OSTEOPOROSIS

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Osteoporosis is defined as a *decrease in the mass of normally mineralized bone*. There is a decrease of whole bone formation and it is generally believed that this occurs primarily due to an increase in bone resorption rather than to a decrease in bone formation.

There are many and varied reasons for osteoporosis and there are distinct population subsets in which it is more likely to occur than in others. There may be various associated diseases that may contribute to its extent, various medications that make its presence more or less likely to occur, and various life styles that may play a role as well. These may act in concert or in conflict and it is for this reason that many refer to it as a syndrome rather than as a disease. Diagnosis is frequently difficult and non-specific until and unless it is advanced or symptomatic. Prevention is debatable and treatment is of only marginal value as based on controlled studies. Anecdotal data is extensive in this multifactorial condition and there is undoubtedly a prolonged subclinical phase during which prevention/intervention would most ideally be undertaken.

The most common areas of symptomatic osteoporosis include the lower back (especially T12 and L1), the femoral neck (just below the lesser trochanter), the middle back, the ribs, and the distal radius. It is noted in general that these are areas with relatively high *trabecular* bone content with lesser amounts of *cortical* bone, though it will be noted later that some of our diagnostic studies are better at determining the presence of osteoporosis in areas where cortical bone predominates. This may make it difficult to translate diagnostic information into valuable and reliable clinical information in a particular patient. There are also localized areas of osteoporosis in specific conditions (e.g., reflex sympathetic dystrophy) and generally accepted diagnostic studies are of little or no value under those circumstances.

Population studies and observations have revealed much information about this syndrome. It is more likely to be present in women than in men, in whites more than blacks (though in Orientals most of all), and in those of advanced age more than in the young. Those persons with a small body frame, a strong family history, a sedentary life style, and nulliparity are more likely to have osteoporosis than those without these features. Of greatest note is that the condition is much more frequent after *menopause* regardless of whether the menopause is physiologic or surgical. In fact, the single most determining factor as to whether these or other modifying conditions will come into play to cause a symptomatic clinical state may well be the peak *bone mass* achieved long before menopause.

No discussion of osteoporosis would be complete without a discussion of menopause. Menopause can be relatively and reliably defined by various clinical and laboratory parameters, the clinical manifestation being cessation of menses. There is very little, if any, overlap of plasma estradiol (E2) levels between premenopausal (>100 pmol/L) and postmenopausal (<60 pmol/L) females, though in the perimenopausal period intermediate values occur. The same is true of plasma follicle stimulating hormone (FSH) levels where premenopausal levels (<20 units/L) almost never overlap with postmenopausal levels (>30 units/L) though, again perimenopausal levels may be intermediate. Plasma luteinizing hormone (LH) levels are of less value due to the presence of pre- and postmenopausal levels overlapping and plasma estrone (E1) values are also of less value since a significant amount is produced in the adrenals and the adrenal fraction obviously becomes more important quantitatively after loss of ovarian function.

Interestingly, the most discriminating menopausal symptom is the "hot flush" which is usually self-limited (less than 5 years) and which is seemingly associated with the highest FSH levels. While osteoporosis is most common and most severe in the postmenopausal female and while menopause can be reliably "diagnosed" by various methods, none of this is helpful in determining which individuals are likely to develop symptomatic disease. As previously noted, the most reliable predictor of that is premenopausal bone mass which usually has its apogee in the third through fourth decades, most frequently at about age 30.

The menopause brings various physiological changes, many of which are directly or indirectly related to osteoporosis. *Estrogen levels* decrease at and after

menopause and it is known that estrogens both increase bone formation and decrease bone resorption. If estrogen loss is very early (e.g., early surgical menopause), bone formation may never be normal. Without estrogen trabecular bone (spine, proximal femur, pelvis) is particularly vulnerable to bone loss while other mechanisms and metabolism may be important with cortical bone (appendicular skeleton). Estrogen deficiency may also sensitize the skeleton to the actions of parathormone (PTH) on bone. Postmenopausal factors besides loss of estrogen include less exercise and mobilization, more frequent chronic illnesses, and even a less adequate diet, all of which may occur with aging.

Another important factor associated with osteoporosis is calcium. Its exact role and relationship is uncertain but some information is available. Serum calcium (for for that matter phosphate and alkaline phosphatase) levels are almost always normal. PTH concentration is also generally normal though both increased and decreased levels have been reported in the postmenopausal female. Vitamin D levels may be as much as 30% lower in postmenopausal osteoporotics compared with non-osteoporotic postmenopausal females. The decrease in vitamin D correlates with a relatively similar decrease in intestinal calcium absorption. Impaired calcitonin secretion, not responsive to intravenous calcium infusion, has been reported in postmenopausal osteoporotic females. The significance of this is uncertain but this differs from age-matched controls in whom there is usually some response to calcium infusion.

Hypercalciuria may be present especially if bone resorption exceeds bone formation (particularly in immobilized or hyperthyroid patients) and *urine hydroxyproline* may also be elevated with increased bone resorption. These can best be determined by measuring a fasting urine calcium: creatinine ratio or fasting urine hydroxyproline: creatinine ratio, respectively, which will obviate the need for 24 hour urine collections and will avoid the immediate influences of dietary calcium and gelatin.

Although the laboratory provides some interesting information in regard to the menopause, calcium metabolism, and other hormonal data related to calcium, none of it is particularly helpful in regard to diagnosis, treatment, or prognosis. On the other hand, there are some radiologic studies that have proven helpful along those lines. Various methods of reading and interpreting plain x-ray films have been developed and while no one method is universally accepted, there is much agreement. Most methods for staging include the vertebrae, the proximal femur, or the distal radius. The former two are more likely to represent potentially symptomatic areas and are representative of trabecular bone to a greater degree than the latter. Most agree on five radiologic stages in regard to vertebrae as follows:

1. vertebral radiolucency
2. vertical trabeculation
3. biconcavity of vertebral body (codfish appearance)
4. wedging (anterior vertebral height < posterior height)
5. compression (decrease in both posterior and anterior vertebral heights).

The two most commonly used indices for evaluation of the proximal femur are the Singh Index which utilizes the amount of visualized trabeculation, and calcar femorale which measures condensation of cortical bone just above the lesser trochanter (greater than 5 millimeters being normal). In all of these methods sequential observations are important. Other radiologic methods for assessment of osteoporosis include:

1. radiographic photodensitometry
2. single photon absorptiometry
3. dual photon abosorptiometry
4. local neutron activation
5. computed tomography
6. scattered radiation.

These can all be used to effectively measure trabecular bone. Dual photon absorptiometry as well as computed tomography have offered the most reliable information to date and can be performed relatively easily and inexpensively.

A final diagnostic procedure to be discussed is bone biopsy. The specimen is usually taken from the iliac crest and care must be take so that the specimen is not demineralized in preparation. One will find a decrease in bone volume or mass with normal mineralization in osteoporosis as opposed to osteomalacia where there is a delay or a decrease in mineralization of an otherwise normal organic matrix. The biopsy may help differentiate etiology since results will vary depending upon cause (e.g., glucocorticoid excess, hyperparathyroidism, thyrotoxicosis, etc.).

Osteoporosis can be subdivided into at least three main types as follows:

1. *simple primary osteoporosis* — there is an increased bony resorption associated with the loss of estrogens following the normal menopause

2. *accelerated osteoporosis* —malabsorption of calcium from the gut is often noted in addition to the increased bony resorption

3. *secondary osteoporosis* — where other conditions

may cause or contribute to the osteoporotic state (some of these conditions are discussed in the next paragraph).

The conditions that may cause or contribute to osteoporosis most frequently are:

1. *Aging* is associated with both cortical and trabecular bone loss. It is postulated that there is a decrease in bone formation secondary to senescent osteoblasts coupled with secondary hyperparathyroidism due to an age-related decrease in intestinal absorption of calcium. Further, there is often less weight-bearing exercise with age.

2. *Gonadal hypofunction* is discussed above in regard to menopause and is in further evidence when one realizes that bone mass peaks at about age 30 and starts to decline about 5-10 years later as follows:

   Male decline: about 0.3% per year
   Female decline:
   about 2% per year x 5 years
   about 1% per year next 5-10 years
   about 0.5% per year after that.

3. *Glucocorticoid excess* causes osteoporosis via many different pathways including impaired bone collagen synthesis, inhibition of cartilage growth, an antivitamin D effect with decreased intestinal calcium absorption as well as a direct inhibition of intestinal calcium transport. Further it is often patients who chronically take corticosteroids that are immobilized and have poor dietary intake because of chronic diseases.

4. *Thyrotoxicosis* causes osteoporosis but usually only in severe cases untreated for a long time. Thyroid hormone (T4) causes both increased bone formation and resorption with the latter seemingly predominating.

5. *Diabetes mellitus* seems to exert its osteoporotic effect through impaired bone formation.

6. *Primary hyperparathyroidism* and the effect of PTH on calcium metabolism at both the intestinal and bone levels have been discussed already to some degree. The presence of developing osteoporosis in these patients is sufficient indication for parathyroidectomy.

7. *Immobilization* seems to contribute to osteoporosis at both the local and systemic levels. There is an increase in osteoclastic bone resorption (oftentimes causing hypercalcemia in the immobilized patient) and a decrease in osteoblastic activity.

8. *Genetic disorders* associated with osteoporosis probably act via a defect in collagen synthesis and include osteogenesis imperfecta, homocystinuria, Menke's Syndrome, Ehlers-Danlos Syndrome, and Marfan's Syndrome (many of these syndromes have more than one presentation and defect).

9. *Juvenile osteoporosis* deserves special mention because it can be such a virulent disease with multiple pathologicic fractures. It is found in prepubertal children and usually remits spontaneously at puberty.

10. *Rheumatoid arthritis* in particular but other systemic inflammatory arthropathies as well are associated with osteoporosis, though it is usually periarticular. Generalized osteoporosis may occur but those patients usually also have compounding factors of immobilization and/or corticosteroids.

11. *Reflex sympathetic dystrophy syndrome* (RSDS) and various similar or identical syndromes that go by different names (shoulder-hand syndrome, Sudeck's atrophy) are examples of localized forms of osteoporosis in which are also found pain and swelling, trophic skin changes, and vasomotor instability of varying degrees.

With such diverse etiologies for the osteoporotic syndrome it is no wonder that there is no ideal approach that would apply to all patients and each patient must be taken on his or her own merits. Since the overwhelming number of symptomatic cases are in postmenopausal females, it is that group that will be discussed most extensively.

As it has been shown that premenopausal peak bone mass is probably the single most important factor and predictor of subsequent osteoporosis, prevention is probably of greater import than subsequent treatment. Achievement of full genetic potential should be attempted by good dietary habits early in life, including adequate calcium intake. In the premenopausal years, including childhood, about 1000 milligrams of calcium per day are usually adequate and in the postmenopausal years, 1500 milligrams. (The usual premenopausal diet contains about 500 milligrams per day and the postmenopausal diet slightly less). Additionally, exercise is important (mobilization) and the avoidance of ethanol, smoking, caffeine, and excessive dietary protein. Ethanol consumption is a known risk factor in males but has not been fully evaluated in females. Cigarette smoking interferes with reproductive endocrine status often

resulting in an earlier menopause and may also predispose to bone loss. Caffeine is known to increase both urinary and fecal calcium loss.

Dietary protein in the process of conversion from energy to fat and vice versa yields sulfate and either the sulfate alone or the associated acid load (from the sulfur-containing amino acids) cause an increase in urinary calcium. Finally, intensive athletic training may cause amenorrhea and subsequently an increased risk of bone loss.

While no individual treatment program is best for all osteoporotics there are various regimens that have merit and these will be discussed.

1. *Calcium*. Higher doses are needed postmenopausally (1500 milligrams/day) than premenopausally (1000 milligrams/day) since there is decreased efficiency of intestinal calcium absorption after menopause (vitamin D levels lower).

Calcium carbonate is probably the best preparation since it contains the greatest percentage of elemental calcium of all the available preparations (40%).

2. *Estrogens*. The oral short acting estrogens (congugated estrogens, diethlystilbestrol, esterified estrogens, estradiol, ethinly estradiol, estropitate, stilbestrol) have been approved for use in osteoporosis while products used as birth control pills have not.

Conjugated estrogens at 0.625 milligrams per day 3 out of 4 weeks in the immediate postmenopausal period for about 5-10 years retards bone loss while higher doses (1.25-2.50 milligrams) may be needed for treatment.

Approved indicates for use include evidence of loss or deficiency of bone mass in a postmenopausal female and estrogen should be used with other measures such as diet, calcium, and exercise.

Estrogens inhibit bone resorption possibly by increasing calcitonin secretion and/or increasing intestinal calcium absorption by increasing vitamin D or vitamin D effect.

Problems associated with estrogen use include:

1. vaginal bleeding
2. uterine cancer induction (use of a progestin such as medroxyprogesterone acetate on the last ten days of the cycle may decrease that likelihood)
3. fluid retention
4. hypertension
5. vascular thromboses.

1:1000 postmenopausal females per year not on estrogens develop endometrial cancer while 5-10:1000 per year on estrogens do. Progestin agents may adversely affect carbohydrate and lipid metabolism.

3. *Vitamin D*. While intestinal calcium absorption is improved, urinary calcium excretion may also be increased, so vitamin D use is best reserved for osteomalacia rather than osteoporosis.

4. *Calcitonin*. Calcitonin inhibits bone resorption and may stimulate bone formation. It is approved for use in osteoporosis and criteria for its use include x-ray findings of moderate to severe vertebral compression, cortical plate fractures, vertebral wedging and vertebral collapse. Low bone mass level or a decrease of 4% or more in a 1-3 year period by quantitative CT scan or dual photon absorptiometry is another indication for calcitonin use as is a history of upper femoral fracture.

Side effects include gastrointestinal (GI) symptoms (metallic taste, decreased appetite, nausea, vomiting). Dermatologic findings of erythema or a mild rash may be present at injection site. Vasomotor (flushing of face or ears) may also be present.

Calcitonin must be given by injection and is approved at 100 Medical Research Council (MRD) units per day subcutaneously or intramuscularly. However, many people use 50-100 MRC units three times per week with seemingly adequate results. It needs to be tried at least 6 months and should be supplemented with 1000 milligrams of calcium and 400 international units (IU) of vitamin D per day.

5. *Sodium fluoride* (NaF). NaF increases bone matrix but that matrix may be undermineralized. GI side effects occur in 15-50% of patients and renal impairment is a contraindication. It is still experimental but is used. Other side effects include skin rash, arthralgias, and osteophytosis. Calcium should be given with NaF.

6. *Diet*. This has been touched on above and should include high calcium foods and the avoidance of too much protein or fiber as well as ethanol, caffeine, and tobacco use.

There are several localized forms of osteoporosis such as RSDS which defy prediction and oftentimes treatment as well. The syndrome includes pain which is usually severe and burning, is rarely segmental, and seems to especially involve an entire hand or foot. Tenderness is generalized but more severe periarticularly. Skin findings include pitting or non-pitting edema (also especially

periarticularly), followed by dystrophic and then atrophic changes. Vasomotor instability occurs and is usually a vasoconstriction or vasodilatation, but Raynaud's phenomenon and hyperhidrosis may occur less frequently.

There are three stages:

1. *Acute* stage lasts 3-6 months and is associated with pain, tenderness, swelling, and vasomotor symptoms.

2. *Dystrophic* stage follows that and also lasts 3-6 months. The initial features leave and trophic skin changes occur.

3. *Atrophic* stage follows and is manifest by atrophy of skin and soft tissues with contractures. The skin is shiny and cool. The extremity is contracted and there is usually no pain.

The x-ray initially may be normal, followed by patchy or mottled osteopenia and even surface erosions (like in RA) may subsequently appear. There is later a diffuse osteopenia and there may be loss of one-third of the mineral content of the affected area.

The pathophysiology of RSDS is still uncertain but there appears to be little evidence of true autonomic nerve dysfunction. Some data suggest there may be a mechanical disturbance of venous and lymphatic flow followed later by sympathetic nervous system stimulation. The latter cannot account for all cases though since even drugs have unquestionably been implicated in the provocation of the syndrome at times. There is however, little relationship of whatever the provocative event may be (severity of trauma, etc.) with the extent of disease.

Overall response of patients with RSDS to any type of treatment is generally poor. Twenty percent of those with the syndrome greater than six months will subsequently have a good response and only 43% of those less than six months will do well (less than half). Treatment includes early mobilization following trauma or myocardial infarction as well as exercise and use of hot or cold packs. Sympathetic blockage (including surgical sympathectomy if response to medical blockage is good) may stop the cycle of pain and transcutaneous nerve stimulation (TENS) may also be helpful. Systemic corticosteroids in doses of 60-80 milligrams of prednisone equivalent per day in divided doses for one to two weeks may also be helpful. Steroids should be tapered to discontinue altogether in three to four weeks.

It is obvious that osteoporosis is a common, multifactorial condition of oftentimes insidious onset. Early diagnosis is difficult, preventive measures are of uncertain value, and treatment is far from ideal and must take into consideration both the specific situation of each patient as well as general principles.

The cost of osteoporosis is staggering and is estimated in this country between $3.8 and $6.0 billion annually (150,000 hip fractures, 250,000 Colles' fractures, 83,000 humeral fractures, 43,000 pelvis fractures, and 7,000 spinal fractures. These figures do not include the cost of loss of income, long term care, and expenses required by the patients. Osteoporosis is complicated by chronic diseases, inadequate dietary intake, and medications that may cause more harm than good. It can complicate surgical procedures, particularly in regard to those of involved bone since one is dealing with inferior stock in the first place.

There are no complete answers as yet but the length of this discussion at least suggests that much is being done to narrow the impotence gap in our understanding and control of this condition.