CHAPTER **16**

OSTEOPOROSIS

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Osteoporosis was last reviewed in the *Update* textbook in 1987. If one studied that article carefully, reviewed it regularly, remembered it clearly, but did not update any information, one would be woefully behind the times and ignorant of almost all presently accepted and acceptable therapeutic approaches. The basics of the disease (or is it a syndrome?) remain the same, but the medical approaches have progressed exponentially.

Osteoporosis is a disease with low bone mass (osteopenia) and microstructural deterioration of bone tissue eventually leading to an increase in bone fragility. Skeletal growth and consolidation occur from birth into the third decade at which time a lifetime peak is reached. By the fourth or fifth decade, both sexes begin a gradually progressive bone loss that continues into the ninth and tenth decades. There are many factors that determine the rate at which this occurs, some of which are under our control (such as calcium intake and exercise) and some of which are not (such as genetics) (Tables 1, 2). Osteoporosis has been increasingly defined as not only the presence of osteopenia but also the presence of microfractures and possibly symptomatology. Bearing that in mind, the risk factors for the "disease" and the fractures will be synonymous.

While the risk factors described in Tables 1 and 2 are not in question, the definition of each variable and the overlap of variables sometimes clouds the picture. For example, genetics determines sex and race and possibly low body weight; as such, it may be inappropriate to consider such variables as separate entities. Similarly, previous fractures may be a surrogate indicator of defective bone quality—either on a genetic or an acquired basis. It is easy to see from these few examples that risk is not as straightforward as it may seem.

There are many laboratory/biochemical markers of bone turnover that may be helpful in quantifying the extent of osteoporosis, but a meaningful review of them is both beyond the scope of this work and probably irrelevant to most practicing clinicians. For example, serum total and bone alkaline phosphatase, osteocalcin and procollagen I extension peptides are all markers of bone *formation,* while fasting urinary calcium, fasting urinary hydroxyproline and urinary pyridinoline (Pyr) and deoxypyridinoline (dPyr) are all markers of bone *resorption*—all with varying degrees of sensitivity and specificity.

Table 1

OSTEOPOROSIS
Definite Risk Factors

1. Genetics - probably accounts for 70% of osteoporosis
2. White or Asian Women
3. Age - risk doubles for each 10 year increase in age
4. Estrogen Deficiency
   a. Menopause
   b. Early menopause
   c. Premenopausal oophorectomy
   d. Premenopausal amenorrhea
5. Chronic Corticosteroid Use
6. Prolonged Bed Rest / Inactivity

Table 2

OSTEOPOROSIS
Probable Risk Factors

1. Low Weight: Height Ratio
2. Positive Osteoporosis Family History
3. High Alcohol Consumption
4. Low Calcium Intake
5. Cigarette Smoking
6. High Caffeine Consumption
7. Previous Fractures

Of greater practical significance are various radiologic modalities in use to determine the extent of osteopenia and the degree of microfracture. The 1987 *Update* lists six radiologic methods for assessing osteoporosis, none of which is the one in use today. Dual x-ray absorptiometry (DEXA) has the greatest degree of reproducibility and ability to detect the smallest changes in mineralization. DEXA has fairly well replaced dual photon absorptiometry (DPA) and works on the same principle, but DEXA uses a radiograph and DPA a radionuclide source. The precision error of DEXA is just a few percent. Quantitative computed tomography (QCT) is also used, and may be best for trabecular bone. Quantitative ultrasound also has its uses and proponents. DEXA however is the present gold standard.

The costs of osteoporosis (especially osteoporosis-related hip fracture alone) are staggering. Various studies have shown that a 50-year-old white woman has a 50% chance of suffering at least one major osteoporotic fracture in her lifetime, that about 17% will have a fractured hip attributable to osteoporosis, that there is a 12% to 20% excess mortality in the first year after hip fracture, that only about one-third of those surviving to one year after hip fracture are able to ambulate without using some aid, that the number of one-year hip fracture survivors wheel-chair bound or bed-ridden is four times the number of those so confined before fracture, and that the 1990 dollar costs of hip fracture in the United States were estimated at close to $10 billion (hospitalizations, surgical procedures, extended care facilities, lost work). Since treatment is so ineffective and expensive, it is logical that prevention is important to both the individuals at risk and to society as a whole.

Since genetics are so intimately involved in osteoporosis and genetics cannot be changed, it is all the more critical that those factors that can be controlled are utilized to the fullest. Prevention is far less expensive than treatment in terms of morbidity, mortality, and dollars. The list of preventive measures is long and not always easy (Table 3).

Table 3

EXAMPLES OF DIFFERENT TREATMENT MODALITIES

1. Patient Strategies
   - Avoid Alcohol
   - Avoid Cigarettes
   - Weight-Bearing Exercise
   - Adequate Dietary Calcium
2. Bone Formation Stimulation
   - Fluoride
   - Anabolic Steroids
3. Bone Resorption Inhibition
   - Estrogen
   - Calcitonin
   - Bisphosphonates
4. Calcium Absorption Stimulation
   - Vitamin D
   - Calcitriol
5. Combination Therapy
6. Sequential Therapy (ADFR)

THERAPY

Calcium

Adequate calcium intake is high on the list of preventive measures and should not be limited to the elderly. Studies have shown that the present United States recommended dietary allowances (RDA) for calcium in children are probably not adequate, since higher supplemental calcium intake in both the birth to 11 years and the 11 to 24 years groups is associated with significantly enhanced bone mass. It has already been stated that higher maximal bone mass is associated with less osteoporosis. Most of human calcium intake comes from milk products and supplemental sources. It is not inappropriate to determine dietary intake at any age group and supplement if necessary, bearing in mind that there are different requirements for different circumstances (e.g. age, sex, concomitant corticosteroid use). As a general statement, adult calcium intake should be at least 800 mg per day, and a post-menopausal female should have 1000 mg to 1500 mg per day.

Exercise

Exercise, especially weight-bearing exercise, helps reduce bone loss and increase bone mass, though its effectiveness in post-menopausal women is somewhat controversial. In addition to its direct effects, exercise generally produces better muscle tone, improved coordination and a better sense of

self-awareness, all of which are likely to be associated with a lesser chance of fracture-producing falls.

There are many medical approaches to osteoporosis, some of which are better than others and many of which can be used concomitantly. Approval of more and different regimens is occurring rapidly, and today's breakthrough may soon find itself tomorrow's dinosaur.

Estrogen

Probably the most widely accepted approach is that of estrogen replacement in the estrogen deficient female, regardless of whether the estrogen deficiency is due to menopause, premenopausal oophorectomy or any other reason. Estrogens are used for many purposes besides osteoporosis (perimenopausal symptoms such as hot flashes, prevention of coronary artery disease, etc.), but this review is limited to its osteoporosis uses. Since the use of estrogens is associated with a small but definite increased risk of endometrial cancer, it is generally accepted that the concurrent administration of a progestin for 11 to 12 days per month is indicated if the woman still has a uterus and is not necessary if she has undergone hysterectomy. There is controversy as to whether estrogen use is associated with an increase in breast cancer incidence, and it appears that different estrogen preparations are associated with different risk levels. Women with a family history of breast cancer seem to be at greatest risk, and close gynecologic follow-up of uterine and breast status is imperative in any woman on long-term estrogen use for any reason.

Further confusing the estrogen therapeutic picture is the fact that long-term use is associated with a definite decrease in ischemic heart disease (by close to 50%), but the addition of progestin negates much of that (probably by the latter's reversal of much of estrogen's favorable effects on serum lipoproteins). Estrogens seem to have no effect on the risk of stroke. Women with breast cancer cannot take estrogens. It is of interest to note that tamoxifen (a synthetic antiestrogen used as a long-term adjuvant therapy in breast cancer that increases disease-free and overall survival) has some estrogen-agonist effects and apparently increases mean bone mineral density as well as conferring similar good effects on decreasing the incidence of cardiovascular mortality.

Contraindications to hormonal replacement therapy (HRT) include abnormal vaginal or uterine bleeding, a history of thrombophlebitis or thromboembolic disease, acute liver disease, pregnancy, and breast cancer. The estrogen picture is far from clear, and is constantly being updated, but is unquestionably on the "plus side" in regard to osteoporosis.

Bisphosphonates

Bisphosphonates, bone-specific stable compounds that bind avidly to hydroxyapatite, suppress bone resorption, and possibly osteoclast differentiation. They are poorly absorbed, and must be taken on an empty stomach with only water. Milk, coffee, orange juice, and other beverages further inhibit absorption. At least one agent (etidronate-Didronel) may cause mineralization defects when given regularly, a problem that is circumvented by treating patients cyclically. Bisphosphonates have greater effects at trabecular bone than do other agents (as does calcitriol, the active hormonal form of Vitamin D), and therefore may be drugs of choice in corticosteroid-induced osteoporosis, a condition with relatively high spinal bone loss.

In addition to etidronate, other approved bisphosphonates include pamidronate (Acredia) which is used intravenously for hypercalcemia of malignancy and Paget's disease of bone, and alendronate (Fosamax; usually given at 10 mg/day on an empty stomach) which does not need to be used cyclically, but does need to be taken on an empty stomach with water. They all increase bone mineral density but oral pamidronate studies have been curtailed because of gastrointestinal (GI) toxicity. Other bisphosphonates include clodronate (similar to etidronate though several reported cases of leukemia associated with it have limited its use), tiludronate (presently undergoing fairly promising studies) and risedronate (a third generation bisphosphonate undergoing studies with seemingly less toxicity).

The most common side-effects of the bisphosphonates are nausea and diarrhea. Etidronate must be given cyclically (usually 5 to 6 mg/kg/day for 2 weeks followed by none for 13 weeks) to avoid impaired mineralization similar to what is seen in Vitamin D deficiency and osteomalacia—expressed clinically by bone pain and fractures. Fairly extensive GI side effects have been seen with oral pamidronate, and have been

found to a lesser degree with clodronate and high dose alendronate. Rapid IV administration of etidronate and clodronate have been associated with acute renal failure (not noted with slow IV administration), and fever and lymphopenia have been noted with parenteral use of any of the bisphosphonates as well as with oral pamidronate. Because of the possible correlation with leukemia, clodronate studies have been curtailed and GI toxicity has done the same for oral pamidronate.

Calcitonin

Calcitonin, a hormone produced by the thyroid gland, is controlled by circulating ionized calcium levels, not by thyroid stimulating hormone (TSH) as are the other thyroid gland hormones. Its effects are opposite to that of parathyroid hormone (PTH), the latter stimulating osteoclastic regulated bone resorption while calcitonin prevents it. It has been used in many hypercalcemic syndromes (malignancy, myeloma, Paget's disease of bone) as well as osteoporotic syndromes (both age-related and corticosteroid-induced). Calcitonin is the only treatment that appears to decrease the pain of osteoporotic fractures and it also decreases the frequency of such fractures. Doses for skeletal pain are either 200 units by nasal spray or 100 units subcutaneously (SQ) daily for 5 of 7 days per week. If pain is not the consideration for use, the dose is 50 to 100 units SQ or 200 units nasal spray three times a week. Eventually, a "one month on, one month off" regimen can be instituted. Nausea and mild GI discomfort are not uncommon with calcitonin. The need for parenteral administration has made injectable calcitonin-salmon (Calcimar) less desirable to some patients, a problem overcome somewhat by calcitonin-salmon nasal spray (Miacalcin); however, some patients find administration of the latter somewhat intimidating as well.

Fluoride

Fluoride has been used for many years in the treatment of osteoporosis with controversial findings and results. It causes a cumulative increase in bone mass, but the bone is not always structurally sound and stress fractures may occur. Additionally, GI irritation and a 25% non-responder rate further limit its use, while the fact that it is cheap and non-patented makes funding of studies difficult. The dose is approximately 50 mg/day.

Vitamin D

The use of Vitamin D, its metabolites and its analogs is also controversial, as are its potential actions. It is an indirect stimulator of bone resorption (certainly not what one would like in the treatment of osteoporosis) but also has several beneficial effects in osteoporosis. It stimulates gastrointestinal (GI) tract absorption of calcium, appears to promote mineralization and inhibits parathyroid hormone (PTH) mediated bone resorption (by increasing calcium absorption). Various studies have shown that several of the Vitamin D preparations reduce the risk of hip and vertebral fractures, normalize calcium absorption in osteoporotic patients (a group with generally poor calcium absorption) and may have a stimulating effect on bone formation. Vitamin D given 400 to 800 IU daily or 50,000 IU per week and especially its active metabolite calcitriol (1,25 dihydroxyvitamin D3; 1,25 (OH)2 D3; Rocaltrol) as 0.25 to 0.5 micrograms per day must be closely monitored for the infrequent but real complications of hypercalcemia and hypercalciuria. Daily doses of calcium should probably be slightly decreased if calcitriol is employed.

DISCUSSION

There are many other approaches to the prevention and treatment of osteoporosis, approaches too numerous to deal with in detail in this paper. There have been observations and studies regarding the potential use of sodium restriction and thiazide diuretics, anabolic steroids, prostaglandin E2 (PGE2), parathyroid hormone (not all its effects are opposite to those of calcitonin), flavonoids (a common plant metabolite occurring rather ubiquitously in fruits, vegetables and beverages-the most studied of which is ipriflavone), strontium, growth hormone and other growth factors, etc. More information on these and other approaches will likely be available in the future. For now, the reader is referred to the references at the end of this article for a more extensive description of these alternatives.

It is increasingly evident that the prevention and treatment of osteoporosis can be approached from different directions (Table 3). Some depend more on patient motivation (avoidance of smoking and alcohol ingestion, both of which are unquestionable risk factors; calcium intake; weight

bearing exercise), others attempt to stimulate bone formation (fluoride; anabolic steroids), still others inhibit bone resorption (estrogen; calcitonin; bisphosphonates), others have more than one effect, and yet others stimulate calcium absorption (Vitamin D; calcitriol). Combinations are frequently used, and sequential therapy (bone stimulators followed by resorption inhibitors followed by a rest period and then repeating the sequence) is under study as well. Furthermore, the agents used should reflect the primary cause of the osteoporosis, the main players being age-related post-menopausal osteoporosis and glucocorticoid-induced osteoporosis.

At that, involutional disease has been divided into Type I and Type II varieties of osteoporosis (Table 4), a classification with some practical utility clinically, but not reflective of distinctly separate syndromes. Rather, there is significant overlap of the two. Type I is noted more in the first 15 to 20 years past menopausal age, is found more frequently in women, is associated with estrogen deficiency, more frequently affects trabecular bone (spine and distal radius), is not associated with an increase in PTH, and is not nearly as affected positively by the addition of dietary calcium. Type II is described more by an older age group (>70), has only a 2:1 female to male preponderance, involves cortical bone (hip, long bones, and vertebrae), has a greater likelihood of calcitriol deficiency, has an increase in PTH, and has a greater likelihood of response to an increase in dietary calcium.

CONCLUSION

Osteoporosis is a condition where osteopenia is associated with microstructural deterioration of bone leading to increased bone fragility. There is progressive bone loss, associated primarily with advancing age—more so in women—after peak bone density is reached during the third decade or so, but also frequently in association with chronic corticosteroid use and mitigated by many other factors (Tables 1,2,5). Prevention is far more important than treatment (Table 6), and the costs to society in terms of morbidity, mortality, and dollars are gargantuan. There are many approaches to treatment and causative factors need to be considered when choosing therapy, bearing in mind the causes in any particular individual are likely to be multiple. Therapeutic modalities have changed and grown exponentially in the last few years, and are likely to continue changing rapidly until more effective and less toxic approaches become available.

Table 4

INVOLUTIONAL OSTEOPOROSIS

	Type I	**Type II**
Age	55-75	> 70
Sex (F:M)	6:1	2:1
Fractures	Vertebrae/Wrist	Hip/Long Bones/Vertebrae
Type of Bone	Trabecular	Cortical
Hormonal Relationships	Estrogen Deficiency	Calcitriol Deficiency
Calcium Absorption	Decreased	Decreased
PTH Increased	No	Yes
Importance of Calcium	Moderate	High

Table 5

SECONDARY CAUSES OF OSTEOPOROSIS

Drugs
- Glucocorticoids
- Anticonvulsants
- Loop Diuretics
- Heparin
- Alcohol
- Factitious Thyrotoxicosis
- Methotrexate (?)

Diet
- Calcium Deficiency
- Scurvy
- Starvation

Congenital
- Osteogenesis Imperfecta
- Homocystinuria
- Hypophosphatasia
- Hemolytic Anemia

Endocrine
- Cushing's Syndrome
- Growth Hormone Deficiency
- Hyperthyroidism
- Prolactinemia
- Hypogonadism
- Hyperparathyroidism
- Type I Diabetes Mellitus

Miscellaneous
- Renal Tubular Acidosis
- Immobilization
- Liver Disease
- Hemolytic Anemia
- Malabsorption
- Lymphoma
- Rheumatoid Arthritis
- Leukemia
- Multiple Myeloma
- GI Surgery

Table 6

TREATMENT OF OSTEOPOROSIS

1. Avoid known aggravating factors (e.g., alcohol)
2. Weight-bearing exercise 30-60 minutes per day
3. Adequate calcium intake, 1000-1500 mg per day
4. Vitamin D, 400-800 IU per day
5. Estrogen replacement, 0.625 mg per day, if not contraindicated (Progestin use if patient has uterus)
6. Bisphosphonates, 5-6 mg/kg/day of etidronate two weeks out of 15, or 10 mg per day of alendronate on empty stomach
7. Calcitonin* 50-100 units SQ or 200 units nasal spray three times a week

*This is the only drug approved for treatment of osteoporotic fracture pain

REFERENCES

1. Lane NE: Osteoporosis. *Rheum Dis Clin North Am* 20(3):1994.
2. Hanley DA:Proceedings: options for the management of osteoporosis. *J Rheum* 3(suppl):1-22,1996.
3. Harrington T: ACR adopts guidelines on steroid-induced osteoporosis *Am Coll Rheum* 15(10):1-4, 1996.
4. Christiansen C: Consensus development conference on osteoporosis, proceedings of a symposium *Am J Med* 95(5A):1993.
5. Aloia JF: *A Colour Atlas of Osteoporosis*. St. Louis, MO:Mosby-Year Book; 1993.