.

Three well known metabolites of vitamin D are 25-OHD, 1,25-$(OH)_2D$ and 24,25-$(OH)_2D$. It is apparent that they differ with respect to regulatory steps in synthesis, biological actions, and effects on bone. Since the metabolism of vitamin D was described in previous grand rounds,[2,3] we shall discuss principally the biological specificity of various metabolites (Fig. 8).

Figure 8. Biological Specificity of Vitamin D Metabolites

	25-OHD	24,25-$(OH)_2D$	1,25-$(OH)_2D$
Renal tubular reabsorption P	+	-	-
Renal tubular reabsorption Ca	+	-	-
Intestinal Ca absorption	+	+	+++
PTH secretion	-	+	+
Osteoclastic resorption	+	-	++
Osteocytic resorption	+	-	++
Osteoblastic matrix synthesis	+	+	-
Mineralization	+	+	-

Effects of vitamin D metabolites on extra-skeletal tissues will be considered first. In the kidney, 25-OHD has been shown to augment renal tubular reabsorption of Ca and P. The action of 1,25-$(OH)_2D$ is much less prominent in this regard,[32] and that of 24,25-$(OH)_2D$ is not known. The most potent metabolite with respect to the stimulation of intestinal Ca absorption is 1,25-$(OH)_2D$. However, both 25-OHD and 24,25-$(OH)_2D$[33] are capable of increasing Ca absorption. Vitamin D metabolites may also influence PTH secretion. Although accumulated data are conflicting, a recent study suggests that 24,25-$(OH)_2D$ inhibits while 1,25-$(OH)_2D$ may stimulate the release of PTH by parathyroid gland.[34]

In bone, 1,25-$(OH)_2$D is believed to be largely responsible for the stimulation of osteocytic osteolysis and of the resorptive activity of preformed osteoclasts, and to act synergistically with PTH to promote formation of new osteoclasts.[6] The action of 25-OHD is much less prominent, whereas that of 24,25-$(OH)_2$D may be negligible. However, 24,25-$(OH)_2$D may mainly account for the stimulation of osteoblastic matrix synthesis and mineralization.[6] Although 25-OHD may share this action with 24,25-$(OH)_2$D, it is not known whether 25-OHD itself, or its metabolic transformation, possibly to 24,25-$(OH)_2$D, accounts for the effects on bone formation and mineralization.[6]

From above discussion of functional specificities of vitamin D metabolites, it is tempting to speculate that a particular form of metabolic bone disease may owe its origin to specific disturbances in vitamin D metabolism. It has been suggested by Frame and Parfitt that osteoporosis might partly result from "deficiency of some metabolites of vitamin D, whereas the complete development of osteomalacia might require deficiency of several or all metabolites".[4]

Another scheme concerns the possibility that osteomalacia may result from a deficient availability of specific vitamin D metabolites which promote matrix synthesis and mineralization. Unfortunately, these hypotheses lack experimental verification. Although 24,25-$(OH)_2$D may be the metabolite which stimulates bone formation and mineralization, its circulating concentration is not necessarily depressed in osteomalacia, and may be low in some patients with osteoporosis. Moreover, this scheme is inconsistent with the apparent pathogenetic and therapeutic role of 1,25-$(OH)_2$D, a metabolite apparently lacking in synthetic and mineralizing potential. The ability of 1,25-$(OH)_2$D to "cure" certain forms of osteomalacia has been attributed to the stimulation of osteocytic resorption, and "redistribution" of mobilized mineral ions to areas of mineralization.[6]

Current data do not justify assignment of any specific abnormality in vitamin D metabolism to a particular form of bone disease. Thus, the traditional concept of metabolic bone disease which attributed a disturbance of vitamin D metabolism to osteomalacia alone needs to be revised. This simplistic view also fails to recognize the important role of circulating concentration of P on osteoblastic activity.[21] Factors which dictate the development of various forms of bone disease are obviously complex, and probably include vitamin D metabolites, other hormones and non-hormonal factors such as circulating P (and Ca).

Osteoporosis

Differentiating features from osteomalacia

The basic abnormality in osteomalacia is the defective matrix synthesis and impaired mineralization, whereas that in osteoporosis is the reduced bone mass resulting from an inappropriately elevated bone resorption. Clinically, symptoms of bone tenderness and muscle weakness are common in osteomalacia; they are encountered much more frequently than in osteoporosis. The tenderness of bone can best be elicited in the rib cages and iliac crest. The muscle weakness may be the result of an impaired synthesis of high energy phosphates associated with a defective phosphate transport. Roentgenologically, pseudofracture is the hallmark

of osteomalacia; it is not found in osteoporosis. Biochemically, severe hypophosphatemia is more typical for osteomalacia than osteoporosis. However, serum P may be elevated in osteomalacia of chronic renal failure and diphosphonate therapy. Serum alkaline phosphatase of skeletal origin is commonly elevated in osteomalacia, and infrequently high in osteoporosis.

Causes of osteoporosis

Different etiologies for osteoporosis are recognized (Fig. 9). They include various hormonal derangements, nutritional or gastrointestinal disturbances, immobilization, ageing process and miscellaneous causes. We shall consider here chiefly the most common cause- postmenopausal osteoporosis or primary osteoporosis.

Figure 9. Causes of Osteoporosis

1. Hormonal
   a. Lack of estrogens or androgens
   b. PTH-excess: primary or secondary
   c. Excess of adrenocorticosteroids
   d. Thyrotoxicosis
   e. Acromegaly
2. Nutritional or Gastrointestinal
   a. Diet: low Ca, high P, high acid ash; malnutrition, alcohol abuse
   b. Gastrectomy, gastrojejunostomy, malabsorption, cirrhosis
3. Immobilization
4. Ageing
5. Other: multiple myeloma, Ehlers-Danlos syndrome, mastocytosis

Postmenopausal Osteoporosis

General comments

Postmenopausal osteoporosis symptomatically affects 4 million women in the United States. It begins 4-5 years after menopause and increases in frequency thereafter. It is estimated that 25% of Caucasian women over 60 years of age suffer from osteoporosis. It is responsible for 700,000 new fractures yearly.[35] The annual cost of hip fractures alone is approximately $1 billion.[36]

The primary abnormality is the reduced amount of bone mass (osteopenia), resulting from bone resorption which is proportionately greater than formation. When the bone mass has decreased to a point where it is insufficient to maintain structural integrity of the skeleton, fractures

and symptoms appear; the term osteoporosis describes this disease state. Trabecular bone is more severely affected than cortical bone. Thus, bones which are rich in trabecular bone and/or which are responsible for weight bearing, are prime targets for fractures. Thus, common sites of fractures are the vertebra, ribs, proximal femur, pelvis and distal radius.

Within each bone tissue, trabecular bone which is not parallel to the line of weight bearing is lost first by osteoporosis. This process accounts for the prominence of vertical striations in the vertebra and serves as the basis for the femoral trabecular pattern index for the staging of osteoporosis.[37] Other early roentgenologic signs include prominence of vertebral end plates and Schmorl's nodes. With advanced disease, vertebral collapse ensues; this development may be manifested by kyphoscoliosis, "dowager's hump", and a decline in height.

In the long bones, there is an accelerated bone loss endosteally with menopause, whereas the bone continues to be deposited externally (periosteally) though at a slower rate. Thus the total width of bone may be greater, but the cortical bone thickness may be less than in the premenopausal state. This finding is the basis for the quantitation of bone density in osteoporosis. For example, the bone mineral content obtained from a single scan of the width of radius by ^{125}I-photon absorptiometry, expressed relative to the total bone width, provides a good measure of bone "density".[38] The bone density so-measured has been shown to decline with menopause, and to be low in osteoporosis.[39,40]

Heterogeneity of postmenopausal osteoporosis

Since the original description of postmenopausal osteoporosis by Albright et al. in 1941,[41] little progress had been made concerning the pathogenesis of this condition until the past decade. The recent application of more sophisticated techniques and approaches for the study of skeletal metabolism has disclosed a multifactorial etiology for this condition, including genetic, nutritional and hormonal factors.

Genetic factors include presumed "senile atrophy" of bone cells,[36] involving particularly osteoblasts. The consequent impairment in osteoblastic matrix synthesis could lead to bone loss even in the absence of primary increase in bone resorption. It has also been suggested that certain persons may be predisposed to develop postmenopausal osteoporosis because their total bone mass is reduced to begin with. In such persons, the amount of bone loss that occurs normally with ageing may be sufficient to cause bone disease. That the initial bone mass may be genetically determined[42] is supported by the finding of higher bone density in black women in whom osteoporosis is uncommon, and lower bone density in Asiatic women in whom osteoporosis is believed to be more prevalent.

An important nutritional factor is the amount of Ca intake required to maintain balance. There is evidence that this requirement for Ca increases with advancing age. This finding may reflect the continued decline in intestinal Ca absorption reported with ageing,[43] and the apparent loss of intestinal adaptation to varying Ca intake in older women.[29]

There are several hormonal disturbances in postmenopausal osteoporosis, which could profoundly influence bone cell metabolism. They include estrogen lack, as well as altered metabolism of PTH and vitamin D metabolites.

On the basis of available data, it is possible to characterize postmenopausal osteoporosis into several subtypes. The classification which I wish to share with you recognizes the important regulatory role of estrogen, PTH, and vitamin D metabolites in the maintainance of normal integrity of bone. Other factors, such as calcitonin and cortisol, are not considered for the sake of simplicity, although they may ultimately prove to be important.[44,45] Though admittedly preliminary and incomplete, this categorization permits a rational approach to the examination of this disorder. It is expected that the various subtypes may present with different derangements in bone cell metabolism, though subscribing broadly to the scheme presented in Fig. 6.

Theory 1. Estrogen lack with suppressed parathyroid function and low Ca absorption (Fig. 10).

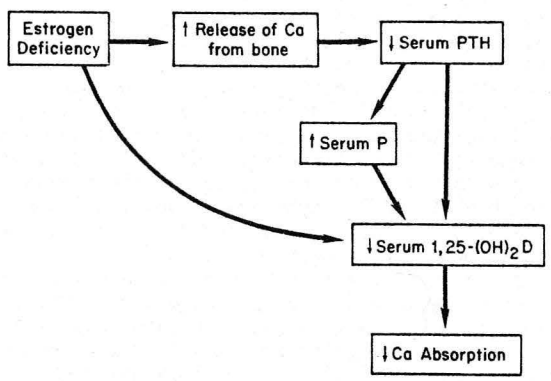


Figure 10

One theory, which has been recently popularized by Riggs et al.,[29,36] considers that bone disease may be a direct consequence of estrogen lack ensuing from menopause. Both qualitative and quantitative changes in estrogen production ensue from menopause.[46-51] During the premenopausal state the predominant estrogen is estradiol (E-2) secreted from the ovarian follicle. Presumed to be of less physiologic importance in the premenopausal years is estrone (E-1) derived from "extraglandular" aromatization of ovarian and adrenal androstenedione. During postmenopausal state, estrogen production can be totally accounted for by E-1 produced from circulating androstenedione; essentially no estradiol is secreted. Besides the qualitative difference in the type of estrogen produced the total amount of estrogen produced is substantially reduced in the postmenopausal state.[46,49,50] Although the extent of conversion of E-1 from androstenedione is increased two-fold,[47] the total amount of

estrogen produced in the postmenopausal state only approximates that of the extremes of the menstrual cycle of the premenopausal state, and is substantially lower than that of the late follicular and luteal phases of the menstrual cycle.[46,49] Serum concentrations of estrogen (E-1 and E-2) has been shown to be reduced in menopause.[50]

This theory assumes that estrogen plays a critical role in bone metabolism. There is considerable evidence which suggests that estrogen might modify the PTH-induced bone resorption. The PTH-induced loss of bone, as measured from decreases in bone content of Ca and hydroxyproline, is accentuated by oophorectomy.[51] In postmenopausal women with hypoparathyroidism, the age-related loss of bone does not develop.[52] In our experience, the bone density, as measured by ^{125}I-photon absorption of the distal third of the radius,[39] is significantly reducedin the majority of white postmenopausal women with primary hyperparathyroidism, unlike in male patients of comparable age with this condition. These findings are consistent with the reports that postmenopausal women constitute the majority of patients with primary hyperparathyroidism[53] and that they comprise the great majority of those with "hyperparathyroid bone disease".[54]

When estrogens are given to patients with postmenopausal osteoporosis or primary hyperparathyroidism, the following changes are usually found:[55-62] retention of calcium and phosphorus; decreases in serum and urinary calcium and phosphorus, urinary hydroxyproline, fasting urinary calcium and bone resorption (by microradiography); and an increase in serum immunoreactive PTH. Thus, despite stimulation of parathyroid function (presumably from the decline in serum Ca), bone resorption is inhibited. These findings support the concept that estrogens decrease the responsiveness of bone to endogenous PTH. Indeed, estrogen has been shown to inhibit the PTH-induced release of calcium from mouse calvaria in vitro.[10] Thus, the development of bone disease in postmenopausal state may be associated at least in part with the loss of the protective effect of estrogens against parathyroid hormone action.

During estrogen lack, one might expect an impaired PTH secretion. Low serum concentration of immunoreactive PTH, measured using CH-14M as antiserum, has been reported in the majority of patients with osteoporosis.[63] Since the fraction of PTH which CH-14M measures is probably the principal secretory product of parathyroid glands,[39] the results suggest that PTH secretion may be impaired in these patients. Further, since PTH may be involved in the mediation of 1,25-$(OH)_2$D synthesis,[22,64] a low serum concentration of 1,25-$(OH)_2$D might be expected, and could explain reduced intestinal Ca absorption found in some patients with postmenopausal osteoporosis.[29]

The following pathogenetic scheme may therefore be constructed: estrogen lack $\rightarrow \uparrow$ PTH-induced bone resorption $\rightarrow \uparrow$ skeletal Ca mobilization $\rightarrow \downarrow$ PTH secretion $\rightarrow \downarrow$ 1,25-$(OH)_2$D synthesis $\rightarrow \downarrow$ intestinal Ca absorption. Two other factors may contribute to impaired 1,25-$(OH)_2$D production during estrogen lack. Though controversial, estrogen is believed to stimulate renal 1α-hydroxylase activity.[65] Estrogen lack could then cause a reduced 1,25-$(OH)_2$D synthesis. Moreover, serum P may rise from an increased mobilization from bone and from reduced renal excretion of P (associated with parathyroid suppression). This rise may then inhibit 1,25-$(OH)_2$D synthesis.[66] The validity of this scheme has been supported by the findings of Riggs et al. of reduced circulating concentrations of PTH and 1,25-$(OH)_2$D, and of low intestinal Ca absorption. Moreover, a short-term treatment with estrogen with estrogen was found to restore these values towards normal.[67]

Unfortunately, these patients (before treatment) were found to have a low urinary Ca excretion, a finding which could not be explained if the sole or primary disturbance had been an enhanced bone resorption. Moreover, despite few reports to the contrary,[68,69] it has not been possible to document that the estrogen deficiency was more severe in the patient with bone disease than in comparable women without bone disease.[36,50] It is unlikely that there is an impaired responsiveness of target tissues to estrogen action, since the concentration of estrogen receptors in the cytosolic fraction of cervical tissue was not found to be different.[70]

Theory 2. Renal hypercalciuria with parathyroid stimulation and low Ca absorption.

Another prominent cause for postmenopausal osteoporosis is renal hypercalciuria and secondary hyperparathyroidism. The existence of this apparently new form of osteoporosis was suggested to us from our extensive studies concerning pathogenesis of hypercalciuria associated with calcium urolithiasis.[71,72] The condition of renal hypercalciuria with nephrolithiasis will be described first in order to provide an appropriate background for the characterization of renal hypercalciuria with osteoporosis.

During recent studies in calcium urolithiasis, it has become apparent that a prominent cause for renal stone formation is the impairment in the renal tubular reabsorption of calcium (renal leak of calcium).[71,72] The following pathogenetic scheme has been implicated for this condition, which has been appropriately termed renal hypercalciuria: renal leak of calcium → parathyroid stimulation → increased renal synthesis of 1,25-$(OH)_2$D → enhanced intestinal calcium absorption. The validity of this scheme was supported by findings that fasting urinary calcium is high in the presence of normocalcemia,[72] circulating concentration of immunoreactive PTH and urinary cyclic AMP are elevated,[71,73] and that serum 1,25-$(OH)_2$D and calcium absorption are typically increased in renal hypercalciuria presenting with nephrolithiasis.[73] Moreover, the correction or renal leak of calcium by thiazide therapy was shown to restore normal parathyroid function, serum 1,25-$(OH)_2$D and intestinal calcium absorption.[73,74]

Despite secondary hyperparathyroidism, clinical osteoporosis is rare in renal hypercalciuria with nephrolithiasis, probably because of the compensatory stimulation of intestinal calcium absorption. However, bone density by ^{125}I-photon absorptiometry disclosed a significantly reduced values in renal hypercalciuria, as compared to values in age- and sex-matched control group.[40]

This elucidation in renal hypercalciuria and nephrolithiasis has led to the recognition that some patients with osteoporosis may present certain biochemical features of renal hypercalciuria. Thus, these patients with osteoporosis shared the following features with patients with renal hypercalciuria and nephrolithiasis: normocalcemia, a high fasting urinary calcium and increased serum immunoreactive PTH and/or urinary cyclic AMP. However, despite evidence for the renal leak of calcium and secondary hyperparathyroidism, the patients presenting with osteoporosis did not have an increased calcium absorption, unlike those with nephrolithiasis. On the basis of preliminary data obtained chiefly in an out-patient setting, we have formulated the following hypothesis (Fig. 11):

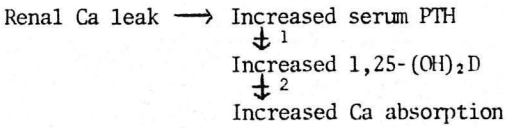


Figure 11. Scheme for Theory 2.

In osteoporosis, the defect may be either in the PTH-dependent stimulation of 1,25-$(OH)_2D$ (block 1) or in the response of the intestinal tract to the 1,25-$(OH)_2D$ action (block 2). The inadequate stimulation of calcium absorption by either means could account for the failure to compensate for the renal leak of calcium and contribute to the development of bone disease. The two proposed blocks leading to an impaired Ca absorption form the basis for the remaining two theories to be described. The histomorphometric analysis of bone may reveal a high turnover state.

Theory 3. Primary renal impairment in the synthesis of 1,25-$(OH)_2D$ (Fig. 12).

This theory assumes that an impairment in the renal synthesis of 1,25-$(OH)_2D$ develops primarily as a part of the ageing process, unlike in Theory 1 where it occurs secondarily to parathyroid suppression. This scheme is supported by following observations: First, the circulating concentration of 1,25-$(OH)_2D$ and intestinal Ca absorption decline with advancing age.[29] (However, this finding could also be explained by secondary effects of parathyroid suppression according to Theory 1). Second, the intestinal adaptation to variation in Ca intake may become lost with ageing.[29] In normal subjects less than 65 years of age, the fractional Ca absorption, measured from a fixed load of Ca (e.g. 100 mg), is inversely proportional to the dietary Ca intake. During a low Ca diet, the intestinal tract "adapts" by absorbing a greater fraction. Conversely, a lower fraction of Ca is absorbed when Ca intake is abundant. This adaptation therefore allows a more constant amount of Ca to be absorbed during wide fluctuations of Ca intake, than would otherwise be possible. The Ca adaptive response may be mediated via PTH and 1,25-$(OH)_2D$. For example, the probable scheme operative during a low Ca diet may be represented by: low Ca diet $\rightarrow \downarrow$ absorbed Ca (total) $\rightarrow \uparrow$ PTH secretion $\rightarrow \uparrow$ 1,25-$(OH)_2D$ production $\rightarrow \uparrow$ fractional Ca absorption. The validity of this scheme is shown by an inverse correlation found between Ca intake and urinary cyclic AMP,[72] and between dietary Ca and serum 1,25-$(OH)_2D$,[29] and positive correlation between serum 1,25-$(OH)_2D$ and fractional Ca absorption.[22,29]

In elderly normal subjects (>65 years of age), the serum 1,25-$(OH)_2D$ is low, and is not altered by variation in Ca intake.[29] Moreover, the fractional Ca absorption is low and insensitive to Ca intake. The results suggest that the Ca adaptive mechanism may be lost in elderly subjects because of an impairment in 1,25-$(OH)_2D$ production. This disturbance could have ensued from either a primary or secondary impairment in 1,25-$(OH)_2D$ production. It is expected that parathyroid function should be stimulated if the defective 1,25-$(OH)_2D$ synthesis were primary

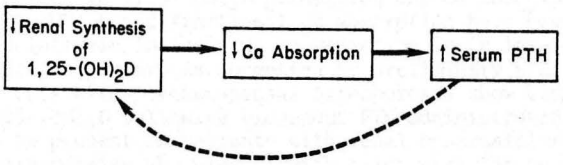


Figure 12

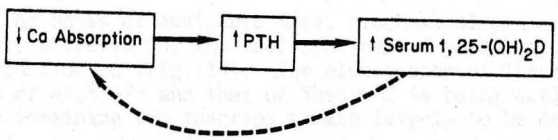


Figure 13

(because of low Ca absorption), and suppressed if it were secondary (Theory 1). The finding of an increasing circulating concentration of PTH with advancing age [79] supports the hypothesis of an age-related decline in renal 1α-hydroxylase activity.

Certain patients with postmenopausal osteoporosis may have a similar defect in 1,25-$(OH)_2$D production and Ca adaptive mechanism. Serum 1,25-$(OH)_2$D and fractional Ca absorption have been reported to be low and relatively insensitive to variation in Ca intake. [29] That this disturbance is primary is suggested by preliminary studies showing that some patients with postmenopausal osteoporosis show blunted increment in serum 1,25-$(OH)_2$D following exogenous PTH administration.[76] This defect may also be present in patients with renal hypercalciuria and secondary hyperparathyroidism who present with a low circulating concentration of 1,25-$(OH)_2$D (Theory 2).

Theory 4. Primary intestinal malabsorption of Ca (Fig. 13).

This theory considers that the intestinal Ca absorption is primarily reduced as a part of the ageing process. The progressive decrease in intestinal Ca absorption with advancing age has been previously noted. [29,43] The decrease in Ca absorption is found in both men and women as they get older. Decreases in other substances, such as d-xylose, carotene and vitamin B_{12} have been reported with ageing. [77] As a consequence of an impaired Ca absorption, the parathyroid function may be stimulated. If the renal 1α-hydroxylase system is not disturbed, there may be an increased production of 1,25-$(OH)_2$D. The operation of this scheme is supported by findings in patients with renal hypercalciuria and secondary hyperparathyroidism, who show a normal rise in serum 1,25-$(OH)_2$D but present with a low Ca absorption (Theory 2). Thus, these patients may have a relative insensitivity of the intestinal tract to 1,25-$(OH)_2$D action.

Biochemical presentations in the four subtypes of postmenopausal osteoporosis

On the basis of available data, biochemical presentations and diagnostic criteria for the four subtypes of postmenopausal osteoporosis may be constructed (Fig. 14). The elucidation of Theory 1 was pioneered by Riggs et al. [29,36] and that of Theory 2 is being actively pursued by us. The remaining two theories remain largely to be delineated.

Figure 14.
Biochemical Presentations of Four Subgroups of Postmenopausal Osteoporosis

	Theory 1	Theory 2	Theory 3	Theory 4
Serum Ca	N	N	N	N
Serum P	hi N	N	N	N
Alkaline phosphatase	N	N	N	N
PTH and urinary cyclic AMP	↓	↑	↑	↑
Serum 1,25-$(OH)_2$D	↓	↑/↓	↓	↑
Fractional Ca absorption	↓	↓	↓	↓
Urinary Ca	↓	↑	↓	↓

In all four theories, bone resorption may be enhanced because of PTH excess, or an increased sensitivity of bone to PTH action from estrogen lack. The reduced Ca absorption probably contributes to the development of negative Ca balance. It is expected that some patients with postmenopausal osteoporosis may present abnormalities subscribed by more than one theory.

Therapeutic considerations

In assessing any treatment, it is important to recognize that osteoporosis is a disease resulting from a long term process. The illness is largely a manifestation of the loss of bone mass which has occurred over many years, and not consequent to an acute derangement involving bone. An effective treatment, which averts the acute process, is not likely to produce an immediate clinical improvement. Even if it were capable of creating "new" bone, the treatment will probably have to be continued for several years before the total bone mass would be sufficiently increased to reduce the risk of fractures. There has been a prevailing view that once bone remodelling units are lost by an osteoporotic process, it is difficult to restore them. This concept is supported by the failure of most treatment programs to augment total bone mass. Thus, the most to be expected from treatment was considered to be a retardation of the rate of bone loss.

The ultimate goal of therapy is to augment mineralized bone volume, rather than simply to retard the rate of bone loss. To do so, it may be necessary to (a) increase bone turnover or raise the number of active bone remodelling units, and (b) augment osteoblastic matrix synthesis, so that formation would outweigh resorption. This goal may have been partly achieved, since there is some evidence, albeit preliminary, that certain treatment programs may cause a small but significant increment in bone mass. Moreover, the classification of postmenopausal osteoporosis into specific physiological derangements discussed previously permits consideration of a more rational treatment program.

Estrogens.[55-61] The use of estrogen would seem logical in patients with estrogen-dependent parathyroid suppression and defective 1,25-$(OH)_2$ D synthesis (Theory 1). Indeed, Gallagher et al.[67] have shown that a short-term treatment with estrogen restores towards normal serum PTH, serum 1,25-$(OH)_2$D and intestinal Ca absorption. It exerts an early positive effect, since bone resorption declines. However, with continued treatment with estrogen (>6 months), bone formation decreases, thereby offsetting the sustained inhibition of resorption.[61] Thus, it is unlikely that estrogen alone could significantly increase bone mass, although it may arrest or reduce the rate of bone loss.

This conclusion is supported by clinical studies of estrogen therapy for postmenopausal osteoporosis. When estrogen treatment is instituted shortly after menopause before a significant bone loss has ensued, there is some evidence that a decline in bone density and development of osteoporosis could be averted.[78] However, this treatment has a limited utility when it is instituted in postmenopausal state after osteoporosis had developed. Moreover, the well-known side effects of estrogen limit its usefulness.

Oral Ca. Since the intestinal Ca absorption is often low in postmenopausal osteoporosis, oral Ca supplementation may have a therapeutic role in osteoporosis. If enough Ca is given orally, the total amount of Ca absorbed may be sufficient to prevent negative Ca balance.[79] The principal effect of oral Ca on bone is a reduction in osteoclastic resorption. However, a reduction in bone formation typically follows with continued treatment.

Vitamin D substances. Vitamin D or its metabolite offers certain advantages over oral Ca. First, it reduces the amount of Ca required to prevent negative Ca balance, by increasing the fractional Ca absorption. Secondly, some metabolites of vitamin D may promote osteoblastic matrix synthesis and mineralization.[6]

The use of 1,25-$(OH)_2$ D in patients with a reduced circulating concentration of this metabolite and a low Ca absorption would seem logical. In a short-term preliminary study, Gallagher et al.[80] showed that 1,25-$(OH)_2$ D increased Ca absorption, and reduced negative Ca balance to zero. Effects on bone histomorphometry are not known.

Although there is no conclusive evidence for the deficiency of 25-OHD in postmenopausal osteoporosis, 25-OHD may have an advantage over 1,25-$(OH)_2$ D in the management of osteoporosis. In a recent study,[81] the administration of 25-OHD was shown to augment the circulating concentration of not only 25-OHD but also that of 24,25-$(OH)_2$ D and 1,25-$(OH)_2$ D (Fig. 15).

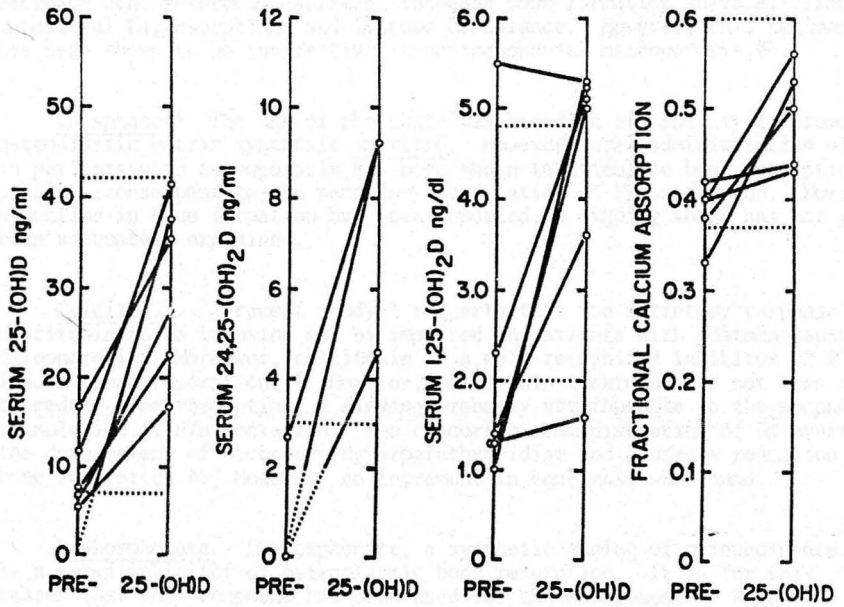


Figure 15.

As previously discussed, 24,25-$(OH)_2D$ and 24-OHD or its metabolites are believed to stimulate osteoblastic matrix synthesis and mineralization (Fig. 8). Thus, it is theoretically possible that the treatment with 25-OHD may promote bone formation, as well as indirectly inhibit bone resorption by suppressing parathyroid function.

Fluoride. Fluoride has been recommended for osteoporosis because of its ability to stimulate osteoblastic matrix synthesis.[82] When it is given alone, an abundance of poorly mineralized osteoid may be found, a finding indicating that the newly formed osteoid does not undergo an adequate calcification. Moreover, there may be an increased resorption as well. However, the addition of vitamin D and Ca to fluoride has been shown to augment the amount of mineralized bone, reduce osteoid volume, and to prevent increased resorption. An increased total bone mass has been reported during long-term treatment with this combined regimen.[36]

Unfortunately, it is not known whether the "fluoridic" bone ensuing from fluoride treatment exerts a clinically beneficial effect in the prevention of fractures. Such bone, containing fluoroapatite, may have reduced elasticity and may not have the same strength as the non-fluoridic bone.[83]

Calcium Infusion. Induced hypercalcemia, achieved by an intermittent infusion of Ca, has been employed on the basis of its ability to suppress PTH secretion and/or stimulate calcitonin secretion.[84] In selected subjects with idiopathic osteoporosis, this treatment has been shown to decrease bone resorption surface, increase bone formation surface, stimulate intestinal Ca absorption, and improve Ca balance. However, this regimen has been shown to be ineffective in postmenopausal osteoporosis.[85]

Phosphate.[86] The use of phosphate was based on its ability to promote osteoblastic matrix synthesis in vitro. However, oral administration of phosphate in patients with osteoporosis has been shown to stimulate bone resorption, probably consequent to the secondary stimulation of PTH secretion. Moreover, a decline in bone formation has been reported, a finding which has not yet been adequately explained.

Calcitonin. A recent study[44] suggests that the secretory response of calcitonin to Ca infusion may be impaired in patients with postmenopausal osteoporosis. Moreover, calcitonin is a well-recognized inhibitor of PTH-induced bone resorption.[87] However, calcitonin treatment has not been shown to reduce bone resorption, a finding probably attributable to the secondary stimulation of PTH secretion. The concurrent administration of Ca averted the development of secondary hyperparathyroidism and caused a reduction in bone resorption.[88] However, no increment in bone mass was found.

Diphosphonate. Diphosphonate, a synthetic analog of pyrophosphate, is a known inhibitor of osteoclastic bone resorption. It is for this reason that this compound has been used for the management of Paget's disease of bone.[89]

However, diphosphonate treatment in patients with osteoporosis[90] did not cause a consistent change in bone resorption. Moreover, a significant increase in non-mineralized osteoid tissue was found, a result indicating that diphosphonate may have inhibited mineralization. A similar inhibition of mineralization was suggested to us from our studies with diphosphonate in primary hyperparathyroidism.[91] The use of diphosphonate in the currently available form (Didronel) is contraindicated in osteoporosis.

Thiazide. Thiazide may be indicated in renal hypercalciuria presenting with osteoporosis (Theory 2). In nephrolithiasis counterpart, this form of diuretic has been shown to "correct" the renal leak of Ca and restore normal parathyroid function, 1,25-$(OH)_2$ D production and Ca absorption.[73,74] In patients with renal hypercalciuria and osteoporosis in whom intestinal Ca absorption is already low, thiazide given alone may reduce the Ca absorption even further. We are engaged in a study concerned with the combined treatment with thiazide and 25-OHD.

Practical Guidelines

From the preceding discussion, it is apparent that the metabolic basis for the three forms of bone diseases and their subtypes has not yet been fully clarified. Thus, it is not possible to construct definitive diagnostic criteria or therapeutic program. However, the following practical guidelines may be useful in approaching patients with metabolic bone disease.

Although osteoporosis and osteomalacia share certain common features, there are striking differences between the two. The dissimilarities are illustrated for the common subtypes,—postmenopausal osteoporosis and vitamin D-deficient osteomalacia, in Figure 16.

The principle forms of bone disease which may be encountered in various disease states are shown in Fig. 17. It is noteworthy that both osteomalacia and osteoporosis may be encountered in gastrointestinal diseases, and all three forms of metabolic bone disease in chronic renal failure. Basic diagnostic criteria and treatment programs are also provided. The initial screen for osteoporosis may include the following laboratory tests and history (Fig. 18).

The following general measures should be considered during treatment of osteoporosis. Adequate nutrition, containing a minimum of 800 mg calcium/day, should be provided. Moderate physical activity (to toleration) should be encouraged, because of well-known effects of stress on skeleton on osteoblastic matrix synthesis. The following drugs should be avoided or their potential deleterious effects recognized: adrenocorticosteroids, P-binding antacids, anticonvulsants, heparin, acidifying agents, phosphates, diphosphonate, and cellulose phosphate.

Fig. 16. Differences between Osteoporosis and Osteomalacia

	Osteoporosis (Post-menop)	Osteomalacia (D-deficient)
Ca_s	N	N/↓
P_s	N	↓
Alk ϕ	N	↑
PTH, cAMP	N	↑
Osteoid	N	↑
Calcif front	N	↓
Bone tenderness	absent	present
Muscle weakness	absent	present
Pseudofracture	absent	present
Response to D Rx	variable	positive

Key: Idiop. = idiopathic; menop = menopausal; D = vitamin D; Ca_s = serum Ca; P_s = serum P; Alk ϕ = alkaline phosphatase; cAMP = cyclic AMP; Calcif = calcification; Rx = treatment; N = normal

Fig. 17. Diagnostic Criteria and Management

Cause	Predominant Bone Disease	Diagnostic Criteria	Treatment
Estrogen-lack	Osteoporosis	Hx, nl Ca_s, P_s, alk ϕ ↓ PTH, ↓ Ca_u	Estrogen, (?), Vit D, Ca, Fl
with TH	Osteoporosis	Hx, ↑ cAMP or PTH, ↑ Ca_u	TZ, Vit D
Primary HPT	Osteoporosis	↑ Ca_s, ↑ PTH or cAMP, Assoc. with renal stones and peptic ulcer	PTH
	Osteitis		
Hyperadrenocortico-steroidism	Osteoporosis	Hx, PE, ↑ F	Adrenalectomy, 25-OH-D
Thyrotoxicosis	Osteoporosis	Hx, PE, ↑ T_3 and T_4, ↑Ca_u	TX
Multiple myeloma	Osteoporosis	abn prot electroph, B-J	Rx myeloma
G-I Disease (resection, cirrhosis, malabsorption)	Osteomalacia	nl Ca_s, ↓ P_s, ↑ alk ϕ, ↑ PTH, ↓ Ca_u	Vit D, Ca
	Osteoporosis	nl Ca_s, nl P_s, nl skel alk ϕ, ↓ Ca_u	Vit D, Ca
Chronic renal failure	Osteoporosis	↑ Ca_s, ↑ P_s, ↑ alk ϕ	P-binding ant-acids,
	Osteomalacia	↑ Cr_s, ↑ PTH	Vit D, Ca, PTX, Renal transplant
	Osteitis		
Renal tubular acidosis	Osteomalacia	↓ CO_2, ↓ Cl_s, ↑ pH_u	HCO_3, citrate,
	Osteoporosis		Vit D
Vitamin D dependency	Osteomalacia	↓ Ca_s, ↓ P_s, ↑ alk ϕ	1,25-$(OH)_2D$
XLH	Osteomalacia	nl Ca_s, ↓ P_s, ↑ alk ϕ	PO_4, ? Vit D
Anticonvulsant Rx	Osteomalacia	Hx, nl Ca_s and P_s, ↑ alk ϕ, nl PTH	Vit D
Diphosphonate Rx	Osteomalacia	nl Ca_s, ↑ P_s, ↑ alk ϕ	D.C. diphosphon-ate Rx
P-depletion	Osteomalacia	Hx, high nl Ca_s, ↓ P_s, ↑ alk ϕ, ↓ PTH, ↑ Ca_u, muscle weakness	D.C. antacids, PO_4

Key: Ca_u = urinary Ca; Fl = fluoride; RH = renal hypercalciuria; TZ = thiazide; HPT = hyperparathyroidism; Assoc. = associated; PTX = parathyroidectomy; PE = physical examination; F = serum cortisol; TX = medical or surgical "thyroidectomy"; abn prot electroph = abnormal protein electrophoresis; B-J = Bence-Jones proteinuria; nl = normal; skel = skeletal; XLH = x-linked hypophosphatemia; D.C. = discontinue

Fig. 18. Initial Screen for Osteoporosis

1. Serum Ca, P, Cr, electrolytes, alk. Φ, protein electrophoresis, PTH, T_3, T_4, F
2. CBC and differential
3. 24-hour urinary Ca, Na, (cyclic AMP), B-J protein, pH
4. Skeletal roentgenogram: hands, L-S, pelvis
5. (Bone densitometry)
6. Hx:
   a. Drugs: anticonvulsants, P-binding antacids, steroids, heparin, thyroid
   b. G-I disease: resection, bypass, malabsorption, chronic diarrhea
   c. Nutritional: reduced intake of dairy products
   d. Menstrual: menopause, oophorectomy, estrogen replacement
   e. Rx: muscle weakness, bone tenderness, loss of height

Key: Cr = creatinine; L-S = lumbosacral; F = cortisol

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