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CALCIUM AND OSTEOPOROSIS

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THE SCOPE OF THE OSTEOPOROTIC PROBLEM

Osteoporosis of the senile or postmenopausal variety is defined as a skeletal disorder in which the absolute amount of bone is decreased relative to that of younger individuals or menstruating women although the remaining bone is normal in chemical composition. Symptomatic senile or postmenopausal osteoporosis syndromes are classically considered to result from the universal loss of bone that normally attends senescence in both sexes. The decrease in bone mass often results in fractures and immobilization in the aged. These not only require significant hospitalization time but also are costly in terms of inactivity and morbidity.

The results of age-related changes in bone mass are of considerable magnitude. Approximately 6.3 million people in the United States are currently suffering from acute problems related to weakened vertebral bones. Perhaps even more significant is the fact that today more than 8 million Americans have chronic problems related to the spine, compared with 6 million reported in

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1963. Moreover, recent epidemiological surveys indicate that a minimum of 10% of females over 50 years of age in the United States suffer from bone loss severe enough to cause hip, vertebral, or long-bone fractures (36, 75); surveys performed in homes for the aged and on ambulatory individuals 50 and 75 years of age who required medical care also disclose the occurrence of symptomatic osteoporosis (i.e. back pain) in 15 and 50% of these populations respectively.

Because the skeletal mass of the female is normally less than that of the male at any age and because the female's rate of bone loss with age is greater than that of the male (12), the consequences of osteoporosis are magnified in the female, which results in the fact that approximately 25–30% of postmenopausal women suffer major orthopedic problems. Approximately three quarters of all deaths from falls occur in patients of age 65 and over, and the female:male vertebral fracture-incidence ratio is 8:1. Decreased bone mass is one of the major factors contributing to the 180,000–200,000 hip fractures that occur annually among women over the age of 65 years (40, 91, 134). The rate per 1,000 population/year of hip fractures in white women due to minimal trauma increases from 2.0 at ages 50–64, to 5.0 at ages 65–74, to 10 at ages over 75 years. The annual incidence of femoral neck fractures in the aging female population is also high; it rises rapidly from 0.13% in the seventh decade to 3.0% in the tenth. It has been estimated that a 35-year-old white woman has an 8% chance of having at least one hip fracture in her life; a white man of the same age has a 3% chance (36). Complications of fractures of the postmenopausal woman in the United States, which presently incur an annual cost of more than $1 billion (106), produce significant morbidity (139) and an average mortality rate of 15–30%. More detailed analyses of these data reveal the following statistics: intraoperative mortality, 9%; hospital mortality, 2–24%; cumulative six-month mortality, 13–44%; and cumulative one-year mortality, 12–67% (97).

Currently, over 25 million Americans (12% of the US population) are 65 years of age or older. This segment of the population increased by 8–9% during 1970–1974 although the increment of the entire US population was less than half that rate. The number of hip fracture patients who reside in nursing homes is also increasing progressively. In the 1960–1976 interval, the number of individuals in US nursing homes increased from 290,000 to one million, and their health care costs increased from $500 million to $10.5 billion (24). At the present rate of population growth, we can anticipate that by the year 2030, approximately 20% of our population will be 65 years of age or older (141).

The universality of these trends is reflected in studies of femoral neck fractures in other countries. All trauma units in the United Kingdom have experienced a rising incidence of femoral neck fractures (76). More specifically, the number of patients with fractures of the proximal femur admitted to the orthopedic trauma unit in Nottingham increased from 290 in 1971 to 612 in

1981 (146). From 1971 to 1977, the rate of increase in the fracture incidence was approximately 6% per year; since 1977, however, it has risen to 10% per year (146). The disproportionate increment of femoral fractures in women older than 75 years is exemplified by the fact that in this same area, the incidence increased from 8/1000/year in 1971 to 16/1000/year in 1981. During this 10-year interval, the same population increased by less than 2% per year (146). Similar trends in Denmark led to the prediction that the incidence of hip fractures will actively double within the next 17 years (63). Obviously, since the world at large is "greying," the number of individuals predisposed to fractures of the hip, femur, forearm, or vertebrae will steadily increase in number unless more sensitive methods are developed to detect those patients at risk and appropriate preventative and therapeutic measures are initiated.

Unfortunately, osteopenia, or bone rarefaction, becomes evident by routine radiographs only when 40–50% of the skeletal mass has been lost. It has, however, been established through the use of dual photon absorptiometry techniques with an average coefficient of variation of 2.3% that in normal menstruating women, vertebral bone mass begins to decline at 20 years of age and continues thereafter in a linear fashion (120) (Figure 1). In contrast, bone mass in the appendicular skeleton, measured with single photon absorptiometry with a coefficient of variation of 3%, does not decrease until the age of 45–50 years (Figure 2) (120); the rate of decline in appendicular bone accelerates in women between the ages of 51 and 65 years and then decelerates again after they are age 65 (120).

Overall bone diminution throughout life is 47% for the vertebrae and 30% for the midradius (120). By age 65 years, half of the female population has

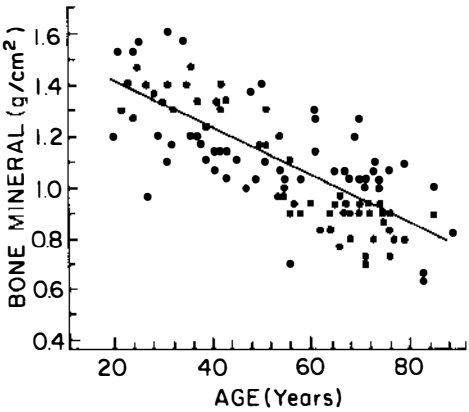

Figure 1 Regression of lumbar spine density in 105 normal women as determined by dual-photon absorptiometry. Equation for regression: $y = 1.59 - 0.0092$ age. Reproduced from *The Journal of Clinical Investigation* 67:330, 1981, with permission of the authors and publisher.

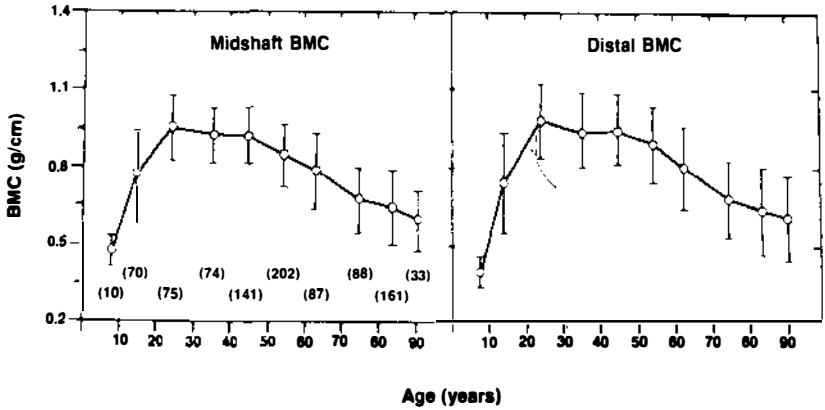

Figure 2 Age-related changes in appendicular (radius) bone mass (BMC) content in 941 white women using single-photon absorptiometry. Population was divided into decades of life; mean values ± SD are plotted at mean age of each group. Number of subjects per group is shown in parentheses. Reproduced from *Geriatrics* Nov. 1978, p. 70, with permission of the authors and publisher.

vertebral bone mass below the 90th percentile for women with vertebral fractures and is considered to have "asymptomatic osteoporosis" (42, 120); by age 85 years, this is true of virtually all women. In normal men, changes in vertebral and appendicular bone mass with age do occur, but at rates significantly lower than those observed in women (120). It is increasingly apparent that the critical level of skeletal mass at which osteoporosis becomes either radiologically or symptomatically manifest is reached much earlier in women who fail to generate their full adolescent complement of bone (130).

HORMONAL ALTERATIONS AND THE OSTEOPOROTIC SYNDROME

Remarkably little is known about the underlying pathological processes that undermine the matrix and cellular aspects of skeletal tissue in the aging, fracture-prone female. There is, however, unanimity of opinion that skeletal mass normally decreases with age. It has been suggested that this age-related loss of bone is an appropriate consequence of senescence and simply reflects age-dependent dysfunction of bone cellular activity (60, 107, 114). Bone growth, modeling, and remodeling in the prepubescent years and the remodeling that continues after ultimate skeletal maturation and epiphyseal closure result from a cybernetic interplay between osteoblast-controlled bone formation and osteoclast-osteocyte–modulated bone resorption. A discordant cybernetic couple between the osteoblast-osteoclast cellular components (60, 61, 107, 114) and an accumulation of mast cells that stimulate bone resorption may contribute to the progressive loss of bone that is characteristic of the aging

process. Since the incidence and prevalence rates of hip fractures in the world at large vary considerably, a variety of other hypothesis have been advanced to explain these differences. These include race; latitude and degree of sunlight exposure; physical activity; excessive alcohol, caffeine and nicotine intakes; and inadequate diets (46).

When epiphyseal closure and longitudinal growth of the skeleton are complete, bone turnover and remodeling continue. Ultimately bone mass begins to decrease with advancing years. Rates of bone loss differ between individuals, and the ultimate fracture risk for any postmenopausal female depends on the rate of loss and the bone mass complement achieved at maturity. A variety of proposed therapeutic regimens are based on the assumption that age-related changes in hormonal production and metabolism either initiate or perpetuate the osteoporotic process. Ovarian hormones, parathyroid hormone (PTH), vitamin D metabolites, and calcitonin all have been implicated in this regard. The changes in circulating steroids that reflect gonadal and adrenal function in aging females become dramatically obvious when one compares the steroid levels of premenopausal and postmenopausal females. Decreased circulating steroid levels in the postmenopausal female result from a combination of decreased ovarian function, decreased stimulation of the adrenal cortex, and an intrinsic, decreased capacity of the adrenal cortex to produce precursors of estrone and estradiol (65). Despite reported beneficial effects of estrogen replacement therapy in postmenopausal patients with fractures and osteoporosis (Figure 3) (21, 56, 77, 110), the relationship between bone loss and circulating ovarian steroids in the elderly postmenopausal female remains ill-defined. It has been suggested that reduced amounts of endogenous estrogens may contribute to the greater loss of urinary calcium and more frequent occurrence of osteoporosis in slender postmenopausal women (33). In favor of this hypothesis are observations that obese postmenopausal women are less likely to develop rapid bone demineralization and crush fractures than are slender women of similar ages (26, 88). Moreover, circulating estrone and estradiol levels as well as peripheral conversion of androstenedione are reduced in slender women in comparison to obese subjects (79, 144, 102). Isolated observations of lower vaginal maturation values in postmenopausal women with osteoporosis compared to those without osteoporosis have also led to the suggestion that estrogen deficiency is more severe in the former. Lower circulating levels of estrone and androstenedione have been reported for osteoporotic females by some investigators (99). Others (118) used age-matched controls and observed similar levels of circulating total estrogens in postmenopausal women with or without osteoporosis and found no significant differences in androstenedione levels between women with accelerated bone demineralization and women with decreased rates of bone loss. Most would agree that the accelerated loss of appendicular bone observed in the immediate

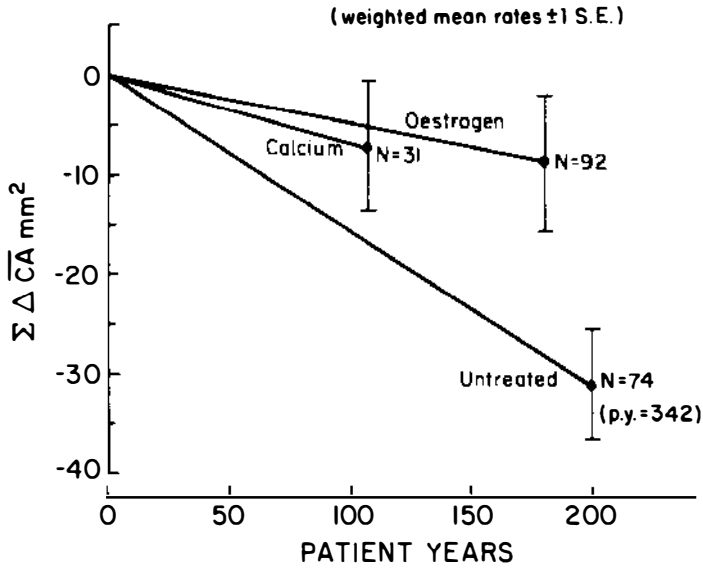

Figure 3 Cumulative plots of the change in mean metacarpal cortical area (CA) in untreated postmenopausal women treated with calcium or estrogen. Reproduced from *Geriatric Medicine Today* 1983, 2:66, 1983 with permission of the authors and publisher.

postmenopausal years could be due in large part to estrogen deficiency and that estrogen replacement, despite its unwarranted side effects (43), is therapeutic. The pathogenesis of the vertebral bone loss observed in normal asymptomatic menstruating females (Figure 1) requires further clarification and more detailed investigation.

It is becoming increasingly apparent that blood PTH levels increase with age (18, 34, 54, 57, 103, 109, 115, 121, 137, 148) and that supranormal levels occur in some patients with symptomatic osteoporosis (103, 115, 137). Although the age-related rise in PTH has been attributed to associated age-related decreases in renal function (18), poor dietary calcium intake, and defective calcium absorptive mechanisms (7, 14, 19, 35, 58, 90, 98) resulting from impaired hepatic (136) and renal (116) hydroxylation of vitamin D and 25(0H)D respectively, the actual causes are still unknown. The contribution of senescent hyperparathyroidism to the normal age-related decrease in bone mass and to the crush fracture osteoporotic syndrome is controversial. Still, it appears naive to ignore the observation that the rates of bone loss in postmenopausal women are greater in those with reduced dietary calcium intakes and higher PTH (11), the relationships between progressive increments in PTH with age, the steadily declining intake of calcium in women (Figure 4), and the early loss of vertebral bone in women (Figure 1), especially in view of the fact that all calcium and bone metabolism experts seem to agree that the primary

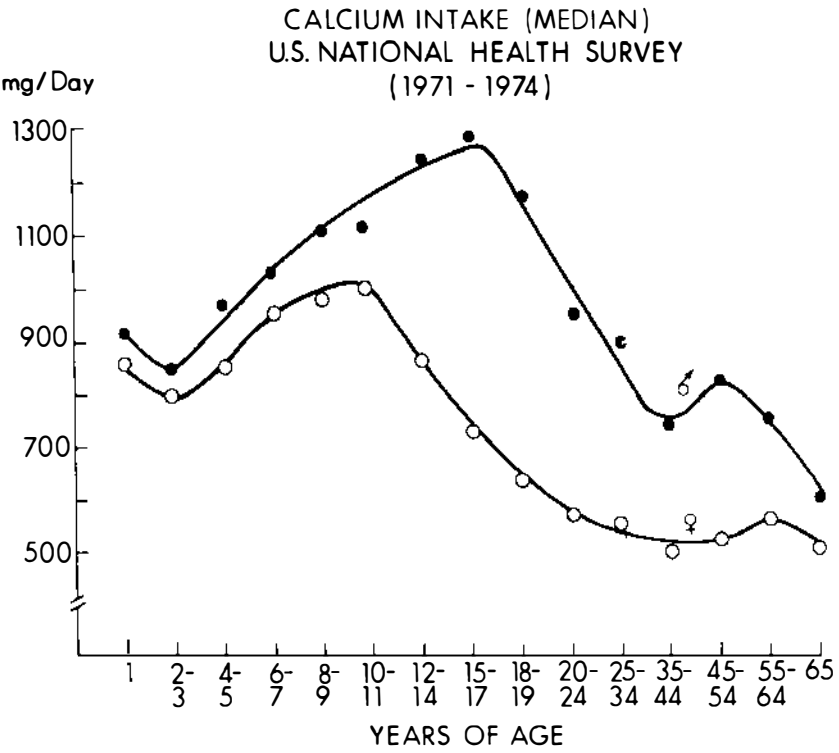

Figure 4 Median calcium intake of men and women in the United States for years 1971–1974. Reproduced from *Federation Proceedings*, 1981, 40(9):2418.

secretagogue for PTH is any pertubation in dietary intake or renal excretion of calcium that depletes the circulating ionized calcium pool (Figure 5).

There is currently little information regarding seasonal and/or age-related changes in blood levels of the vitamin D metabolites 25(0H)D, 24,25$(OH)_2$D, and 1,25$(OH)_2$D (87). Available data suggest that synthesis of 25(0H)D and 1,25$(OH)_2$D decreases with age (103, 115, 116). The apparent impaired conversion of 25$(OH)D_3$ to 1,25$(OH)_2$D appears to be secondary to a decrease in factors that abnormally stimulate 25$(0H)D_3$ 1α-hydroxylase activity, rather than a primary defect in enzyme reserve capacity (127), because the 1α-hydroxylase is normally responsive to PTH (116). Some investigators attribute osteoporosis and age-related decrease in intestinal calcium absorption to low 1,25$(OH)_2$D (116); others suggest that marginally low levels of circulating vitamin D metabolites in geriatric patients could at least contribute to the osteomalacic syndrome and to the progressive increments in the incidence of femoral neck fractures (1, 15, 16, 23, 27, 41, 95, 96, 104, 109, 126, 140, 147).

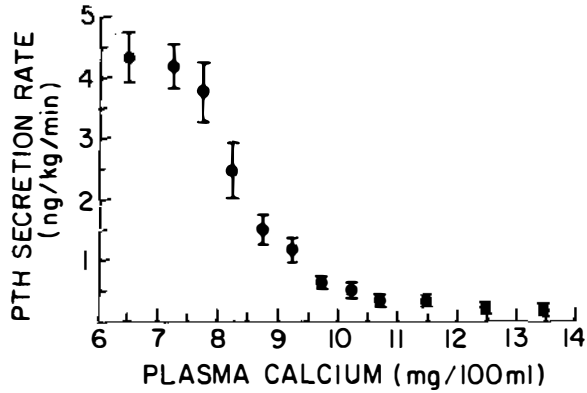

Figure 5 PTH secretion rate. Values were obtained from isolated glands of calves perfused with different concentrations of calcium. Note sharp increase in PTH output over the range of 8–10 mg/100 ml and the persistent small amount of PTH present in the parathyroid effluent even at serum calcium concentrations of more than 11 mg/100. Reprinted from R. V. Talmage et al. (eds), 1975, *Calcium Regulatory Hormones*, pp. 122–24, Excerpta Medica, Amsterdam, with permission from the authors and publishers.

The role of calcitonin in the day-to-day control of skeletal remodeling processes in humans is still uncertain. Calcitonin levels are lower in females than males (50, 52), and the values also decrease with advancing age (122, 125). To date, low (89) and normal (20) calcitonin levels have been observed in osteoporotic patients. It has also been speculated that a lifelong relative deficiency of calcitonin could play a role in age- and sex-related bone loss in some women, particularly during the estrogen-deficient, postmenopausal years (50). Increments in blood calcitonin levels observed in estrogen-treated females (135) should be considered in this regard.

Decreased appendicular bone density has also been recorded in hyperprolactinemic women with amenorrhea and has been correlated with serum estrogen levels (67). In humans, prolactin does not alter serum PTH and $1,25(OH)_2D$ or calcium absorption (71), so we must presently assume that estrogen deficiency per se is directly or indirectly responsible for the appendicular osteopenia in these women.

CALCIUM DEFICIENCY AND BONE

The nutritional status of the aged in the United States has been evaluated on innumerable occasions and found to be relatively inadequate in terms of Recommended Daily Allowances (RDA) (41, 101, 104, 111, 143). An increasing volume of data has accumulated that implicates calcium deficiency in the development of edentalism, mandibular bone loss (25, 70), and the osteopenic postmenopausal fracture syndrome (2, 3–6, 8, 13, 31, 47, 48, 53, 55, 94, 117,

124, 128, 129, 138, 142, 143). Although dietary sources of calcium should provide sufficient calcium for the average US woman to maintain a positive calcium balance, it has been well documented that the average woman's calcium intake is consistently below the RDA (2, 3, 142, 143). Moreover, there is increasing concern that the RDA of calcium, which was established earlier at 800 mg/day, may prove inadequate to maintain bone integrity (47, 48). It should be emphasized in this regard that as early as 1955, the Household Food Consumption Survey of the US Department of Agriculture cited calcium as one of three nutrients most often ingested at levels below the RDA (143). Subsequent dietary surveys revealed not only that at any age men ingest more calcium than women (2, 4, 142) (Figure 4), but that during the period of life when bone mass is approaching its peak value (18–30 years), more than two thirds of all US females ingest less calcium than the RDA. This observation becomes significant in view of the fact that women who fail to generate their full adolescent bone complements are destined to develop symptomatic osteoporosis at earlier ages. An additional insult to the integrity of bone occurs after the age of 35, when more than 75% of all females ingest less than the RDA on any given day. With calcium intakes of 450–500 mg/day, normal perimenopausal and postmenopausal women develop negative calcium balances of more than 40 mg/day; this results in bone loss of approximately 1.5% per year (48). As cited above, elderly postmenopausal women do not absorb oral or dietary calcium as well as younger, menstruating women. Estrogen loss at menopause also results in a decrease in renal calcium conservation. The intestinal adaptability to changes in calcium intake is also blunted by age (58) and becomes inadequate to maintain the homeostatic equilibrium between bone and circulating calcium that characterizes the adolescent and young adult periods of life. Consequently, it is naive to assume that the efficiency of calcium absorption necessarily adapts to low-calcium diets and that the total amount of calcium consumed is relatively unimportant (8). Defective renal adaptation to low calcium intakes, with mild but persistent hypercalciuria, most probably also contributes to the negative calcium balances (48) seen in the fracture-prone osteoporotic individuals. Probable causes are relative degrees of immobilization that necessarily attend senescence, peculiar diets containing excessive carbohydrate, and proteins with low phosphate and high sulfate content.

Little is known about the factors that modulate or condition intestinal absorption of calcium in senescent individuals or about the relation between relative calcium deficiency and senescent bone loss. As noted above, circulating levels of $1,25(OH)_2D$, the active vitamin D metabolite that stimulates calcium absorption, not only decrease with age but are also much lower than anticipated in fracture-prone postmenopausal individuals. The absorptive efficiency of the intestine for calcium also depends on the amount of exposure to ultraviolet light (96), vitamin D intake, the sex and age of the individual, and

the food source and total calcium content of the source. During periods of active skeletal growth, children may absorb up to 75% of ingested calcium; normal adults with daily calcium intakes of 400–1000 mg absorb 30–60% (85). Dietary factors that increase calcium absorption include certain amino acids, e.g. lysine and arginine, and lactose. Cocoa, soy beans, kale, spinach (and other high oxalate-containing foods), foods containing fiber and substances that bind calcium (e.g. unpolished rice), and bran or wheat meal (59, 86, 112), which contain hexaphosphoinositol, also decrease the intestinal absorptive efficiency for calcium. Other factors that decrease calcium absorption include tetracycline antibiotics, the ingestion of alkali, decreased free acid secretion, increased gastrointestinal transit time, phsychological stress, immobilization, thyroid hormone, cortisol or any of its synthetic analogues, and anticonvulsant medications (44).

The effect of inorganic phosphorus on calcium absorption is controversial. Early reports of inhibition of calcium absorption induced by supplemental phosphate feeding (73) conflict with later studies that demonstrated no effect of dietary phosphorus increments on calcium absorption (132). Calcium absorption is more efficient in males than females. This may be related to reported stimulation of calcium absorption in women who were administered androgens (62). Despite the recognized inverse relation between calcium absorption and intake, prolonged fasting results paradoxically in decreased absorption (32). Absorption does increase as calcium intake rises; absorptive capacities of more than 1.0 g/day at intakes of 7.5 g have been documented (49). Although it has been reported that human subjects absorb calcium significantly better when it is given to them as the lactate rather than as the gluconate salt (133), it has also been observed that no difference exists in the utilization of calcium from milk, gluconate, lactate, carbonate, or sulfate salts (108).

The negative calcium balances observed in osteoporotic patients on low but seemingly adequate calcium intakes have been ascribed to slow and noncompensatory adaptation with relative hypercalciuria and to lactose intolerance resulting from intestinal lactase deficiency (12).

We must still acknowledge that in the past, an unequivocally significant relationship between calcium intake and bone loss and resultant fracture was not uniformly demonstrated in all geographical surveys (37–39, 131). The marked differences in ethnic diversity, protein (82) and fiber intake, sunlight exposure, and physical activity that characterize population groups from diverse geographical areas may mask the effect of differences in calcium intake alone. Evidence that calcium deprivation leads to osteoporosis in man presently stems primarily from more recent epidemiological studies that demonstrate lower calcium intakes by symptomatic osteoporotic and fracture-prone individuals than by age-matched normal control subjects and others (45, 55, 70, 105, 117, 119, 128, 138, 145), a relationship between bone mass and calcium

intake (84) (Figure 6), and the retardation of bone loss and fracture incidence (72) in elderly, fracture-prone individuals on low-calcium diets who are treated with calcium supplements (119) (Figure 3).

The average daily phosphorus requirement of adults in the United States and European countries is estimated at 0.8–1.5 g/day (92, 111). The primary sources of dietary calcium are milk and cheese, while major sources of phosphorus are milk, poultry, fish, and meat. Nonnutritious carbonated beverages containing excess phosphorus as phosphoric acid also contribute to the phosphorus intakes of adolescents and young adults. The availability and excessive consumption of phosphorus-containing ingredients should be acknowledged as a factor that may contribute to the observed age-related increments in PTH in humans cited earlier; thus it would also contribute to the subtle but progressive asymptomatic osteopenia. Relevant to this possibility are reports of elevations of circulating PTH in man after oral doses of sodium phosphate (113); circadian changes in serum phosphate in humans of a magnitude associated with increments in PTH (81); increased urinary hydroxyproline (a measurement of bone resorption) and cyclic AMP (an index of PTH secretion) in subjects receiving diets containing 0.7 g calcium and 2.1 g phosphorus per day for four weeks (17); and observations of progressive bone loss and elevations in PTH in animals fed diets relatively deficient in calcium and rich in phosphorus (29, 64, 68, 69, 100).

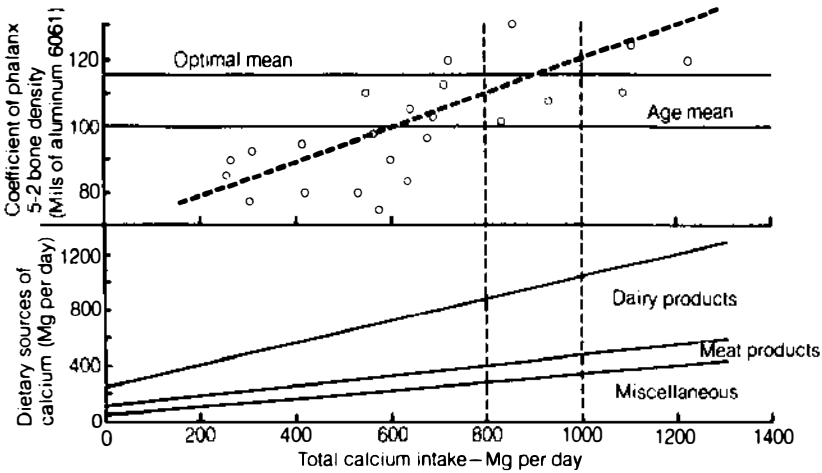

Figure 6 Relationship between bone density and calcium intake from various sources in 23 postmenopausal women 53 to 60 years of age. Reproduced from *Postgraduate Medicine*, 1978, 63:171 with permission of the authors and publisher.

Most if not all dietary phosphorus is absorbed as free phosphate. The efficiency of phosphate absorption is a function of both the dietary intake and the food source (92); approximately 60–70% is absorbed on normal intakes, and maximal absorption (up to 90%) is achieved on very low intakes (100). The absolute amount of phosphate absorbed from the intestine increases with increasing intake. Various dietary forms of organic phosphate esters, such as the phytic acid of cereals and seeds, are not readily available to man because the human intestine is relatively deficient in the enzyme phytase, which is essential for hydrolysis of the organic esters. Experiments performed in England during World War II revealed that bread made from high-extraction flours contained enough phytic acid to demineralize the skeleton slowly; as a result, chalk was compulsorily added to the nation's wheat meal during the war and after it was over. As noted above, phosphate ester compounds may also interfere with intestinal phosphate absorption because they form insoluble calcium complexes within the intestinal lumen. Vitamin D increases intestinal phosphate absorption in certain animal species (28); however, a direct effect of vitamin D or its biologically active metabolites on phosphate absorption in man is still to be adequately demonstrated. There is no known effective physiological mechanism regulating the intestinal absorption of phosphate in man; the control of the phosphate economy is achieved primarily by variations in dietary intake and renal excretion (83). Dietary phosphorus is absorbed to a greater extent than calcium and consequently, the renal excretion of phosphorus is much greater than that of calcium (83).

The relationship of skeletal metabolism, calcium-phosphorus homeostasis, and high protein intakes, which appear to affect the skeletons of elderly women more adversely than those of men (82), is also a matter of controversy. Although high protein intakes increase the excretion of calcium in humans (10, 22, 51, 78, 80), stimulated release of PTH, as estimated by a variety of immunoassay procedures, has not been observed (10, 66, 123). The calciuric effect of high-protein diets has been attributed to increments in glomerular filtration rates (51, 66); sulfur-containing amino acids of dietary proteins (123, 149); and stimulation of insulin (9), glucocorticoid, and growth hormone (149) secretion. An evaluation of these diverse observations must be attempted with caution and with the recognition that a high-protein diet rich in phosphorus results in a decrease in urinary calcium (51), a phenomenon that can be attributed to the direct effect of PTH on increasing renal tubular reabsorption of the calcium filtered by the glomeruli.

Despite the uncertainty that prevails regarding the amount of calcium required to prevent or retard bone loss in aging individuals, it has been established that patients with fracture-prone osteoporosis and asymptomatic elderly individuals require increments in dietary calcium in order to prevent negative calcium balances. The age-related decrease in circulating $1,25(OH)_2D$ sup-

ports the theory that abnormal intestinal adaptation to changes in dietary calcium and the decreased calcium absorption that normally attends senescence result at least in part from age-related changes in circulating $1,25(OH)_2D$. Although it is not universally acknowledged, it appears likely that there is a relationship between these observations and others detailing an increased incidence of osteomalacia in fracture-prone, elderly individuals with decreased sunlight exposure, inadequate vitamin D intakes, and low circulating 25(0H)D.

RECOMMENDATIONS

As noted above, osteomalacia is common in elderly women. It may result in considerable disability because of pain, muscular weakness, and small cortical fractures that often are not detected by routine radiological procedures. These symptoms are often attributed to the "rheumatic pain-backache" syndrome, which physicians accept as a normal result of the relentless aging process. Because bone loss is a phenomenon of aging, it is often impossible to determine the extent to which osteomalacia contributes to the changes observed in routine skeletal surveys. Since the osteomalacia of the elderly is primarily the result of deficient vitamin D intake and inadequate exposure to sunlight, the physician must thoroughly analyze the patient with vague and general pains, low backache, muscle weakness and stiffness, and bone tenderness before he ascribes this symptom complex to "senile" or "postmenopausal" osteoporosis, "osteoarthritis", or "rheumatism." A dietary survey, evaluation of food habits and sunlight exposure, and in epileptic populations, adequate appraisal of anticonvulsant medications that result in osteomalacia (44) are strongly recommended for individuals with low blood 25(OH)D levels; elevations in alkaline phosphatase and low 24-hour urinary calcium values (below 50–70 mg) are also consistent with osteomalacia but represent crude diagnostic parameters (30, 87, 136). A bone biopsy is often essential to establish the diagnosis (1, 11). The preventive approach includes insuring adequate sunlight exposure and vitamin D intake of 500–1000 IU/day (104). Once diagnosed, osteomalacia should be treated with vitamin D in doses of 25,000–50,000 IU biweekly for 4–6 weeks and elemental calcium intakes of 1.0–1.5 gm per day. In relatively immobilized patients, individuals with inadequate sunlight exposure, or others on anticonvulsant or glucocorticoid medications, preventive therapy with vitamin D should increase calcium absorption and minimize the risk of osteomalacia developing as an additional complication of age-related osteoporosis.

At this juncture, data from prospective long-term studies detailing the effect of calcium supplementation in retarding bone mass in asymptomatic menstruating women (Figure 1) are still unavailable. Although most studies show that fracture-prone, osteoporotic individuals have lower calcium intakes than nonosteoporotic controls, we still need long-term studies to define the protec-

tive effect of calcium supplementation on the skeleton and to determine the efficacy of adequate dietary calcium intake on decreasing fracture incidence. Nevertheless, we should acknowledge that there is a progressive rise in PTH in aging individuals who have calcium intakes significantly below the RDA and that calcium supplementation does effectively alter the negative calcium balance of perimenopausal and postmenopausal females. The negative calcium balances, increased rates of skeletal and alveolar bone loss, and increased fracture incidence in calcium-deficient populations should no longer be ignored. Moreover, until more definitive studies are available, the beneficial effects of increments in dietary calcium, either by dietary means or with appropriate calcium supplements, in retarding the rate of bone loss or decreasing bone resorption in the menstruating female must be acknowledged. Diets of elderly women should include milk or milk products (skim milk has approximately 1 mg of elemental calcium per ml) and/or supplementation to insure an intake of 1.0 g of elemental calcium per day, because calcium supplementation does improve bone density in this population (72). Although estrogen therapy improves calcium balance and retards the rate of bone loss, similar improvements in calcium balance can be achieved by merely increasing the daily elemental calcium intake by 500 mg (46). A variety of commercially available calcium-containing compounds are appropriate as supplemental agents (Table 1); however, calcium carbonate contains more elemental calcium per unit tablet weight and should be considered more appropriate if adequate supplementation and patient compliance are deemed essential. In this regard, the physician is well advised to become familiar with the elemental calcium contents of calcium supplements and should keep in mind that the elemental calcium content, the

Table 1 Elemental calcium content of some commonly used calcium supplements

Calcium salt	Theoretical tablet size (mg)	Elemental calcium content (mg)
Calcium glucobinate (6.5% calcium)	1200[a]	78
Calcium gluconate (9% calcium)	1200	108
Calcium lactate (13% calcium)	1200	156
Chelated Calcium (20% calcium)	1200	240
Dibasic calcium phosphate (23.3% calcium)	1200	280
Calcium Carbonate (40% calcium)	1200	480

[a]Available as liquid.

important ingredient, should be differentiated from the gross weight of the tablet (Table 1). Moreover, the physician must be sympathetic to problems that arise with respect to patient compliance whenever calcium supplementation requires the special diets and burdensome amounts of oral medications that are required with increasing frequency in the elderly. Although hypercalciuria may be considered to represent a potential toxic effect of increasing calcium intake, this is highly unlikely because of the relatively low level of calcium excretion of normal women (93) and because for a given change in dietary calcium intake, urinary calcium increases by an average of only 6% (74). In diseases characterized by increased intestinal calcium absorption and/or hypercalciuria such as sarcoidosis, hyperparathyroidism, "idiopathic" hypercalciuric stone-forming syndromes, and vitamin D intoxication, urinary calcium may increase to even higher levels.

SUMMARY

It has become increasingly apparent that the pathogenesis of osteoporosis is complex, poorly understood, and ill-defined. Calcium deficiency and/or calcium malabsorption and the homeostatic response to this biological insult may ultimately prove to be one of the pivotal factors in conditioning or modulating the skeletal response to senescence. Until we know more about the prevention and potential reversibility of age-related changes in bone cell function, hormonal secretion and metabolism, and dietary patterns that prove deleterious to skeletal health, clinicians will be confronted with an ever-increasing population of aging, fracture-prone, osteoporotic patients. Because calcium supplements improve the calcium balance of perimenopausal and postmenopausal women and because improvements in calcium balance can be correlated with increased skeletal mass, it appears desirable to focus our efforts on diets and/or calcium supplements that guarantee an adequate supply of this essential mineral. Because calcium replacement may simply retard bone resorption and may not restore bone already lost by the fracture-prone, osteoporotic female, dietary analyses and appropriate modification of calcium intakes should be made at least in the third and fourth decades of life, with the goal of retarding the inexorable loss of skeletal tissue as early as possible.

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