AGE-RELATED
(Type II)
OSTEOPOROSIS

Medical Grand Rounds
University of Texas Southwestern
Medical Center at Dallas

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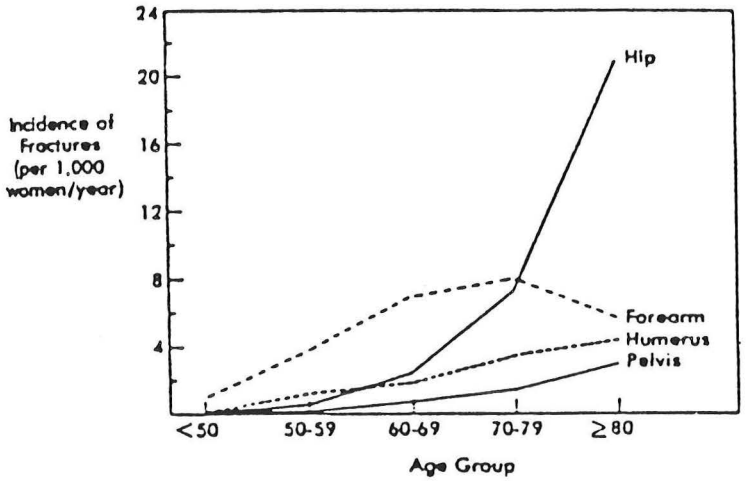
INTRODUCTION

Primary Osteoporosis is an age-related disorder characterized by decreased bone mass and by increased susceptibility to fractures in the absence of other identifiable causes of bone loss (1). Fractures often occur with minimal or no recognized trauma (2). The sites most often involved include the vertebra, hip, and forearm. Osteoporosis is a common problem resulting in at least 1.2 million fractures in the United States each year (3). Approximately 20 million Americans suffer from osteoporosis comprised mostly of elderly individuals especially of the female sex. One third of women of the age of 65 will have vertebral fractures and by extreme old age, one of every three women and one of every six men will have had a hip fracture (4). Hip fractures are the most important consequence of the osteoporotic syndrome. The first year after fracture mortality rate is about 12-20 per cent higher than in persons of similar age and gender who have not suffered a fracture (2). There is considerable impact on mobility, function, and independence. Patients who sustain hip fractures are at increased risk of being placed in a long term care facility. Fifteen to 25 % of patients remain in long-term care institutions for at least one year after hip fracture (5, 6, 7,).

Vertebral fractures from osteoporosis often result from minimal trauma. Patients present with back pain which is usually managed conservatively with analgesics with resolution of symptoms in a few months. Some patients develop multiple fractures that result in kyphosis often referred to as a "dowager's" hump which may result in a chronic pain syndrome. Frequently fractures may be noted on routine x-rays without any history of trauma and in the absence of pain (8). Some investigators have found that by age 80 the majority of white women have at least one partial deformity of their spine (2). The degree of disability resulting from vertebral fractures is unknown.

Fractures of the distal forearm (Colles') are the most common fractures among white women until age 75 (see figure 1.) but are much less likely to result in hospitalization or require rehabilitation compared to hip fractures (2, 9).



Age-specific incidence rates of hip fracture per 1,000 women per year.

The direct medical cost of treating osteoporosis in women aged 45 and older was $5.2 billion dollars in 1986 (9). Of the 321,909 hospitalizations in women over the age of 45 admitted for this diagnosis, more than half were for hip fractures and 80% occurred in women aged 75 and older.

The enormity of the problems posed by osteoporosis are likely to grow when we consider the demographic changes our society is undergoing. In 1987 there were 29.8 million people over the age of 65 years in the United States (compared to 3.1 million in 1900) or 12% of the population (10). In the year 2030 it is anticipated that there will be 65.6 million persons over 65 which will make up 22% of our population. The elderly population itself is becoming older with those over 85 years growing at the fastest rate. In addition, the sex ratio of the elderly continues to change to an increasingly disproportionate number of women to men.

Recently, there has been progress made in the pathophysiology, diagnosis and management of primary osteoporosis, but much of this work has focused on non-elderly postmenopausal women. Major studies often exclude or include few patients over 70 years and information obtained from these studies may not be generalizable to older individuals(11, 12, 13, 14, 15, 16). Much emphasis has revolved around strategies to preserve bone mass or prevent bone loss. However, the applicability of studies in perimenopausal women may not be relevant to the elderly state where loss of bone mass may have already occurred and attempts to preserve mass at this point may have limited impact if at all (17, 18, 19). These factors puts the clinician caring for older patients (virtually anyone practicing adult medicine) in the quandary of using treatment guidelines designed largely for those under 60 years old for those much older. Yet, as suggested above, there are substantial clinical, physiologic, epidemiologic, and functional differences between perimenopausal women and those over 70yrs (17). On the basis of these differences Riggs (20, 21) has postulated at least two distinct syndromes of involutional osteoporosis, type I or "postmenopausal" osteoporosis, usually affecting women within 15 to 20 years after menopause (51-75yrs), and type II or "senile" osteoporosis. This latter group has also been referred to as age-related osteoporosis in an attempt to distinguish between those factors effecting bone volume related to aging itself versus changes related solely to menopause. During this grand rounds I will review the age related changes in bone physiology as it relates to osteoporosis and osteoporotic fractures and review the logic and available evidence for using the currently available approved treatments (calcium, estrogen, and calcitonin) for osteoporosis in older patients. Stated simply, what should we recommend for our 80 year old patient whom we are seeing for the first time and has never been treated for osteoporosis?

PHYSIOLOGIC AND CLINICAL DIFFERENCES BETWEEN TYPE I (POSTMENOPAUSAL) AND TYPE II (SENILE) OSTEOPOROSIS

Since 1947 it had been postulated and then debated whether there exists two different forms of involutional (primary) osteoporosis (20, 22, 23, 24). Approximately over the past ten years Riggs from the Mayo Clinic has reviewed extensive data from his group and outlined the epidemiologic and physiologic model that distinguishes two different syndromes of involutional osteoporosis, type I and type II (see table 1).

Table 1 The Two Types of Involutional Osteoporosis.

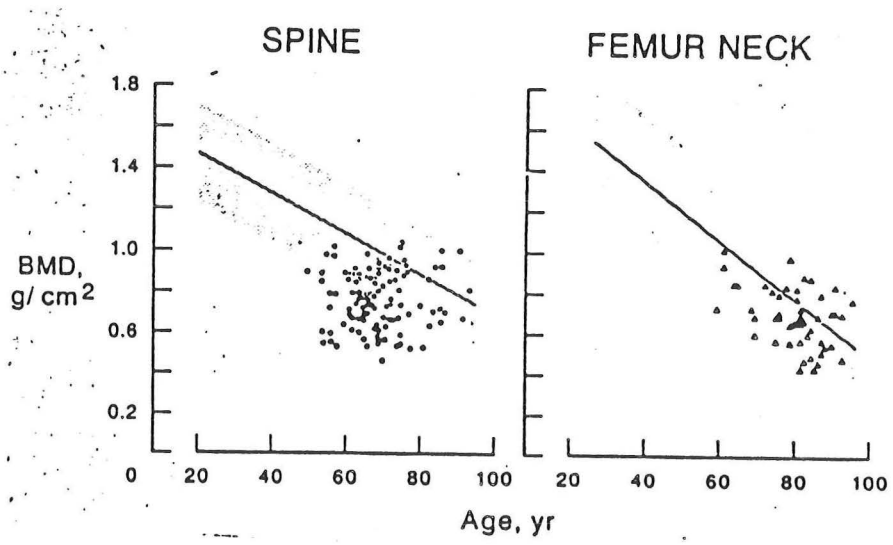
	Type I	Type II
Age (yr)	51–75	>70
Sex ratio (F:M)	6:1	2:1
Type of bone loss	Mainly trabecular	Trabecular and cortical
Rate of bone loss	Accelerated	Not accelerated
Fracture sites	Vertebrae (crush) and distal radius	Vertebrae (multiple wedge) and hip
Parathyroid function	Decreased	Increased
Calcium absorption	Decreased	Decreased
Metabolism of 25-OH-D to $1,25(OH)_2D$	Secondary decrease	Primary decrease
Main causes	Factors related to menopause	Factors related to aging

Clearly there is overlap between the two groups, some individuals may have both forms, and some patients with osteoporosis when studied simply fail to demonstrate the physiologic findings we would anticipate. This is not surprising however given the multifactorial nature of osteoporosis and the heterogeneity of this segment of our population. The classification nonetheless does provide a useful framework to clinically approach this problem. Type I osteoporosis generally effects women within 15 to 20 years since menopause and results predominantly in compression fractures of the spine, and distal forearm (Colles"). It is thought to affect a relative minority of women (2). The primary etiology is thought to be estrogen deficiency. Estrogen has an inhibiting effect to the bone mobilizing influence of parathyroid hormone. In its absence, parathyroid hormone (PTH) increases bone turnover and mobilization of calcium from bone. The enhanced release of calcium from bone subsequently lowers serum PTH which secondarily reduces the renal 1 alpha-hydroxylation of 25-hydroxyvitamin D so that gastrointestinal absorption of calcium is impaired (4). Immunoreactive parathyroid hormone levels have been found to be lower in patients with type I osteoporosis then age matched controls (20). Trabecular bone is particularly susceptible to estrogen deficiency and the predominate site of bone loss involves those bones with a high percentage of trabecular bone, namely the vertebral body and distal extremity.

Perforation and resorption of trabecula lead to decreased "connectivity" of bone leading to structural weakness and resulting in fractures when exposed to minor forces or at times spontaneously. In general, type I osteoporosis is thought to be a high turnover state but histomorphometric studies have shown bone turnover to be high in about 25%, normal in about 45%, and low in 30% (4). It has been postulated in those individuals that present with a normal or low bone turnover picture may have reached a "burned out" state (4). Although estrogen deficiency appears to the major contributing factor to be the development of type I osteoporosis there are other important factors that must be involved since not all postmenopausal women develop this disease and yet have similar estrogen levels (25).

Type II osteoporosis affects individuals over 70 years and although it predominantly affects women, the female to male ratio (2:1) is much closer than the 6:1 ratio found in type I. The site of fractures are mainly the hip and vertebral body and less frequently the proximal humerus, tibia and pelvis. The most significant morbidity and mortality result from hip fractures. In the spine patients may be more susceptible to wedge fractures that may lead to the dorsal kyphosis commonly referred to as a dowager's hump. This is in contrast to the typical "crush" compression fracture noted in type I osteoporosis. The pathologic process in type II osteoporosis is believed to result in a low bone turnover state that results in the gradual thinning of trabecula as well as the cortices. Eventually the decline in bone mass falls to a point in which the bone strength is reduced to a level below the fracture threshold so that minor trauma results in fracture. This fall in bone mass appears to be age-related and the entire elderly population is likely to be at risk. Although there is a greater decline in bone mass in individuals with hip fractures compared to age matched controls, the difference is small with much overlap noted between groups (see figure 2).

Figure 2



As opposed to the predominant trabecular bone loss seen in type I both cortical and trabecular bone are affected in type II. The biochemical changes thought to be responsible for the development of type II osteoporosis appears related to the aging kidneys impaired ability to synthesize 1,25-$(OH)_2$ vitamin D because of an age-related decrease in renal 1-

alpha hydroxylase activity (26, 27). The fall in 1,25-$(OH)_2$ vitamin D results in impaired intestinal absorption of calcium and phosphorus. The resulting decrease in intestinal calcium absorption stimulates PTH secretion which leads to further bone resorption especially in the absence of estrogen. Parathyroid hormone tends to affect cortical bone to an even greater degree than trabecular bone (119) possibly playing a role in the increased incidence of hip fractures noted (28). Osteoblasts are also known possess 1,25-$(OH)_2$ vitamin D receptors suggesting that 1,25-$(OH)_2$ vitamin D may play a direct role in the regulation of osteoblast function. Other factors that may contribute to type II osteoporosis include impaired calcium absorption because of relative achlorhydria commonly found in the elderly (29, 30), poor dietary intake of calcium (31), suboptimal dietary intake of vitamin D, inadequate exposure to sunlight as well as reduced skin capacity to produce vitamin D (32, 33). There also appears to be an age related decrease in osteoblast function which may play a role in uncoupling of bone remodeling. Since under the appropriate stimuli osteoblast response is normal, factors other then senescence are probably responsible. An alteration in one of the many local growth factors may play a role in uncoupling bone remodeling (35).

NORMAL BONE REMODELING

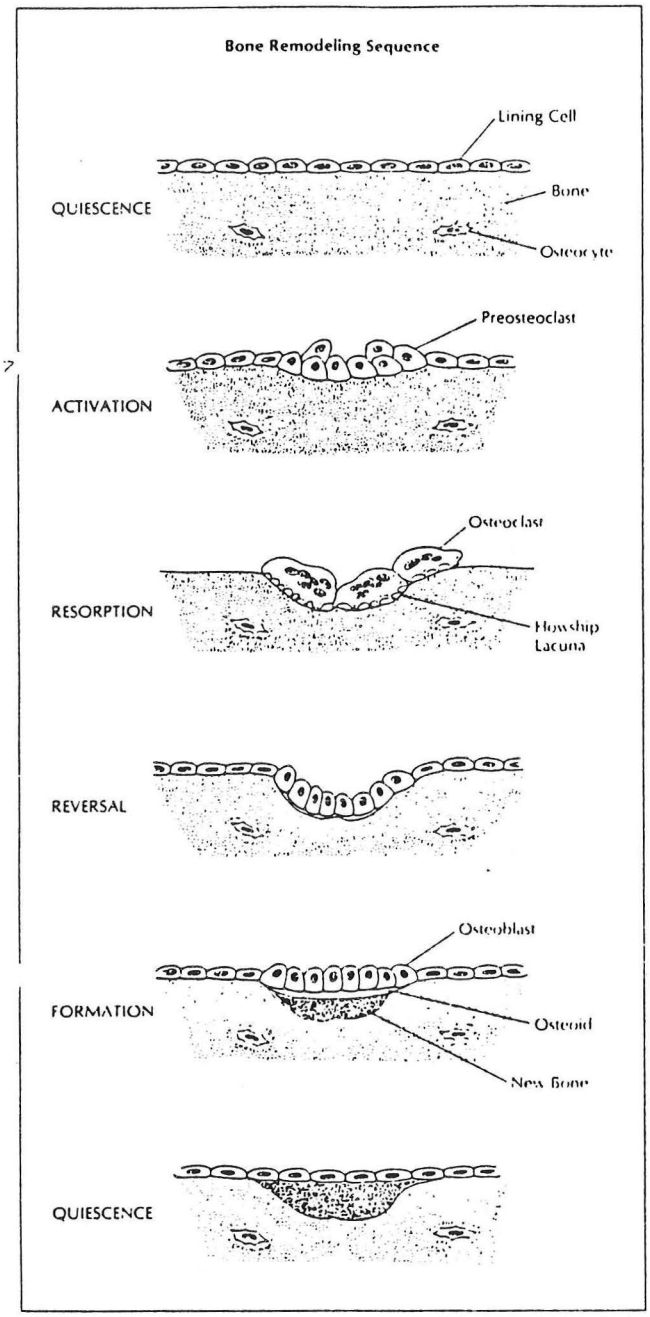
It is useful to review certain aspects of normal bone anatomy and physiology before considering the changes we see in osteoporosis. Bone is composed of both mineral (70%) and organic (30%) components. The former is largely hydroxyapatite crystal composed mostly of calcium and phosphorus and the later mostly of type I collagen. Two major forms of bone exist. Cortical or compact bone forms the shell of bones and is the predominant form of bone found in the shaft of long bones and makes up about 80% of our skeleton (34). Trabecular (also referred to as spongy or cancellous) is the predominant form found in the vertebra, flat bones and the distal end of long bones (see table 2).

Table 2

Approximate proportions of coritcal and trabecular bone at various sites in skeleton

Site	Cortical (%)	Trabecular (%)
Hip		
Trochanteric region	50	50
Neck	75	25
Vertebrae	<33	>66
Forearm		
Distal	30-50	50-70
Middle	95	5

Trabecular bone is made up of a lattice-like series of thin plates (trabeculae) which forms the inner meshwork of bones. Although trabecular bone contributes to only 20% of the skeleton it has a larger surface area then cortical bone and tends to be more sensitive to metabolic influences so that conditions that produce rapid bone loss tend to affect trabecular bone more quickly than cortical (2). Bone is a dynamic tissue that undergoes continuous remodeling throughout life. To understand the pathophysiology of osteoporosis it is important to appreciate normal sequence of bone remodeling. The basic unit that is responsible for remodeling is known as the Bone Remodeling Unit (BRU). Bone remodeling occurs in a highly ordered manner in which first bone resorption is followed by bone formation (see figure 3).



Bone remodeling begins with the clustering of mononuclear phagocytes on the bone surface. These cells eventually fuse to become multinucleated osteoclasts that dig a resorption cavity, or Howship lacuna, into the bone. Meanwhile, osteoblast precursors are attracted to the site; as they mature, they secrete collagen and matrix constituents, known as osteoid, to form new bone. (Adapted from A. M. Parfitt)

Figure 3 Hospital Practice April 15, 1989

This process is tightly coupled so that under normal circumstances the degree of resorption and formation are equal and there is no net change in bone volume or mass. The first step is the activation of surface lining cells that probably respond to bone resorbing hormones and release proteolytic enzymes. These enzymes allow access to the mineralized bone by osteoclasts. Osteoclasts then resorb bone by dissolving bone mineral and degrade bone matrix resulting in the formation of a cavity. Osteoclasts are then replaced by osteoblasts which fill the cavity with an organic matrix (osteoid) composed primarily of collagen. This new bone is then mineralized. The entire process can take three to four months.

This highly complex sequence of events (overly simplified here) is mediated by calcium-regulating hormones, systemic hormones, local (paracrine) factors as well as mechanical and electrical forces (35) (see table 3).

Table 3

Some Factors Influencing Bone Metabolism

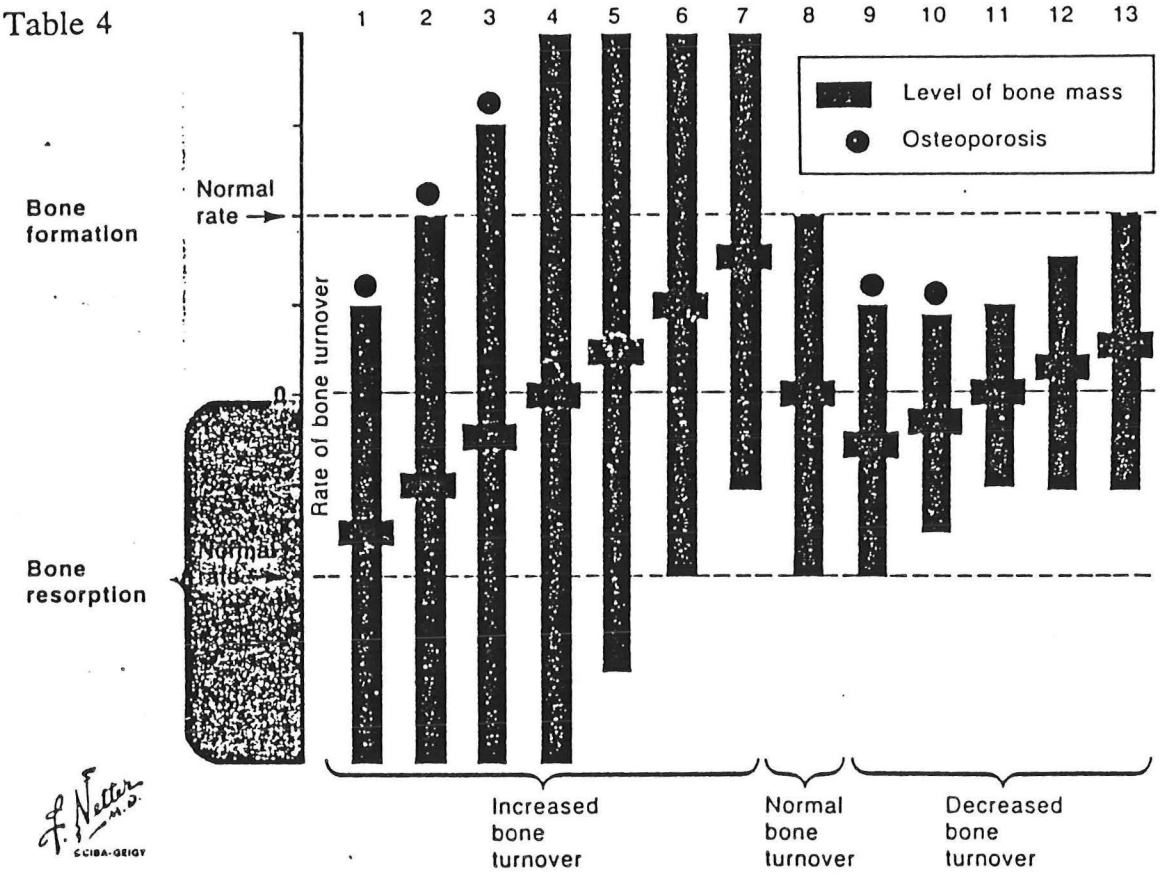
	Predominant Effects	
	on resorption	on formation
Calcium-regulating hormones		
Parathyroid hormone	+	+
1,25-Dihydroxyvitamin D	+	−, (+)
Calcitonin	−	0
Systemic hormones		
Growth hormone	0	(+)
Glucocorticoids	(+)	−
Thyroid hormones	+	+
Insulin	0	+
Estrogens	(−)	(−)
Local factors		
Prostaglandin E_2	+	+
Interleukin-1	+	−, (+)
Interferon-α	−	−
Insulin-like growth factor 1	0	+
Transforming growth factor-β	−, (+)	+

Assignment of a predominant effect for each factor is based on current data (from in vivo studies if available). A plus sign denotes an increase, a minus sign a decrease, and a zero no effect. The symbols in parentheses indicate indirect mechanisms. For example, 1,25-dihydroxyvitamin D can increase bone formation by increasing the calcium and phosphorus supply, whereas growth hormone probably acts largely through insulin-like growth factor 1. Glucocorticoids can increase bone resorption indirectly by producing secondary hyperparathyroidism. The remaining symbols in parentheses represent indirect mechanisms that are probably mediated by changes in local prostaglandin E_2 production. Several other growth factors, not listed here, can increase bone resorption by increasing prostaglandin E_2 production.

It is important to remember that bone resorption is closely coupled (presumably by local factors) to formation in each bone remodeling unit. If this relationship is altered we refer to it as the uncoupling of bone resorption and formation. If the uncoupled state results in increased bone formation and decreased resorption there will be a net increase in bone mass. Such is the case in patients with osteopetrosis. In patients who have normal bone resorption but increased bone formation there is a net increase of bone mass and this describes the circumstance seen in normal growth and development. In osteoporosis there is a reduction of bone mass due to a proportionately greater amount of bone resorption than formation (see table 4).

Table 4

Bone-Formation/Bone-Resorption Combinations



From Kaplan FS. Osteoporosis. Clinical Symposia, 1987 39:8.

Example 8 illustrates normal bone turnover with bone formation and resorption coupled at a normal rate maintaining bone mass.

Example 2 depicts Type I osteoporosis with increased bone turnover with a normal rate of bone formation but increased bone resorption resulting in a net loss of bone mass.

Example 9 represents Type II osteoporosis with decrased bone turnover, normal bone resorption and decreased bone formation resulting in a net loss of bone mass.

The other examples represent a variety of other possible bone formation/resorption combinations.

The loss of bone affects bone mineral and matrix equally; thus, the remaining bone is grossly normal. When the bone mass is decreased to a point where it is insufficient to support the normal structural integrity and weight bearing function of the skeleton, fractures occur with minimum trauma.

BONE LOSS. AGE-RELATED OR ESTROGEN DEFICIENCY?

Although osteoporosis is generally classified in terms of primary or secondary osteoporosis it is important to realize that an individual's bone mass is the result of a variety of factors and interactions that one has been exposed to which ultimately determines that person's bone mass. These factors include race, age, sex, nutrition, activity, and hormonal status. In addition, certain diseases and long term use of some medications or toxins can result in osteoporosis (see table 5).

Table 5

RISK FACTORS FOR OSTEOPOROSIS

(Secondary Osteoporosis)

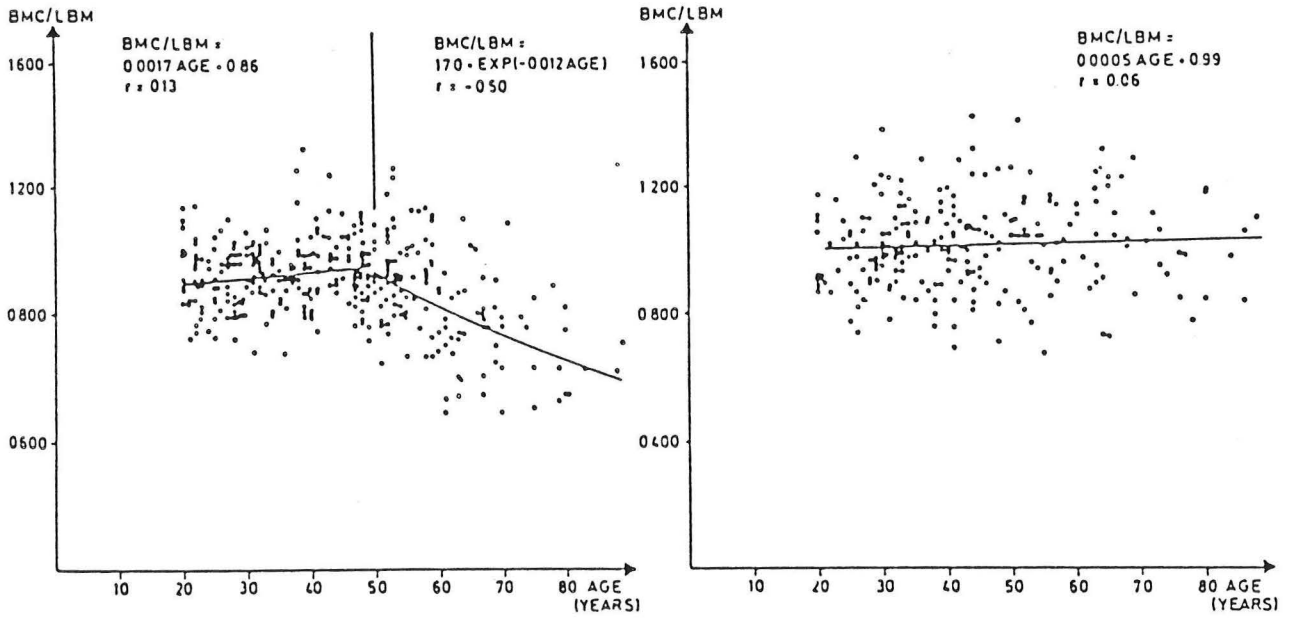
- Endocrine abnormalities
  - Hyperadrenocorticism
  - Thyrotoxicosis
  - Hyperparathyroidism
- Gastrointestinal diseases
  - Malabsorption
  - Intestinal resection
  - Cirrhosis
- Malignant diseases
  - Multiple myeloma
  - Lymphoma
  - Leukemia
- Immobilization
  - Renal failure
- Drugs
  - Glucocorticoids
  - Excess thyroxine
  - Dilantin
  - Barbiturates
  - Heparin
  - Ethanol
  - Cigarette smoking

- Postmenopausal (within 20 years after menopause)
- White or Asian
- Premature menopause
- Positive family history
- Short stature and small bones
- Leanness
- Low calcium intake
- Inactivity
- Nulliparity

Realizing this there are a number of differences between the pattern of bone loss between perimenopausal and elderly women.

Peak bone mass is thought to occur at around 35 years. The absolute mass is higher in men than women and in blacks than Caucasians or Asians. There is some controversy around the pattern of bone loss after this point. In general there appears to be no significant bone loss until menopause when an accelerated loss of bone occurs which is predominantly trabecular. After ten year to fifteen years the rate of loss declines and appears to follow an age related curve. Nilas did a cross sectional study (36) of the bone mass of 178 healthy women between the ages of 29 to 78. The bone mass was measured at the forearm, and spine by single-photon and dual-photon absorptiometry respectively (SPA and DPA). He found no significant premenopausal or age related bone loss regardless of site and bone composition. However, bone mass declined in all sites in a uniform pattern with increasing menopausal duration. There was also no biochemical evidence of increased bone turnover until the menopausal state when urine calcium/creatinine and hydroxyproline/creatinine ratios significantly rose. Bone loss was correlated more to menopausal duration than age. That is, age differences of 5 years did not lead to differences in turnover measurements or bone mass in women of the same menopausal status. Thomsen (37) studied the forearm bone mineral content (BMC) in 574 healthy (no fractures) white subjects, male and female between the ages 20-89 years (only approximately 40 over age 70 years) and found no age related bone loss in men when corrected for lean body mass and no significant change in BMC in women with age until menopause. Thereafter a decline of 15% per decade was found up to the age of 70 years, after which it was 10% per decade. When corrected for lean body mass there was a decline of 12% per decade (see figure 4).

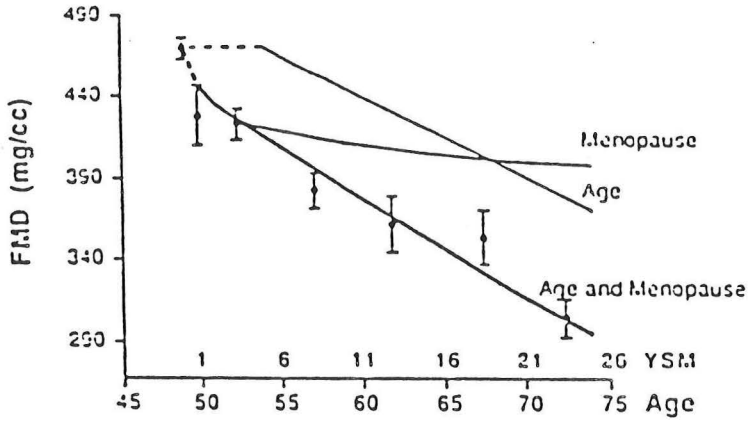
Figure 4



Relationship between bone mineral content (BMC) corrected for lean body mass (LBM) in 350 normal women (left) and 227 normal men (right).

Cann also demonstrated an accelerated loss of vertebral (trabecular) bone at menopause using quantitative computed tomography (38). The decrease in vertebral bone mass in males followed a linear regression. Schaadt (39) reported the results of a cross sectional study of healthy individuals. This study included 113 women between the age of 20-89 years in whom he measured lumbar, femoral neck and femoral shaft bone density by DPA. He found the lumbar spine BMC remained stable until the time of menopause (fifth to sixth decade), the femoral neck BMC decreased linearly from young adulthood to old age and the shaft BMC remained unaltered until the eighth decade and then declined significantly. Nordin (40) estimated the relative contribution of menopause and age in the forearm bone mineral density of 485 healthy postmenopausal women up to age 75 years. In this cross sectional study they calculated by using pairs matched for years since menopause that there is a linear age component of forearm bone loss that starts at about age 55 years, and continues at a rate of about 1% per year at least to the age of 75 years. There is also a self-limiting menopause component. This accounts for the loss of about 11% of bone in the first 5 years and a further 5% in the next 20 years (see figure 5).

Figure 5



Calculated mean FMD values as a function of age and YSM separately and together, assuming a menopausal age of 49 yr. The *lower line* is the sum of the *upper two lines*. The measured mean values by age groups in the 146 subjects who reached the menopause at 48–50 yr have been superimposed. The first data point at 469 mg/cc is derived from our previous set of normal premenopausal women (9).

This data would suggest that age related bone loss over time ultimately accounts for more bone loss then can be attributed to the menopause and estrogen deficiency. The authors point out that this analysis applies to the forearm where there is a predominance of cortical compared to trabecular bone; it is known that measurements of bone mass at a given site do not necessarily reflect changes taking place elsewhere in the skeleton (41). As opposed to the above studies Riggs (42) did a cross sectional controlled study that measured the bone mineral density (BMD) of the lumbar spine, radius, and in the proximal femur in 205 normal patients (male and female) between the ages 20-92 years and found a linear

diminution of bone for both men and women at the hip and lumbar spine. The rate of bone loss in the men however was two thirds of that for women at the hip and one fourth that of the spine. In 31 patients with hip fractures (11 also had vertebral fractures) the BMD at the lumbar, mid and distal radius sites did not differ significantly from normal. There was a slight but significant difference at the intertrochanteric site. There was considerable overlap in values compared to controls. In a third group of 84 women (divided into groups 51-65, 66-75, and >75 years) with non traumatic vertebral fractures due to osteoporosis the 51-65 yr group had deviations in their BMD that were significantly lower than normal at all three scanning sites (lumbar, mid and distal radius). The deviation was much greater at the lumbar site but for those over 75 years there were no significant decreases from normal (see figure 2). The 66-75 years group had intermediate changes. It was the authors' interpretation that there findings suggested two distinct syndromes of osteoporosis, a small subset (5-10%) of women manifest by vertebral fractures and referred to as postmenopausal osteoporosis. These women have lost a disproportionate amount of trabecular bone. Geusens found a similar decrease in bone mass at menopause that was twice as great in the lumbar spine as at other sites. The other form, "senile osteoporosis" (or type II) occurs in persons over 75 years which may affect more than half of the population of aging women and a fourth of the population of aging men. The bone loss is proportionate for cortical and trabecular bone in this group and is only slightly more in those with fracture then in the remainder of the aging population. Conflicting results from a smaller study from the same group (43) compared the BMD in three groups of 14 women with mean ages of 54 (oophorectomized), 52 (perimenopausal), and 73 (postmenopausal) years and the mean intervals since menopause of 22,0.3, and 22 years respectively. The decrement in the BMD in the oophorectomized and postmenopausal group were comparable suggesting most of the bone loss occurring in women during the first two decades after natural menopause is attributable to estrogen deficiency rather than to aging itself. Of course the number of patients studied were small and the mean age of the postmenopausal group was only 72.6+/-0.9. Two patients from the postmenopausal group and two from the oophorectomized group had vertebral fractures so that this was a mixed group of patients making the results from a small number of patients studied hard to interpret.

There are have been few longitudinal studies to assess bone loss in general and in the elderly in particular. A longitudinal study by Riggs et al (44) that studied the BMD of 139 normal woman at the midradius and lumbar spine found no significant fall in radial BMD until after menopause but they noted a significant premenopausal loss of BMD occurs as well as post menopausal. Although, there were only three women over age 70 yrs with a mean follow up of three years (longest group) there was minimal decline in vertebral BMD and in the four patients over 70 yrs with a mean follow up of two years there was also a suggestion of minimal change in BMD. The BMD from the midradius best fit a linear regression but again, the number of people of 70 yr was small and there was overlap. A longitudinal study by Quigley (18) followed 397 (51-80 years) healthy postmenopausal women for three years. Bone density of the distal radius was measured and found a significant decline in BMD in subjects between 51 to 70 years but not 71 to 80 years (decline of 1.1% +/- 0.4 later). The longest longitudinal study is by Hui et al. They followed the

mid radial bone density of 268 women, some with osteoporosis. There were 42 women between the ages 73 to 95 years followed for at least six years. Of this group, 13 (31%) had a significant increase in BMD, 12 (29%) a significant decrease and 17(40%) without significant change.

Although there remains considerable debate about the course of bone loss associated with aging it is reasonable to conclude that there is an accelerated bone loss associated with menopause that is predominantly estrogen related. This accelerated phase of bone loss gradually slows approximately ten years after menopause after which time the rate of loss continues but at a reduced rate parallel to the linear age related-reduction in cortical bone. The bone loss associated with estrogen deficiency is predominantly from the axial skeleton which is mostly trabecular bone. Other biochemical factors may affect bone density during the premenopausal period but this remains unclear. The appendicular skeleton begins to lose bone later and is associated with a more gradual linear decline as noted above. This bone loss is predominantly cortical. Age-related bone loss may actually cease in some older individuals. It has been speculated that some individuals may get to a point in time where such a large amount of bone has been lost that there is little left to lose. In addition, there is evidence that indicates that trabecular and cortical bone compartments may be independently modulated which may have therapeutic implications (45).

FACTORS IN BONE STRENGTH AND FRACTURE RISK

Although bone mineral content is related to structural strength it is not the only determinant of fracture risk (46, 47, 48). In fact Cummings (49) critically reviewed 15 case-control studies comparing bone mass and hip fractures and found that patients with fractures did not appear to be distinctly more osteopenic than persons of similar age. The fracture threshold is a term used to define the bone density value below which the risk of fracture is enhanced. It is a useful concept but is not precise. For example a group of patients studied here were determined to have a spinal bone density fracture threshold of 1.3g/cm^2. Patients with bone densities of 1.3 or greater sustained no fractures, those between 1.0 and 1.3 g/cm^2 had few fractures but below 1.0g/cm^2 the fracture rate was higher and increased further with declining bone density. However, there was a wide scatter of individual fracture rates below 1.0g/cm^2. In other words, some patients had no fractures in spite of very low bone densities This highlights a number of issues. First, we must keep in mind that the outcome measure of consequence is fracture and not bone mass itself. Second, fractures occur because of intrinsic changes in the bone which makes it susceptible to fracture, that is bone fragility. Bone mass is only one factor contributing to bone fragility. Other factors that probably work in combination with bone mass include accumulated fatigue damage, and reduced trabecular connectivity (50, 51, 52, 49, 53). These latter two factors are not measured by techniques that assess bone mass. The former may play more of a role in hip fractures and the latter to vertebral fractures. Other factors that contribute to fractures are frequency of falls, trauma, reduced soft tissue mass that may impair the ability to absorb the energy from a fall, and changes in the postural response to falls in older individuals (54).

Parfitt (50) has reviewed age related structural changes in bone. He proposed two structurally different forms of bone loss, rapid and slow (see table A).

Table A

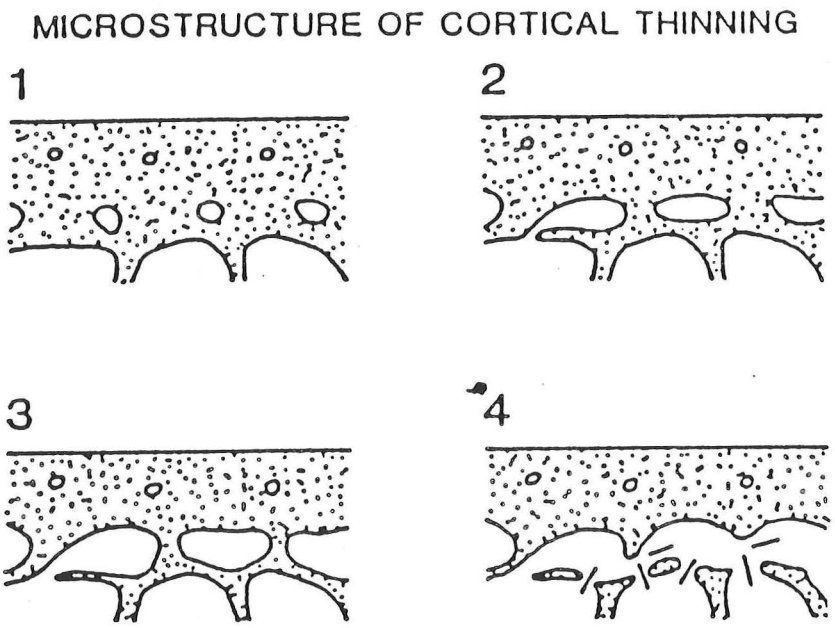
Comparison of rapid and slow bone loss

Characteristic	Rapid	Slow
Timing	Early	Late
Trabecular structure	Perforation and disconnection	Simple thinning
Cortical structure	Subendosteal porosity	Simple thinning
Remodeling mechanism	Deeper resorption	Shallower formation
Probable cell defect	Unrestrained osteoclasts	Too few osteoblasts
Reduction in strength	More than predicted[1]	As predicted[1]

[1] From reduction in mass or mineral content

The rapid bone loss is the result of excessive depth of osteoclastic resorption cavities that lead to focal perforation of the trabecular plate which leads to discontinuity of the bone structure. This may have major implications for the treatment of osteoporosis. Ideally to restore bone strength you would need to restore lost trabecular plates and rods but this seems unlikely by present therapeutic means. In the cortical bone there is subendosteal perforation of the cortical plate leading to the formation of a trabecular-like structure which is then subject to more of the same process of excessive osteoclastic bone cavity formation (see figure B).

Figure B



These structural changes lead to a greater reduction in bone strength then would a reduction in bone mass by itself. A second form of slow bone loss is the result of inadequate filling of bone cavities that result in simple thinning of trabecular and cortical structures. The reduction in bone strength in this circumstance is proportional to the reduction in bone mass lost. In addition to these changes of bone loss, bone formation can occur on the periosteal surface of bone which is due to the overfilling of resorption cavities and may partially offset the structural weakness resulting from the endosteal resorption. A similar process of bone formation may occur on trabecular bone.

THERAPEUTIC CONSIDERATIONS IN TYPE II OSTEOPOROSIS

The following is a review of the commonly prescribed medications used in the treatment of osteoporosis. Most of these agents prevent osteoclastic bone resorption and can be referred to as anti-resorptive agents. They generally do not augment bone mass other than transiently because of the commensurate decline in bone formation following inhibition of bone resorption. The rate of bone formation declines due to the coupling of bone formation and resorption. This is particularly important to keep in mind when interpreting results from short term studies (less than two years). Claims of increased bone mass under these circumstances may not be valid. The application of these agents in the elderly poses a number of questions. First of all, are these agents likely to be of use if bone mass has already declined to a degree that renders patients at risk for fracture? Are small improvements in bone mass sufficient to significantly improve bone strength and prevent fractures? That is, a one or two percent increase per year in bone mass by some agent may be statistically significant but it may not raise the bone mass to a point, such as exceeding the fracture threshold, where we would anticipate a reduction in fracture incidence. Lastly, factors other than a reduction in bone mass are likely to contribute to skeletal fragility (55). It may be possible therefore that some agents may favorably affect bone strength but may not result in significant changes in bone mass. Unfortunately we do not have an in-vivo method to study bone strength other then bone mass at the present time. It is imperative that clinical studies include fracture rates as well as bone density in evaluating the effect of a particular medication. The following discussion will review the theoretical benefit of each agent as it relates to the elderly and what information is presently available to support or refute its use in this age group.

Vitamin D

Although this agent has not been approved by the FDA for use in the treatment of osteoporosis it is commonly used for such purposes. It has been postulated that one of the primary age-related changes that predispose the elderly to bone loss is a decline in the production of 1,25-$(OH)_2$ vitamin D as reviewed above (4). It seems reasonable than that by replacing or supplementing vitamin D that you could at least stop if not reverse further bone loss. There have actually been few studies that have specifically evaluated vitamin D metabolism and its use in the treatment of osteoporosis in the elderly. Most but not all studies show a fall in 1,25-$(OH)_2$ vitamin D levels with aging (56, 57, 58) In a small study comparing normal young adults to elderly patients with osteoporosis both groups had normal serum 1,25-$(OH)_2$ vitamin D levels but when stimulated with an infusion of PTH there was no significant response in the elderly group compared to a nearly doubling of serum 1,25-$(OH)_2$ vitamin D levels in the normal volunteers. Serum calcium levels went up in both groups. These findings raise the question that perhaps elderly patients may not be able to respond adequately when dietary calcium intake is low (59). Tsai et al (26) provided further evidence that altered vitamin D metabolism may play a role in elderly osteoporotic patients by comparing the serum 1,25-$(OH)_2$ vitamin D response to an IV infusion of PTH between four groups. Those studied included normal premenopausal women, normal

postmenopausal women , normal elderly and elderly women with hip fractures (mean ages 37, 61, 78, and 78 respectively). They found there was a blunted response in the elderly in general but significantly more so in those with hip fractures. Silverberg (60) found similar findings in patients with spinal osteoporosis. Zerwekh et al (61) measured the response to long term administration of 25-hydroxyvitamin D in a group of postmenopausal women ages 44-74 (mean age 62). They found two groups could be distinguished. One group (responders) had an increase in intestinal calcium absorption as well as a significant increase in serum 1,25-$(OH)_2$ vitamin D as compared to a group of nonresponders who showed no increase in the intestinal absorption of calcium or in 1,25-$(OH)_2$ vitamin D. The mean age of the responders was 63.7 years compared to 58.6 years in the nonresponders. Interestingly Francis et al (62) studied two groups of women with and without vertebral fractures. Both groups had low baseline 25 vitamin D and 1,25-$(OH)_2$ vitamin D levels. After treatment with 25-hydroxyvitamin D the group without fractures (mean age 80.4 +/-1.6 yr) had a significant increase in serum 25-OH vitamin D and 1,25-$(OH)_2$ vitamin D as well as intestinal calcium absorption. The group with fractures (mean age 76.8 +/-1.3 yr) had an increase in both vitamin D levels but there was no increase in the intestinal absorption of calcium. This study therefore raised the question that an impairment in intestinal calcium absorption independent of vitamin D may exist in women with vertebral fractures.

Most studies have not shown a clinically beneficial effect from vitamin D in patients with osteoporosis or normal elderly. Orwoll (63) reviewed the effect of cholecalciferol (vitamin D) and supplemental calcium in a three year double blind placebo controlled longitudinal study in 86 normal men from ages 30 to 87 years. They found a linear decline in the bone mass in both axial and appendicular skeleton. There was no difference in the amount of bone loss between the supplemented group and placebo group. The mean dietary intake of calcium in these patients at baseline was high at over 1159 +/- 576 mg/d. There was a small reduction in the PTH level in the supplemented group. Orwoll (64) also studied 39 women with severe osteoporosis (vertebral) over two years who received in a randomized double blind fashion either 40 ug of 25-OH vitamin D and 1200 mg of calcium or placebo and 1200 mg of calcium per day. The mean age was 69+/- 7 years and duration since menopause was 23 +/- 9 years. Proximal and distal forearm density was measured as well as bone histomorphometry. The patients who received 25-OH vitamin D showed an increase in serum 25-OH vitamin D levels as well as increased intestinal absorption of calcium reflected in increased urinary calcium levels but there was no increase in 1,25-$(OH)_2$ vitamin D levels or other biochemical parameters measured. Radial bone mineral content remained stable in both groups. New fractures were uncommon in both groups, there was no report of hip fractures. Bone histomorphometry at baseline revealed a low bone turnover state. On repeat bone biopsy there was no difference compared to the first except for an increase in rate of mineralization in both groups. This was possibly due to supplemental calcium and provides no evidence of an independent benefit from 25-OH vitamin D.

Ott (65) in a double blinded randomized controlled trial studied 86 women between 50 to 80 years (mean 67+/-1.0) with vertebral fractures over two years with calcitriol (1,25-$(OH)_2$

vitamin D) versus placebo and could find no improvement in bone mass, fracture rate, or difference in bone histomorphometry. There were no hip fractures during the study. In another double-blinded randomized controlled trial Aloia (66) studied 12 patients with osteoporosis (vertebral fractures) 50 to 80 years old (mean age 64) for two years who received either calcitriol or placebo. In the experimental group, bone density increased compared to control but there was no significant difference in fracture rate or bone histomorphometry between groups. There was no report of hip fractures in either group. In 11 of 12 patients taking calcitriol hypercalcemia developed and one patient required I.V. saline therapy. A fall in creatinine clearance was seen in two patients. There have been other reports of vitamin D toxicity complicating the treatment of osteoporosis (67). Jensen (68) found no beneficial effect from 1,25-$(OH)_2$ vitamin D on forearm bone densities in a double-blind placebo controlled trial in seventy four 70 year old women. The trial was only one year in duration and no information regarding fractures was reported. Seven out of nineteen patients on 1,25-$(OH)_2$ vitamin D developed hypercalcemia which required a reduction in dosage. In a later report from the same group an increase in vertebral fractures was found in those who received 1,25-$(OH)_2$ vitamin D (69). In a study by Gallagher (70) et al they found that 12 osteoporotic women (no age data) taking 0.5ug a day of 1,25-$(OH)_2$ vitamin D over two years noted an increase in trabecular bone volume in the presence of a negative calcium balance suggesting that trabecular bone volume may have improved at the expense of cortical bone. There was mild hypercalcemia in a number of patients but it was otherwise well tolerated.

In summary there is limited information which supports the widespread use of pharmacologic doses of vitamin D or its metabolites at this point in time. As reviewed elsewhere (17) there are a number of groups of elderly, particularly those institutionalized or homebound that may be particularly at risk of developing vitamin D deficiency. In these individuals or those whose dietary intake of vitamin D may be suspect it may be reasonable to supplement with the recommended daily allowance of 400 IU of vitamin D per day. In addition, patients with impaired intestinal calcium absorption such as those with intestinal resection or other malabsorption syndromes should receive supplements. It should be kept in mind that pharmacologic doses of vitamin D can have toxic consequences. Care should be taken in individuals on thiazide diuretics. It should be remembered that there is also evidence that 1,25-$(OH)_2$ vitamin D can increase bone resorption (27) in addition to its beneficial effect on intestinal absorption of calcium. More work needs to be done to fully understand and evaluate the potential benefits this agent may provide in type II osteoporosis.

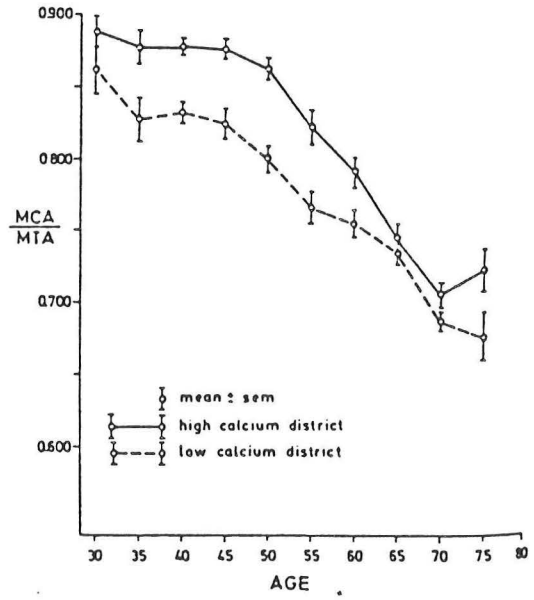
CALCIUM

Calcium has widely been recommended to the female populace as a means to prevent osteoporosis. The sale of calcium supplements have sky rocketed in recent years with roughly $166 million being spent in 1987 (72) In the elderly there are a variety of ways in which calcium may be beneficial. Age-related bone loss is in part mediated via inadequate dietary intake of calcium and/or impaired absorption which result in a negative calcium balance. Since 99% of total body calcium is found in bone the daily demands to maintain calcium homeostasis are drawn from this source. When there is inadequate provision of calcium, PTH is released which promotes bone resorption. This is facilitated in the absence of estrogen. In addition PTH preferentially effects areas high in cortical bone. In this way calcium homeostasis is maintained at the expense of bone mass. It is reasonable to speculate that if the daily consumption of calcium were increased to levels that would provide a positive calcium balance one could prevent further bone loss from occurring and perhaps even increase bone mineralization.

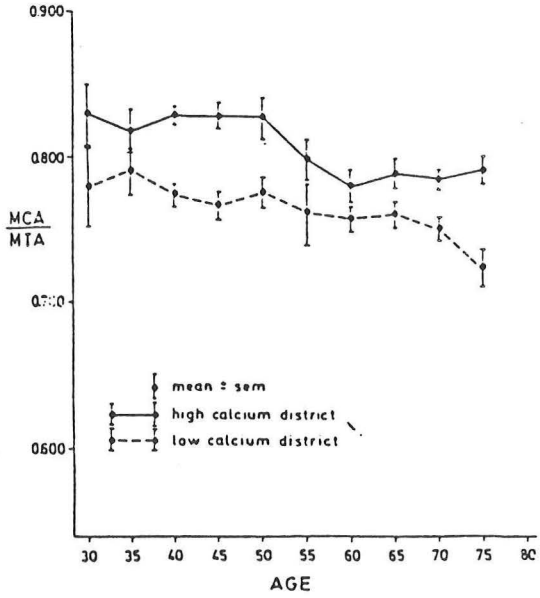
The average daily intake of elemental calcium in those over 65 is approximately 500mg per day. This is far below the recommended level of 1,500mg for postmenopausal women not treated with estrogen (1000mg per day in those on estrogen) (1,2). A number of studies have shown that daily calcium intake in patients with osteoporosis is below age matched controls (73).

Matkovic et al (74) studied two populations from different regions in Yugoslavia which were similar except for their dietary intake of calcium. The group with a higher dietary intake of calcium were noted to have higher indices of cortical bone volume. This difference was apparent at 30 years of age suggesting that peak bone mass was already established by this early age. Both populations experienced a decline in cortical bone volume with age so that by age 65 years they were almost identical (see figures 6 and 7).

Figure 6

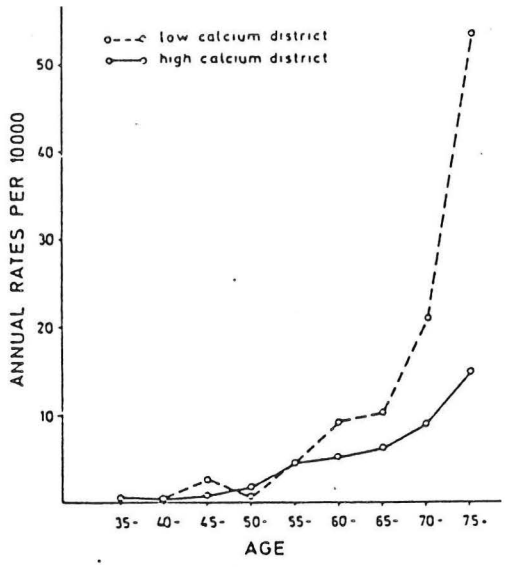


Metacarpal cortical/total area ratio (MCA/MTA) in women in both districts in relation to age.



Metacarpal cortical/total area ratio (MCA/MTA) in men in both districts in relation to age.

Figure 7



Annual proximal femur fracture rate in women in both districts in relation to age.

Of interest is that after age 70 the slope of the curve in women from the low calcium area continues to be negative but that from the high area became positive. This is less pronounced in the men. The annual fracture rate in those from the high calcium district was 50 per cent lower than those form the "low" calcium district. There was no difference in the rate of colles' fractures between the two groups.

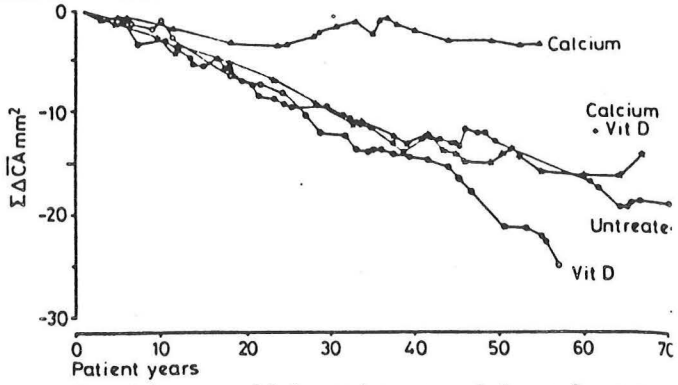
Riggs et al (75) could find no evidence that insufficient dietary calcium was a major cause of bone loss at the midradius or lumbar spine in normal women (mean age 61). In a group of early postmenopausal women whose calcium intake ranged from below 550 mg to above 1150 mg per day and who were supplemented with 500 mg of calcium per day over two years, Nilas (76) noted similar rates of fall in BMC in all groups. Chapuy (77) however studied 134 elderly individuals with a mean age of approximately 75 yrs and 62% of patients with a daily calcium intake of less than 500mg and a low vitamin D intake in all patients (<5 ug/d). Patients were randomly divided into a control group or a treatment group which received 1000 mg of calcium and 800 IU of vitamin daily and over a six month period. A significant fall from baseline (which was elevated compared to controls from young adults) in serum PTH , and alkaline phosphatase levels was noted compared to control patients. Unfortunately the study duration was only six months and no bone density measurements were obtained. Nonetheless, this study suggests that abnormalities of calcium and bone metabolism in the elderly can be affected by calcium and vitamin D supplementation.

A number of other studies have been carried out to assess the effect of calcium supplementation on bone loss in normal subjects (76, 78, 11, 79, 80, 81, 82, 83,) (see table). Most of the subjects studied were early postmenopausal and few elderly subjects were included. Many of the studies compared the effect of no treatment, estrogens, or calcium on bone loss (81, 78, 11, 80). Two general impressions can be reached from these

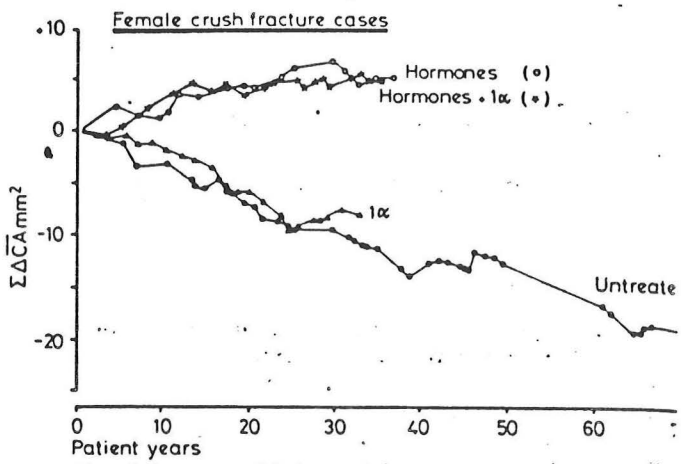
investigations. One is that calcium supplementation probably provides no significant benefit in preserving spinal (trabecular) bone mass. The other is that supplemental calcium may reduce the rate of bone loss from appendicular (cortical) sites but it is less effective than estrogen in doing so in the groups studied. In one of the few studies that suggested that calcium may slightly increase or stabilize spinal bone mass (79) calcium citrate was used which has better gastrointestinal absorption compared to the other commonly used calcium salts. This is particularly true in the setting of low gastric acid secretion, a state that is not uncommon in the elderly. Lastly, in a three year study of healthy men ages 30-87 years, calcium and cholecalciferol supplementation provided no benefit in reducing bone mineral loss at either axial or appendicular sites.

There have been surprisingly few studies that have assessed the effect of calcium in patients with osteoporosis. Of the handful of such studies that have been carried out almost none of them have included patients over the age of 70 years and outcome measures such as impact on vertebral or hip fractures seldom performed. Nordin et al (84) studied twenty postmenopausal women mean age 64.3+ 1.9 (18 yrs mean since menopause) who received supplemental calcium and had a history of osteoporotic vertebral fractures over approximately two years. They received 1200 mg of elemental calcium a day. They were documented to have good intestinal calcium absorption by radiocalcium techniques. Hand radiographs determined the cortical area ratio of the second metacarpal of the right hand. Spinal x-rays were also sequentially obtained to assess for any new fractures. These patients were compared to a variety of other treatment groups as well as 44 control patients who received no treatment that had vertebral fractures. The calcium group achieved a positive calcium balance (in some but not all) , had no significant change in mean cortical area of metacarpal bone, and experienced no new vertebral fractures. The untreated group had a negative calcium balance, cortical bone values fell significantly from baseline but was not statistically different from the calcium group and the spinal fractures increased but because of wide individual variation this was not statistically significant (see figure 8).

Figure 8



Cumulative sequential changes in mean cortical area of metacarp of postmenopausal women with spinal osteoporosis treated with calciu vitamin D, or calcium+vitamin D. The untreated group is also shown.



Cumulative sequential changes in mean cortical area of metacarp of osteoporotic postmenopausal women treated with hormones, 1αOHI or hormones+ 1αOHD$_3$. The untreated group is shown for comparison.

There is no information regarding the history of hip fractures. Hansson and Roos reported a three year, controlled prospective study in (85) on the effects of fluoride and calcium and

spinal bone mineral content in postmenopausal women with spinal fractures. The patients were divided into different treatment groups which included a group which received only 1 gm of calcium (no fluoride), and a placebo group. There were 22 patients in calcium group with a mean age of 64.6 years. Spinal x-rays and lumbar BMC by DPA were obtained. Although there was a greater decline in BMC in the placebo group than the calcium group neither group had a significant decline over the three year study. There were few vertebral fractures noted in all groups. The author points out the average daily intake of calcium in Sweden is 800 mg a day, substantially higher than the 500 mg a day reported in this country. This may have had some bearing on there results. The group that received 30mg of fluoride a day and calcium did note an increase in BMC of the spine and sustained no new fractures. There is no information regarding hip fractures. Lee et al (86) took twenty women with a mean age of 70 (range 62-84) years all with daily calcium intake of less than 500 mg and put them on a high calcium diet with calcium rich foods and calcium capsules to obtain a mean daily calcium intake of 1150 mg. These patients were reported to have "osteoporosis" based on a hand radiograph and no actual fracture status was reported. Of the twenty patients studied they report an increase in metacarpal bone density in eleven patients, stability in three and a decease in six. Jensen carried out a double-blinded placebo-controlled trial (68) in seventy- four 70 year old women with osteoporosis over a 12 month period. Patients were randomized to one of four treatment groups one of which was a calcium only group in which they received 500mg a day of calcium. Another group received estrogens and calcium, another estrogens, calcium and 1,25-$(OH)_2$ vitamin D and one group received 1,25-$(OH)_2$ vitamin D and calcium. All groups received the same amount of calcium. BMC at two distal sites of the forearm was obtained. One in which consisted of 80% cortical bone the other site (more distal) 40% cortical. Twenty four patients completed the calcium only regimen. The patients first underwent an observation period for six months before being started on any treatment. There was a 1.9% decline in BMC during this period. During the following 12 months on treatment there was a statistical difference between the groups receiving hormone and the other two groups. There was a roughly 2% increase in the BMC in the hormone treated groups when measured at the predominantly cortical site and virtually no change was noted in the calcium only group and a 1.7% decline in the calcium and calcitriol group. The difference between the last two groups was not statistically significant. There was no fracture data provided and in this relatively short study it is unclear if any of the treatment outcomes were of clinical significance. Orwoll (87) studied 39 patients with osteoporosis for two years (mean age 69 years) and divided them into two groups receiving 1200mg of calcium per day with or without 25-OH vitamin D. BMC of the distal radius by SPA was performed. Thirty one patients completed the study and 25 patients underwent a transiliac bone biopsy. Five repeat biopsies were performed in each treatment group at the end of the study. Overall, there was no significant decline in bone density in both groups. New vertebral fractures in both groups were rare. In general there were no differences between both groups. Of note however, the bone biopsies suggested an improvement in the rate of matrix mineralization. The authors point out that this could possibly be beneficial in the repair of microdamage and the prevention of fatigue fractures. Although there was no untreated control group the results of the study suggest that calcium provided the benefit noted since there were no significant differences between groups. The

biochemical analysis found no change in PTH level from baseline. There is also no report of hip fractures from this small study.

In a study by Albanese et al (88) the fifth finger radiodensity was measured in a variety of patients. In one group of five patients (ages 56-76 yr) with a variety of different fractures, were given supplemental calcium and noted to have an increase in phalanx bone density in a twelve weeks period. This response in such a short period of treatment make the validity of the results highly suspect. In another study by the same authors they studied two groups of healthy elderly women between the ages of 76 and 89 years. One group of 12 received supplemental calcium so that the average daily calcium intake was approximately 1200mg and another group of 17 received no supplement (placebo group) resulting in an average daily intake of 450 mg. During the three year period of the study they found a significant increase in the density of the supplemented group and a decrease in the density of the placebo group. Both groups had similar fifth digit bone density at base line but there is no description of how patients were randomized or if those interpreting the radiographs were blinded to the treatment that the patients were receiving. In a recent report by Watts et al (14) on the effects of etidronate in postmenopausal women the placebo group received 500mg of calcium carbonate daily. This group experienced no spinal bone loss (some increase was noted) as measured by DPA over a two year period. The placebo group in a study by Riggs (16) received 1500mg of calcium carbonate and patients in this group were also noted to maintain stable lumbar spine bone densities over a four year period. Stability was also noted in the hip over the same time period. Most of the patients in both of these studies were under 70 years old.

In summary, calcium appears to work as an antiresorptive agent. A review of clinical studies suggest it is probably more effective in the elderly (type II osteoporosis) than in younger patients. It may be particularly helpful at sites which consist mostly of cortical bone. Specifically it stabilizes bone loss, may improve mineralization, and reverse some of the biochemical disturbances of bone metabolism. In addition, some indirect evidence suggests that calcium may help prevent hip fractures. This comes from population based studies of users of thiazide diuretics (see below). Further research needs to be pursued in regard to the optimal form of calcium to be used. As with other agents, investigations need to be specifically carried out in the elderly. Now that the means to measure bone density in the hip are available, this area should be studied and along with fracture rates reported as outcome measures in clinical trials. In terms of dosage recommendations, those individuals not on estrogen supplements should receive 1500mg of elemental calcium daily. In those on estrogen the dose is 1000mg daily. In those patients where there is concern about the possibility of vitamin D deficiency or malabsorption, some vitamin D supplementation will be required. Generally, 400IU of vitamin D daily will suffice. In those with malabsorption syndromes calcium citrate may be better absorbed. Also, calderol (25-hydroxyvitamin D) can be used, usually in doses of around 20-40ug a few times a week. In the latter situation, serum and 24 hour urine calcium may need to be monitored to insure effective dosing of calcium and to monitor for hypercalcemia.

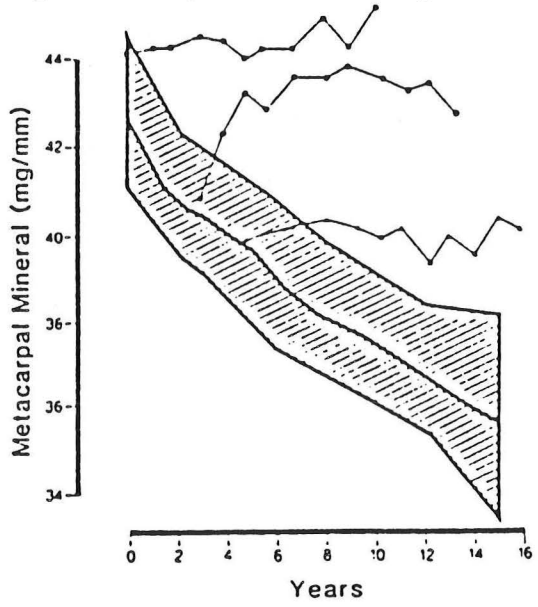
ESTROGEN

Estrogen has been found to be effective in preventing bone mineral loss in postmenopausal women. Many questions remain regarding its use in the elderly patient. One question is, are estrogens effective in preventing further bone loss in an individual who is 20 or 30 years postmenopausal? If estrogens continue to prevent bone loss regardless when started does it offer any benefit in preventing fractures or if fractures have already occurred is it of any value? The decision to use estrogen for the prevention or treatment of osteoporosis will depend in part on the results of studies assessing the risk or potential benefit to the cardiovascular system as well as issues surrounding and the risk of breast cancer, and thromboembolism.

Estrogen acts primarily by the inhibition of bone resorption. The exact mechanism in which estrogen maintains bone mass is not known. Until recently estrogen was believed to act indirectly on bone perhaps via calcitonin. Recently however, estrogen receptors have been found on osteoblasts suggesting a direct mechanism of action (89). Since estrogen inhibits bone resorption it must act to inhibit osteoclasts which ultimately is responsible for bone resorption. It is presumed that a second messenger generated by osteoblasts act on the osteoclast inhibiting their activity or recruitment (90). Although studies have demonstrated that estrogens reduce bone loss or even slightly increase bone mass these effects may be transient due to ultimate recoupling of bone formation with resorption (91). I will review the literature as it may pertain to the use of estrogen in the elderly. Once again , the amount of information for those over the age of seventy five is limited and here too the need for double blind randomized prospective studies is much needed.

It is well established that estrogen therapy given in the perimenopausal and early menopausal period is effective in maintaining bone mass. In a study by Lindsay et al (92) they found that metacarpal bone density was preserved for at least five years when estrogen is initiated up to six years after oophorectomy. These findings have been expanded to sixteen years (90) (see figure 9).

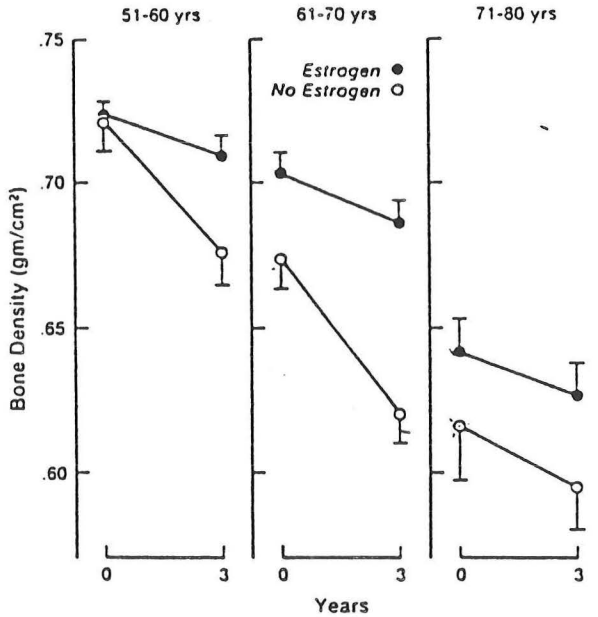
Figure 9



The effects of mestranol on bone mass in three groups of women in whom treatment was begun immediately, 3 years or 6 years after bilateral oophorectomy. The hatched area represents the pattern of bone loss in the placebo-treated group (mean ± SD), while only the means of the three estrogen-treated groups are shown (from reference (11)).

Another group reported similar results (93) showing preservation of bone mass for ten years even when estrogen was started three years since the last menstrual period(however at a lower baseline then if started immediately after menopause). Subsequent (94) data from Lindsay showed that when a group of patients (post oophorectomy) who had been on estrogen for four years (with stable bone mass) were withdrawn from estrogen a subsequent increase in bone loss ensued such that by eight years the previously treated groups bone density was not different from those who received no treatment since oophorectomy. In a double-blinded, placebo-controlled trial of 21 postmenopausal osteoporotic (vertebral fractures) women who received estrogen the BMC of both the lumbar spine and femoral shaft increased and biochemical evidence of improved intestinal absorption of calcium and decreased bone resorption was noted (12). The mean age of the patients was only 55 yrs and approximately six years since menopause. The duration of the study was only one year. The applicability of this study for the elderly is limited but of note is the apparent beneficial effect of estrogen on the femoral shaft and calcium absorption. Other studies have been reviewed above in comparing the effectiveness of estrogen compared to calcium. The sum of those studies, mostly in relatively young subjects, demonstrate the effectiveness of estrogen in preserving bone mass. The only prospective study that evaluated the effect of estrogens in older postmenopausal women is that of Quigley et al (95). They studied 397 healthy postmenopausal women between the ages of 50 to 80 years. Patients received either estrogen (estradiol or conjugated estrogen) and 1000mg per day of calcium or no estrogen and 1500mg per day of calcium. Bone density was monitored at the distal radius by SPA over a three year period. Unfortunately the patients were not randomized. Patients self selected which treatment they wanted and baseline bone density values were not equivalent in many of the subgroups limiting overall value of their results. Nonetheless, there are a number of findings to note. Estrogen reduced the rate of bone loss in those 51 to 70 years old; however the rate of bone loss was the same in those 71 to 80 years (n=90) old (see figure 10).

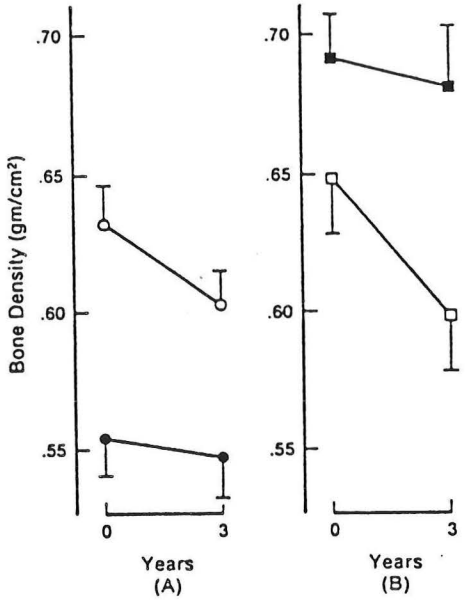
Figure 10



Mean (± SEM) bone density readings (gm/cm²) in postmenopausal women subdivided by 10-year age increments (51 to 60, 61 to 70, and 71 to 80 years) treated with either estrogen (●——●, Estrace, 1 mg, or Premarin, 0.625 mg) or no estrogen (○——○) during a 3-year interval.

The baseline bone density in the estrogen users was higher than the nonusers, suggesting that the two groups were not comparable. The over sixty five group was further divided into four groups which consisted of those who never used estrogen but started for the first time after 65 yrs, those who used estrogen and decided to continue to not take any, those who have used it before and elected to continue to use it, and those that had been using it within five years of the start of the study but decided to not take any (see figure 11).

Figure 11



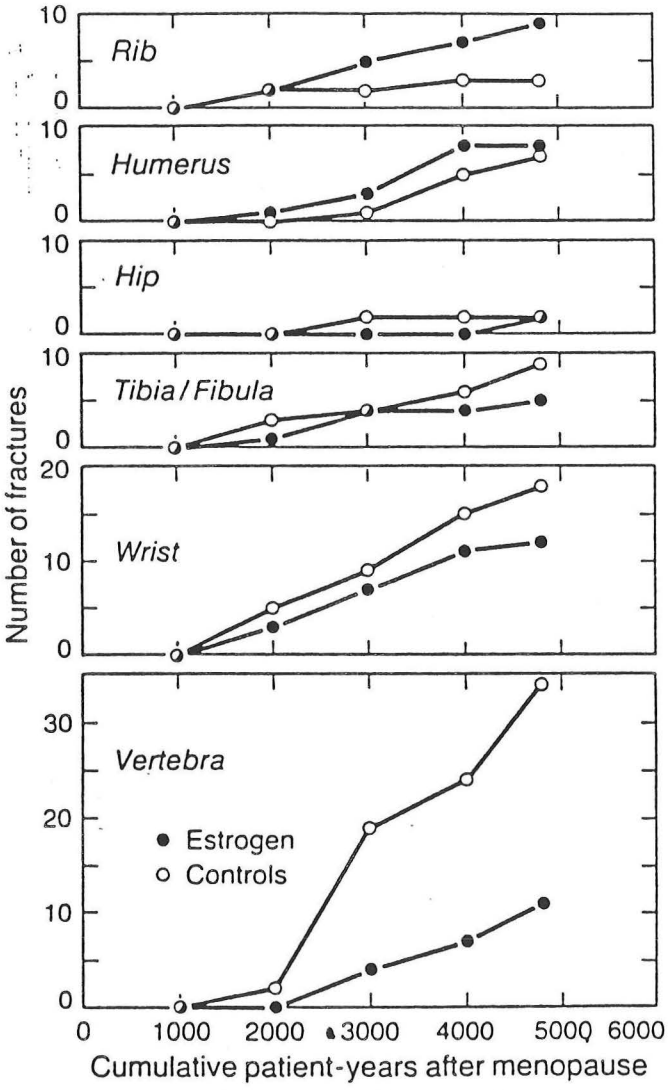
Mean (± SEM) bone density (gm/cm²) in postmenopausal women 65 years or older who previously had: A, Never taken estrogen and then started (●——●) or declined (○——○) to take estrogen at the initiation of the study, or B, Taken estrogen and then continued taking estrogen (■——■) or discontinued estrogen within 5 years of initiation of the study (□——□).

The groups who elected to take estrogen had the least fall in bone density, those that elected not to take estrogen had significantly larger falls in bone density. Here again the marked differences in baseline values of the subgroups limit the value of the study. In particular, those over 65 years who decided to take estrogens for the first time had a baseline bone density which was markedly reduced compared to those who decided not to take estrogen. As the author points out, it may be that the little decline that occurred was not because of a therapeutic effect from estrogen but because so little bone was left to lose. In addition, this study was carried out in normal women, only the bone density of the distal radius was assessed, and this study does not directly address the issue of fractures.

No prospective study has demonstrated that estrogen therapy can prevent fractures in the elderly with established osteoporosis. There have been a number of case-control, observational, prospective population based studies that have consistently suggested a reduction in the risk of hip fracture. Weiss et al (96) carried out a case control study of postmenopausal women between 50 to 74 years of age and found that women who had

taken estrogens for at least six years and during the time of the study had a 50 to 60 per cent lower risk of hip and forearm fractures then those who had not taken estrogens or those who had taken them for only less than six years. In another case-control study Ettinger (97) also showed an inverse relationship to postmenopausal estrogen use and fractures (see figure 12).

Figure 12



Cumulative fractures according to type by postmenopausal patient-years at risk in the 245 women and controls.

They found that the incidence of osteoporotic fractures was 50% less than controls. The major fracture reduction can be seen in vertebral fractures. The number of hip fractures was small and there was no differences noted by between the two groups by the end of the evaluation period. The authors appropriately point out that to show a protective effect of estrogen replacement therapy on hip fracture incidence a large cohort of women who had been on replacement therapy for at least twenty-five years and were at least 75 years would

have to be studied. The authors also performed quantitative computed tomography (QCT) of the lumbar spine and SPA of the radius on a subgroup of subjects from both estrogen and control groups. Significantly higher bone mineral values in the estrogen patients was demonstrated and as expected this was particularly true for areas that are composed of predominantly trabecular (vertebral) compared to cortical bone.

The retrospective cohort study from The Framingham Heart Study also found evidence to suggest that estrogen use was associated with a lower relative risk of hip fractures who had taken estrogens. This was particularly true for recent users and those under 74 years (98). Lastly, a large prospective, population-based cohort study from Sweden (99) studied women over the age of 35 years who received noncontraceptive estrogen compared to the background population. Hospital records were monitored for first hip fractures. Those taking estrogen had fewer hip fractures then predicted. Those who appeared to have the greatest benefit were those under the age of 60 years but no significant benefit was noted in those over 70 years. Less than 6% of the cohort (23,088) were over the age of 70 years.

From the above the following can be suggested. In general, in patients with type II osteoporosis estrogen therapy is not indicated. However, in elderly women who have been taking estrogen since menopause I would continue the use of this medication in the absence of any contraindications. The lowest effective dose of conjugated estrogen (or its equivalent) that preserves bone density is 0.625mg daily. Adequate calcium supplementation needs to ensured even in those patients on estrogens.

CALCITONIN

Calcitonin inhibits osteoclast activity and therefore inhibits bone resorption. A two year trial of subcutaneous calcitonin was equally effective compared to estrogen in preventing early postmenopausal (ages 38-64 yr) bone loss in healthy women (100). A one year controlled randomized trial using intranasal calcitonin was also effective in preventing bone loss in healthy women who were within three years since menopause (101). Calcitonin may have a role in type I (postmenopausal) osteoporosis similar to that of estrogen. There is no evidence of its long term efficacy or a decrease in fracture rate. Tachyphylaxis can develop in some individuals (102) and there is a group of patients who are nonresponders to treatment. The latter may reflect the difference in its effectiveness in those patients with a high bone turnover and those with a normal bone turnover. Civetelli et al (120), found that calcitonin improved bone mineral content in the spine and slowed loss of femoral bone in patients with high-turnover osteoporosis and was ineffective in maintaining femoral bone content and only maintaining spinal bone content in patients with normal bone turnover. Its parenteral administration and high cost (about $360 per month) has also limited its routine use. The development of intranasal administration and lower costs due to synthetic production may eventually lead to its more widespread use as an antiresorptive agent in those where their use is contraindicated or in men with idiopathic osteoporosis (103). Because of the generally low bone turnover state in the elderly, and since a large amount of bone loss will have already taken place, there is no evidence to support the use of calcitonin in the elderly with type II osteoporosis.

OTHER AGENTS

FLUORIDE

Since the elderly patient with osteoporosis is already likely to have lost substantial volume of bone mass agents that would augment bone mass would be an ideal agent to treat this group of individuals. Fluoride is one such agent that may prove useful in this context. Fluoride stimulates bone formation but this agent is not currently approved for use in osteoporosis. There have been a number of concerns surrounding its use in osteoporosis. First, the frequency of significant side effects has been reported to be high. These include gastrointestinal upset including GI bleeding and musculoskeletal complaints. Of more concern has been the possibility that fluoride stimulates the production of bone that is poorly formed and has inferior structural properties compared to normal bone resulting in reduced strength. There has also been concern that an increase in bone mass may occur at the expense of bone from another site. In particular, fluoride may increase trabecular bone while reducing cortical bone. The results of a recently reported prospective controlled trial showed that trabecular bone mineral density increased and cortical bone mineral density decreased in those who received sodium fluoride. Fluoride was not effective in reducing vertebral fractures and the fluoride group sustained more non-vertebral fractures than the placebo group. In particular, there were six non-traumatic hip fractures in the fluoride group and three in the placebo group. The difference was not statistically significant (16). The median age of the subjects were 68 years with a range of 9 to 35 years (median 21) since menopause. However, the above trial was conducted with a plain sodium fluoride preparation at a higher dosage than is customarily used. Thus, fluoride toxicity or over burden could have contributed to poor response.

Studies at Dallas suggest that the above problems with plain sodium fluoride might be overcome by using a slow release fluoride preparation. In an uncontrolled trial patients receiving slow release sodium fluoride appeared to have a decrease in fracture rate, an increase in bone lumbar bone density without a reduction in radial or femoral bone density (71). The medication was well tolerated and did not appear to increase nonvertebral fractures. On bone biopsy examination, bone appeared normally mineralized; by ultrasound analysis improved strength was noted (118). The patients age range was from 29 to 82 (mean 62) years. However, there was no subgroup analysis reported with respect to age. It is unclear whether fluoride would be effective in the elderly. It would seem that fluoride may show its greatest promise in those with type I osteoporosis that have enough residual bone intact that an increase in bone mass would result in greater strength. In the elderly where severe bone loss may have already occurred, trabecular disconnectivity may already be present and so that bone augmentation may not improve bone strength and prevent fractures.

ETIDRONATE

Etidronate is one of a family of compounds known as biphosphonates that inhibit osteoclast mediated bone resorption. There have been two recently published reports in well designed studies regarding the reduction in the incidence of vertebral fractures in patients that received etidronate (14, 15). Lumbar bone density increased significantly (5.3%) in the treatment group. Of note, the increase in bone density was linear during the three year treatment period in the study by Storm et al. However, there was a 25% reduction in the number of patients evaluated at three years making a comparison difficult. Few patients in either study exceeded 75 years and femoral neck bone density was not reported in either study. There were very few hip fractures in both studies but all occurred in the treatment group. Bone density measurements in the forearm did not suggest a deleterious effect on cortical bone. Since diphosphonates can impair bone mineralization its effect on fracture repair especially in low bone turnover states may be a major disadvantage to their use in the elderly. More investigations will be required before their use in the elderly can be justified (104).

THIAZIDES

Thiazide diuretics reduce urinary calcium suggesting the possibility that these agents could improve calcium balance and possibly be of benefit in preventing or treating osteoporosis. In a retrospective study by Wasnich (105) hypertensive men (50 to 80 yrs) taking 25mg of hydrochlorothiazide were found to have higher bone mineral contents than hypertensive patients not on thiazides or individuals without hypertension. The groups were matched for age, body-mass index and activity level, and all were comparable. Transbol (106) studied normal postmenopausal women during a three year placebo controlled trial. Subjects received either 5mg a day of bendroflumethiazide or placebo. These women were within three years of menopause. The investigators reported that distal forearm bone mineral content initially did not fall in the treatment group but that after six months the treatment and placebo group experienced the same rate of decline in BMC. More interestingly LaCroix et al (107) prospectively studied the incidence of hip fractures in people over the age of 65 years in three communities. They found that thiazide use was associated with a reduction in the risk of hip fracture during a four year follow-up period. The association held up even after consideration of other risk factors including impaired mobility, low body-mass index and older age. Further clinical studies need to be carried out to verify these results. In addition the overall risk/benefit ratio of using diuretics (hypokalemia, hypercalcemia, lipid abnormalities) in the elderly needs to be assessed. These results may also provide indirect support for the use of supplemental calcium to prevent osteoporotic hip fractures. Whether thiazides provide additional benefits other than possibly improving calcium balance is not known.

EXERCISE

There have been a number of studies that have shown an improvement in bone mass after subjects have participated in exercise programs (108, 109, 110). At the same time there are no present studies showing it prevents osteoporotic fractures. Besides increasing bone mass exercise may improve agility and muscle strength leading to a reduction in falls and thereby preventing fractures. On the other hand perhaps the more mobile a individual becomes one may create more opportunities to fall. Exercise certainly provides other desirable benefits other then that reflected in bone mass. Improved self image, cardiovascular fitness, improved intestinal motility and less constipation, and improved endurance are some of the possible outcomes exercise can provide. One factor that is important to remember is that these benefits occur as long as exercise continues and one rapidly resorts to the pre-exercise baseline once exercise ceases. Certainly in those patients that are willing an exercise program should be prescribed (111).

FALLS AND THEIR PREVENTION

It could be argued that the prevention of falls is the mainstay of treatment of type II osteoporosis. There is evidence that the tendency or frequency to fall and the neuromuscular response to a fall may be more important in determining the risk of hip fracture than bone mass (49, 54). On the other hand, a history of falls does not discriminate all elderly patients with fractures (112). Since it appears both falls and reduced skeletal resistance determine fracture risk it is important to incorporate both factors in our treatment approach. The assessment for and prevention of falls therefore should be part of the medical evaluation. The differential diagnosis of falls is long and the actual final cause is frequently multifactorial. Assessment for sensory defects, gait and balance and careful scrutiny of medications are some areas that need particular attention (113-117). Environmental factors need to be reviewed as well (see tables 6 and 7). The elderly patient that falls may seem like an overwhelming problem that cannot be helped. However, the underlying cause can often be identified and prevention strategies can reduce disability (114).

Table 6

Intrinsic Risk Factors for Falling and Possible Interventions

Risk Factor	Interventions	
	Medical	Rehabilitative or Environmental
Reduced visual acuity, dark adaptation, and perception	Refraction; cataract extraction	Home safety assessment
Reduced hearing	Removal of cerumen; audiologic evaluation	Hearing aid if appropriate (with training); reduction in background noise
Vestibular dysfunction	Avoidance of drugs affecting the vestibular system; neurologic or ear, nose, and throat evaluation, if indicated	Habituation exercises
Proprioceptive dysfunction, cervical degenerative disorders, and peripheral neuropathy	Screening for vitamin B_{12} deficiency and cervical spondylosis	Balance exercises; appropriate walking aid; correctly sized footwear with firm soles; home safety assessment
Dementia	Detection of reversible causes; avoidance of sedative or centrally acting drugs	Supervised exercise and ambulation; home safety assessment
Musculoskeletal disorders	Appropriate diagnostic evaluation	Balance-and-gait training; muscle-strengthening exercises; appropriate walking aid; home safety assessment
Foot disorders (calluses, bunions, deformities)	Shaving of calluses; bunionectomy	Trimming of nails; appropriate footwear
Postural hypotension	Assessment of medications; rehydration; possible alteration in situational factors (e.g., meals, change of position)	Dorsiflexion exercises; pressure-graded stockings; elevation of head of bed; use of tilt table if condition is severe
Use of medications (sedatives: benzodiazepines, phenothiazines, antidepressants; antihypertensives; others: antiarrhythmics, anticonvulsants, diuretics, alcohol)	Steps to be taken: 1. Attempted reduction in the total number of medications taken 2. Assessment of risks and benefits of each medication 3. Selection of medication, if needed, that is least centrally acting, least associated with postural hypotension, and has shortest action 4. Prescription of lowest effective dose 5. Frequent reassessment of risks and benefits	—

Table 7

ENVIRONMENTAL SAFETY CHECKLISTS —SUMMARY OF THE MOST IMPORTANT ITEMS FROM SEVERAL PUBLISHED LISTS

- The Home Setting
  - All living spaces
    - Remove throw rugs.
    - Secure carpet edges.
    - Remove low-lying furniture and objects on floor.
    - Reduce clutter.
    - Remove cords and wires on floor.
    - Check lighting for adequate illumination at night (especially bathroom pathway).
    - Secure carpet or treads on stairs.
    - Eliminate furniture that is too low to rise from.
    - Avoid waxing floors.
    - Ensure telephone is reachable from floor.
  - Bathroom
    - Install grab bars in tub/shower and by toilet.
    - Use rubber mats in tub/shower.
    - Take up floor mats when not using tub/shower.
    - Install raised toilet seat if too low.
  - Outside
    - Repair cracked sidewalks.
    - Install handrails on stairs, steps.
    - Keep shrubbery trimmed back on access path to house.
    - Install adequate lighting outside doors and in walkways leading to doors.
- The Institutional Setting
  - Observe bed for proper height.
  - Observe floors for use of throw rugs.
  - Assess lighting, especially pathway to bathroom.
  - Observe outside patient areas for cracked sidewalks or unsafe stairs.

SUMMARY

Although there is substantial overlap, two clinical syndromes of involutional osteoporosis can be described. Type I osteoporosis or postmenopausal osteoporosis affects primarily early postmenopausal women. Trabecular bone is the major site of bone loss. Clinically, patients most commonly present with spinal fractures. Of the presently available medications estrogen is the mainstay of therapy. In those patients where estrogen is contraindicated calcitonin could be considered. Calcium alone appears to be less effective when compared to estrogen.

Type II osteoporosis affects those over the age of 70 years or 25 to 30 years postmenopausal. It is largely related to age-related bone loss. Both cortical and trabecular bone is involved. Clinically, the most important consequence of this disorder are hip fractures. As opposed to type I osteoporosis estrogen is probably of little benefit in these patients. Presently, the most effective treatment is increased calcium intake. In those patients not on estrogens the recommended intake is 1500mg of elemental calcium daily (1000mg if patients are receiving estrogen therapy). Calcitonin is not recommended for use in type II osteoporosis. If there is a possibility of vitamin D deficiency 400IU of vitamin D daily should be added. In those with malabsorption syndromes 20 to 40ug of 25-OH-vitamin D (Calderol) a few times a week should be added. Serum and 24 hour urine calcium will help monitor and titrate therapy. Because of a greater risk of side effects and possible role in bone resorption I would not recommend the routine use of 1,25-$(OH)_2$ vitamin D (calcitriol). In addition, efforts to assess the risk and initiate efforts to prevent falls cannot be over emphasized. The role of newer agents such as fluoride and the diphosphonates in the treatment of type II osteoporosis is not clear at the present time. They will likely be more efficacious in the treatment of type I osteoporosis.

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