Osteoporosis: Beyond Bone Mineral Density (Part I)

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Summary

Primary osteoporosis occurs with bone loss as people age, while secondary osteoporosis is caused by other factors such as medications and medical conditions. Debilitating acute and chronic pain in the elderly is often attributed to fractures from osteoporosis and can lead to further disability and early mortality. Osteoporosis is generally viewed as a disease of low bone mineral density (BMD) as defined by a T-score. However, T-scores and, hence, BMD criteria may not accurately reflect fracture risk. Thus, if clinicians are too reliant on the idea that BMD/T-scores are the major concern in fracture risk, they may fail to recognize other danger signs and miss preventing painful, costly, and life-shortening fractures in patients. Early detection and treatment of risk factors for osteoporosis and osteoporotic fractures are essential for practicing clinicians. Family physicians will frequently be the doctors who recommend screening for osteoporosis and who are uniquely positioned to ensure both detection and appropriate treatment. Understanding bone histology, the physiology of bone turnover, and current research on the prevention and treatment of osteoporotic fractures including pharmaceutical and nutritional interventions can contribute towards the development of an integrative approach to treating this condition.

***Disclosure**: The authors manufacture a dietary supplement for bone health.*
***Editor's note**: This is the first of a 2-part article.*

Osteoporosis is a major health concern in the United States and globally. According to US data obtained by the National Health and Nutrition Examination Survey (NHANES III, 1988-1994), 13% to 18% of women (4-6 million) over the age of 50 had osteoporosis, and 37% to 50% (13-17 million) had osteopenia.[1] Additionally, the estimated prevalence in men was 3% to 6% (1-2 million) for osteoporosis and 28% to 47% (8-13 million) for osteopenia. In the intervening years, the overall prevalence of osteoporosis has increased. In 2004, more than 10 million people in the United States had been diagnosed with osteoporosis,[2] a number that by 2020 is projected to increase to 14 million diagnosed cases.[3]

Osteoporosis is classified as either primary or secondary. Primary osteoporosis occurs with bone loss as people age, while secondary is caused by other factors such as medications (eg, glucocorticoids) and medical conditions (eg, Cushing's disease, hypogonadism, malabsorption).[4] Debilitating acute and chronic pain in the elderly is often attributed to fractures from osteoporosis and can lead to further disability and early mortality.[5,6] In Caucasian women and men aged 50 years or older, the remaining lifetime risk of a hip, spine, or forearm fracture is estimated at 40% and 13%, respectively.[7] A 2005 report estimated that of the nearly 2 million osteoporosis fractures in the United States that year, 27% were vertebral fractures, 19% were wrist fractures, 14% were hip fractures, 7% were pelvic fractures, and 33% were "other" fractures. Nonvertebral fractures represented 73% of total fractures, with 71% of all fractures occurring in women.[3] It is startling to note that 12% to 40% of patients with osteoporosis who suffer hip fractures die within 6 months.[8]

In addition to its deleterious impacts on health, the economic effect of osteoporosis is significant and growing. In 2005 the cost for treating the more than 2 million osteoporotic fractures in this country was almost $16.9 billion.[3] Of that, the largest cost ($12.8 billion) was spent on treating fractures in women, largely because they suffer a greater number of hip fractures than men (73% vs 69%, respectively). Although in 2005 only 14% of all osteoporotic fractures were of the hip, they accounted for 72% of the total costs of treating osteoporotic fractures. By 2025 the estimated cost of treating more than 3 million expected fractures is projected to increase more than 48% to $25.3 billion.

Osteoporosis is generally viewed as a disease of low bone mineral density (BMD). This observation was first noted in 1940 when Fuller Albright, MD, of Massachusetts General Hospital observed decreased bone mass in ovariectomized pigeons.[9] In 1994 the World Health Organization (WHO) codified this paradigm by creating the official diagnosis of osteoporosis as having low BMD as defined by a "T-score." A T-score is a number of standard deviations from peak bone mass of healthy men or women, as appropriate, aged 20 to 29. A T-score of -2.5 or less is diagnostic of osteoporosis, while a T-score of -1 to -2.5 is diagnostic of osteopenia.

However, one of the reasons for this article is that T-scores and, hence, BMD criteria may not accurately reflect fracture risk. In a longitudinal observational study, BMD tests were conducted at peripheral sites on postmenopausal women of 50 years or older (mean age 64.5 ± 9.3 years; range 50-104 years) without a previous diagnosis of osteoporosis.[10] Each woman received a baseline, in-office BMD test on the heel using single x-ray absorptiometry, forearm using peripheral dual-energy x-ray absorptiometry (DEXA), or finger using peripheral DEXA. Twelve months later participants completed a questionnaire asking if they had suffered any fractures since the study began and, if so, at which sites. While the fracture rates were, indeed, highest in women with the lowest T-scores, 82% of women who reported fractures of the wrist, forearm, hip, rib, or spine had a peripheral T-score greater than -2.5, and 67% had T-scores greater than -2.0. That is, the majority of fractures occurred in women who did *not* have a diagnosis of osteoporosis. A second study concluded that at age 50 years, the 10-year risk for fractures of the hip, spine, forearm, or proximal humerus in women with osteoporosis is approximately 45%; how-

ever, the study found that 96% of all fractures in those locations occur in women without osteoporosis.[11]

Thus, if clinicians are too reliant on the idea that BMD/T-scores vary consistently with fracture risk, they may fail to recognize other danger signs and prevent painful, costly, and life-shortening fractures in patients. Understanding bone histology, the physiology of bone turnover, and current research on the prevention and treatment of osteoporotic fractures can contribute towards the development of an integrative approach to treating this condition.

Factors That Influence Bone

During childhood and throughout puberty, the rate of bone creation is faster than the rate of bone loss; therefore, bones become larger and stronger. Bones continue to grow from birth until somewhere between the ages of 30 to 35.[12] Once peak bone mass has been achieved in the early 30s, men and women begin to lose bone at 0.5% to 2% per year, with considerable individual variation in the rate of bone loss.[13,14] In women, an accelerated rate of loss occurs during menopause and for about 10 years thereafter.[15] As people of both sexes age, the risk of osteoporosis and of osteoporotic fractures increases.

Thus, we have come to realize that the skeleton that supports us does not stop changing once we've reached our full growth. Beyond natural aging factors, drugs, diet, and our own activities all have a continuing influence, for better or worse, on our bony structure.

The Osteoporotic Effects of Drugs, Cortisol, and Cadmium Toxicity

Glucocorticoids—including cortisone, prednisone, hydrocortisone, dexamethasone, and methylprednisolone—can all cause osteoporosis. Systemic corticosteroid use, such as of oral prednisone, for more than 6 months has been found to increase the risk for osteoporosis.[16,17] One major reason for this is likely that corticosteroids modulate the immune system toward production of tumor necrosis factor-alpha, a marker of inflammation that stimulates bone resorption.[18]

Even very small doses of oral glucocorticoids (< 2.5 mg/day over approximately 6 months) are associated with a 20% to 200% increase in risk of vertebral fractures.[19] And one study found that for each 10-mg increase in dosage between patients, there was a 62% increase in risk for bone fracture.[20] This risk may be necessary and acceptable to control a disease process. However, if there are ways to reduce or halt the dosage of corticosteroids it would be advisable, since the risk for fracture decreases after stopping the medication.[19] If patients must take corticosteroid drugs, its deleterious effects on bone density may be reduced by supplementation with 45 mg per day of vitamin K_2 (as MK4).[21,22]

The body's own production of cortisol can also contribute to osteoporosis. People with Cushing's disease, a rare condition in which the body produces excessively high, uncontrolled amounts of cortisol, are at an increased risk for osteoporosis and bone fractures. Two recent studies have shown that even normal, healthy people can also be producing enough cortisol to negatively affect bone. In a study of 34 "healthy" men ages 61 to 72 years, bone density was inversely correlated with cortisol levels.[23]

While not typically mentioned in conventional texts on osteoporosis, cadmium toxicity is also a risk factor. Tobacco smoke is one of the most common routes of exposure to cadmium, though it is also found in high amounts in food grown in contaminated soil, and in fish and shellfish caught from polluted water. At high doses, cadmium is toxic to the kidneys, which decreases the body's ability to make active vitamin D.[24] Producing less vitamin D decreases the ability to absorb dietary calcium and the body reacts by taking calcium from bones and other tissues such as muscles and nerves to use in the blood stream. Chronic exposure to even small amounts of cadmium can decrease BMD[25,26] by directly disrupting the balance between bone formation and destruction.[27] The most useful diagnostic test for cadmium exposure is a 24-hour urinary cadmium excretion standardized for creatinine. Even as little as 1 μg cadmium per gram of creatinine has been associated with decreased bone density.[26]

Dietary Influences

Poor diet also increases cortisol. The standard Western diet with its high meat proteins and low fruit and vegetable intake acidifies the blood and increases cortisol. When an acidic diet is eaten long-term, chronically elevated cortisol may contribute to the known osteoporosis-promoting effects of this nutritional spectrum.[28] The intricate relationship between diet and bone health is still being untangled, but what is beyond dispute is that diet affects bone health.

One of the reasons that a meat-dense diet is problematic is that methionine, a sulfur-containing amino acid found in high concentrations in animal protein, can be converted in the body to homocysteine, a homologue of the naturally-occurring amino acid cysteine. Homocysteine interrupts the proper formation of collagen,[29] the main protein in bone and joints, which leads to bone degradation. But in addition to its bone-destroying effect, homocysteine directly damages blood vessels[30] and also reduces levels of glutathione, an important antioxidant.[31] Not only is homocysteine an independent risk factor for osteoporotic hip fractures,[29,32] it is also a risk factor for cardiovascular disease.[33]

According to several studies, coffee (whether caffeinated or decaffeinated was not specified in the studies) can increase calcium excretion in the urine; however, this does not occur if people consume the dietary reference intakes or more of calcium per day.[34,35] Interestingly, another study analyzed both diet and coffee consumption and the risk of fractures. It was conducted in Norway and more than 40 000 men and women, ages 47 to 68 years, participated. Only in women consuming a diet high in nondairy animal protein and low in calcium was the risk for fractures increased. Women drinking 9 or more cups of coffee per day combined with low calcium intake also were at increased risk. The study concluded that, when drunk in moderation and in combination with a healthy diet and adequate calcium intake, coffee does not appear to increases one's risk for osteoporosis.[36]

Exercise

Not participating in routine aerobic, weight-bearing, and resistance exercises increases the risk of osteoporosis, broken bones, and an early death.[37-41] Appropriate exercise may prevent

the onset of osteoporosis and has also been shown to increase BMD and decrease fracture risk. One year of weight-bearing exercise training in community-living women (ages 66 to 87 years) improved Ward's triangle BMD by 8.4% ($P<.01$) compared to controls.[42] Additionally, exercise can increase muscle mass, strength, and balance, thereby decreasing the risk for falling and suffering an osteoporotic fracture.[43] Muscle strengthening and balance exercises (eg, qigong, tai chi) have been shown to decrease risk for fall and fall-related injuries by 75% among women aged 75 years and older.[44]

Integrative Clinical Approaches

Family physicians will frequently be the doctors who recommend screening for osteoporosis and who are uniquely positioned to ensure early detection and appropriate treatment.

In forestalling fractures, reducing risk for falling is crucial, as are implementing strategies that have been shown in clinical trials to significantly reduce fracture risk. Encouraging appropriate exercise and counseling patients to optimize their diet is also appropriate. However, exercise and dietary changes may be difficult in the elderly if they are unable to cook for themselves, have dementia, or lack independent means of transportation.

Assessing Fracture Risk

The large number of risk factors for osteoporosis can make clinical decision-making difficult. If all of these risk factors were given equal importance, practically everyone would be getting a DEXA scan. Although a full evaluation of the relative risks for each of these risk factors is beyond the scope of this review, several useful tools are available.

Guidelines

ACOG: In January 2004, the American College of Obstetricians and Gynecologists (ACOG) published its guidelines for osteoporosis screening. In that document, it recommended that BMD testing (1) should be advised for all postmenopausal women 65 years old or older; (2) may be recommended to postmenopausal women less than 65 years old with 1 or more risk factors for osteoporosis (see Table 1 for risk factors); and (3) should be performed on all postmenopausal women with fractures (whether previous or current fractures was not specified, but, clinically, it would be good practice to look at both).

Table 1. ACOG Risk Factors for Osteoporosis[45]

Medical History That Increases Risk	Insulin-dependent diabetes mellitus
History of prior fracture	Lymphoma and leukemia
Family history of osteoporosis	Malabsorption syndromes (eg, lactose intolerance)
Caucasian race	Mastocytosis
Dementia	Multiple myeloma
Poor nutrition	Multiple sclerosis
Smoking	Pernicious anemia
Low weight and body mass index (BMI)	Rheumatoid arthritis
Estrogen deficiency resulting from early menopause (age younger than 45 years) or bilateral oophorectomy prolonged premenopausal amenorrhea (>1 year)	Severe liver disease, especially primary biliary cirrhosis
Long-term low calcium intake	Spinal cord transaction
Alcoholism	Sprue
Impaired eyesight	Stroke (cerebrovascular accident)
History of falls	Thalassemia
Inadequate physical activity	Thyrotoxicosis
Medical Conditions That Increase Risk	Tumor secretion of parathyroid hormone-related peptide
Acquired immunodeficiency syndrome or human immunodeficiency virus	Weight loss
Amyloidosis	**Medications That Increase Risk**
Ankylosing spondylitis	Aluminum (eg, aluminum-containing antacids)
Chronic obstructive pulmonary disease	Anticonvulsants (phenobarbital, phenytoin)
Congenital porphyria	Cytotoxic drugs
Cushing's disease	Glucocorticosteroids and adrenocorticotropin
Eating disorders	Gonadotropin-releasing hormone agonists
Female athlete triad (disordered eating, amenorrhea, and osteoporosis)	Heparin (long-term use)
Gastrectomy	Immunosupressants
Gaucher's disease	Lithium
Hemochromatosis	Progesterone, parenteral, long-acting
Hemophilia	Tamoxifen (premenopausal use)
Hyperparathyroidism	Thyroxine (at supraphysiologic doses)
Hypogonadism, primary and secondary	Total parenteral nutrition
Hypophosphatasia	**Additional Risks**
Idiopathic scoliosis	Cadmium toxicity[25]
Inadequate diet	Endogenous, non-pathological cortisol production[23]
Inflammatory bowel disease	Low antioxidant status[46]

Table 2. NAMS Risk Factors for Osteoporotic Fractures[4]
Advanced age
Low bone mineral density (BMD)
Previous fracture (other than skull, facial bone, ankle, finger, or toe as an adult)
History of hip fracture in a parent
*Thinness (body weight < 127 lbs [57.7 kg] or low BMI [<21 kg/m])[2]
Current smoking, any amount
Low calcium or vitamin D intake
More than 2 alcoholic drinks/day
Oral or intramuscular glucocorticoid use for >3 months
Increased fall risk from: Impaired vision, dementia, poor health/ frailty, low physical activity, history of recent falls

WHO: Two years prior to the publication of the ACOG guidelines, J.A. Kanis, of the WHO Collaborating Centre for Metabolic Bone Disease at the University of Sheffield Medical School in England, published an evaluation of the 10-year risk of osteoporotic fractures.[11] He concluded that factors other than low BMD increase the risk for fractures. These factors include age, previous fragility fractures, glucocorticoid therapy, high bone turnover, family history of hip fracture, low bodyweight, neuromuscular disorders, cigarette smoking, and poor visual acuity (if someone can't see well, they're more likely to bump into something and/or misstep and fall, thereby increasing there risk for fracture). In fact, a history of a previous fall is a greater indicator for fracture risk than is BMD alone because a previous fall indicates the potential a future fall, which is a risk for fracture.[47]

NAMS: In 2006 the North American Menopause Society (NAMS) published a position statement on managing osteoporosis.[4] It concluded that fracture risk "depends largely on factors other than BMD." Combining a BMD with a physical examination (discussed below) and risk factors for osteoporotic fractures (see Table 2) provide a more comprehensive risk assessment. The NAMS guidelines also take falling into account and provide some practical and relatively inexpensive suggestions for decreasing falling risk, which clinicians can easily discuss with patients (see Table 3).

The Fracture-risk Assessment Tool

Fortunately for clinical decision-making, WHO has aggregated the data and created a free, online clinical-assessment tool called the Fracture-Risk Assessment Tool, or FRAX. This easy-to-use application provides a 10-year probability of fractures given a person's ethnicity, body mass index, medical history, and age. FRAX can be accessed at http://www.shef.ac.uk/FRAX/index.htm. This tool can help clinicians decide quickly with whom they should implement therapies to reduce fracture risk.

Physical Exam

While no single physical examination finding, or combination of findings, can rule in osteoporosis or spinal fracture without further testing, a physical examination can raise or lower clinical suspicion and provide important data as to the strength of a recommendation for further evaluation.

Table 3. NAMS Recommendations for Fall Prevention[4]
Lighting • Provide ample lighting • Have easy-to-locate light switches for rooms and stairs • Use night lights to illuminate walkways
Obstructions • Remove clutter, low-lying objects • Remove raised door sills to ensure smooth transition
Floors and carpets • Provide nonskid rugs on slippery floors • Repair/replace worn, buckled, or curled carpet • Use nonskid floor wax
Furniture • Arrange furniture to ensure clear pathways • Remove or avoid low chairs and armless chairs • Adjust bed height if too high or low
Storage • Install shelves and cupboards at accessible height • Keep frequently used items at waist height
Bathroom • Install grab bars in tub, shower, near toilet • Use chair in shower and tub • Install nonskid strips/decals in tub/shower • Elevate low toilet seat or install safety frame
Stairways and halls • Install handrails on both sides of stairs • Remove or tape down throw rugs and runners • Repair loose and broken steps • Install nonskid treads on steps

Some pieces for physicians to consider include the following:

Thoracic Fracture: An occult thoracic fracture may be suspected if the measured distance from the wall to the a patient's occiput (wall-occiput distance) is greater than zero centimeters when the patient is standing with both heels touching the wall.[48]

Lumbar Fracture: An occult lumbar fracture may be suspected if the distance between the inferior margin of the ribs and the iliac crest, called the rib-pelvis distance, is less than 2 fingerbreadths.[48]

Height Loss: A 2005 study by Kerry Siminoski, MD, and colleagues from the University of Alberta, Edmonton, Canada, evaluated the relationship between height loss and vertebral-fracture risk in 985 postmenopausal women.[49] Dr Siminoski concluded that a height loss of greater than 2.0 cm over 3 years was 35.5% sensitive and 93.6% specific for detecting new fractures when compared against radiographic morphometry.

Physical Characteristics: Osteoporosis risk also increases if a person has fewer than 20 teeth because this may indicate bone resorption in the jaw, which may indicate body-wide bone resorption and osteoporosis. It also increases if a person has a self-reported kyphosis or weighs less than 51 kg (approximately 112 pounds*).[48] For a list of these physical examination risk factors, see Table 4.

Now that you are aware of the complex issues surrounding osteoporosis, including the building blocks that influence bone

*Low weight is an accepted risk factor for osteoporotic fractures, but there is a discrepancy between the weight NAMS thinks is too low (127 lbs [57.7 kg]) and the weight reported in *JAMA* as too low (112 lbs [51 kg]). Clinicians are advised to judge on a case by case basis and to err on the side of caution.

Table 4. Physical Examination Maneuvers Suggesting Presence of Osteoporosis or Spinal Fractures[48,49]
Wall-occiput Distance Inability to touch occiput to the wall when standing with back and heels to the wall
Weight Less than 51 kg (approximately 112 pounds)
Height Loss of ≤ 2.0 cm over 1-3 years
Rib-Pelvis Distance Less than 2 fingerbreadths between the inferior margin of the ribs and the superior surface of the pelvis in the midaxillary line
Tooth Count Fewer than 20 teeth
Self-reported Humped Back Patient report that back has become humped

and the risk factors for osteoporotic fractures, in the next issue we will discuss pharmacological and nutritional therapies for treating the disease.

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