

Osteoporosis: The Need for Prevention and Treatment

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ABSTRACT

Osteoporosis is a preventable, potentially crippling disease characterized by low bone density and increased bone fragility that affects millions of people. The seeds of this pernicious disease are sown during adolescence, when the skeleton is most active in absorbing dietary calcium and building up nearly all the bone mass that will carry the teenager throughout life. Dietary intake of calcium, vitamin D and vitamin K, particularly vitamin K2, is critical during this life stage for optimal bone growth; unfortunately, the majority of adolescents in the USA do not consume adequate amounts. In addition, many adolescents are now using oral contraceptives or intrauterine devices that prevent ovulation, thus inhibiting formation of progesterone required for the development of osteoblasts. Oral contraceptives also lower blood levels of vitamins B6 and B12, both of which are necessary to prevent elevated levels of homocysteine, whose impact on bone can be significant. In addition to “the pill,” many commonly prescribed medications disrupt normal bone remodeling and promote osteoporosis. Other remediable factors that cause excessive bone loss include insufficiencies of key nutrients, such as vitamin D3, vitamin K2, and calcium, required for healthy bone remodeling. It is important to recognize key risk factors and manage those that can be modified to prevent disease and/or minimize risk of fracture. This article presents an overview of osteoporosis, pathophysiology of disease, diagnostic tests, risk factors, and clinical recommendations for healthy bones.

Keywords: Osteoporosis; Osteopenia; Treatment

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INTRODUCTION

Osteoporosis is a common, chronic, potentially crippling, and debilitating disease marked by decreased bone mass and deterioration of bone tissue. It is caused by an imbalance in bone remodeling, resulting in increased risk of fracture. Osteoporosis affects an estimated 10 million people in the USA, and is expected to increase with an aging population.¹ Several million more Americans have osteopenia (low bone mass) and are at increased risk of developing osteoporosis. Combined prevalence of osteoporosis and osteopenia is estimated to be 44 million American women and men,¹ accounting for 55% of the population who are aged 50 years and older.

It is estimated that approximately one in every five US residents will be ≥ 65 years of age by the year 2030. The prevalence of osteoporosis and associated fractures is also expected to increase due to increases in life expectancy and an aging population, resulting in substantial increases in cost to Medicare and Medicaid in the USA and other healthcare programs across the globe.

The economic burden of osteoporosis is mainly attributable to the increased risk for fractures. Worldwide, it has been estimated that the prevalence of osteoporosis-related fractures is 56 million people, of which 2 million occur in the USA.^{1,2} Fractures resulting from osteoporosis are a major public health concern that has an associated direct and indirect cost reported to be between US\$17 and \$20 billion annually in the USA.³ By 2025, the cost of fractures related to osteoporosis is expected to rise to US\$25.3 billion.⁴ Fractures most often occur in the wrist, hip, and spine. Hip fractures are reported to be the most expensive type of fracture (US\$8,358–\$32,195 each), whereas fractures of the forearm or wrist are the least expensive to treat (US\$1,855–\$12,136 each).⁵ Aside from the burden on the healthcare system, fractures are also associated with disability,^{6,7} psychological deterioration,^{8,9} chronic pain,¹⁰ and increased mortality.^{11–14} Furthermore, vertebral fractures, specifically, can lead to stooped posture and a decline in height.¹⁰ Rates of disability are high in patients with hip fractures, with 50% of patients never being able to

walk again without assistance^{15,16} and 25% requiring long-term care.¹⁶ Of greater concern is the fact that the 5-year mortality rate after a hip or vertebral fracture is approximately 20% greater than that for an age-matched, non-osteoporotic population, and increases if a second fracture occurs. Men fare worse than women; a woman's risk of death doubles after a hip fracture; a man's risk more than triples.¹¹

Osteoporosis is a preventable and treatable disease; however, adherence to treatment protocols is poor, possibly due to potential adverse effects associated with medication use, personal understanding of the disease, and willingness to take medication, both because the disease is initially asymptomatic and also because of increased awareness of adverse side effects of current medications. It has become widely known that bisphosphonates and denosumab may cause fragility fractures in as little as 2 years, and that these medications may also cause numerous other adverse effects including osteonecrosis of the jaw, atrial fibrillation, and an increased risk of esophageal cancer. Teriparatide is now known to cause elevated cortisol levels, which promotes bone loss, and also carries lifetime increased risk for osteosarcoma. Even if an individual experiences none of the adverse effects caused by these medications, their maximum recommended usage span is only 3–5 years, whereas bone remodeling is a life-long process with approximately 10% of the skeleton undergoing renewal at all times.¹⁷ Some accept osteoporosis as a consequence of aging,¹⁸ whereas others confuse it with osteoarthritis.¹⁹ Furthermore, although elderly men represent a population at risk for osteoporosis, <10% of those affected receive treatment,²⁰ as few physicians check men's bone mineral density (BMD) because it is assumed that osteoporosis is not of concern for men. Denosumab and teriparatide are now being heavily marketed as preventive therapy for men, which is likely to increase awareness of men's risk for osteoporosis.^{21–24} Although much focus is placed on postmenopausal women due to the highest incidence of disease in this age group, osteoporosis also affects premenopausal women, men, and adolescents.²⁵ Men account for nearly 40% of new osteoporotic fractures occurring worldwide.² Onset

in men generally occurs 5 to 10 years later than in women and they have greater morbidity and mortality as a result of fractures than women.^{26–28} The risk for lifetime fracture is 50% for women and 13–25% for men, which may be attributable to later onset of disease and shorter life expectancy in men.

There are two types of osteoporosis, primary osteoporosis and secondary osteoporosis. Primary osteoporosis is characterized by problems in the bones themselves. Primary osteoporosis includes Type I (postmenopausal), Type II (elderly women and men), and idiopathic (adult and juvenile women and men). Secondary osteoporosis, also known as Type II, is characterized by bone loss due to another underlying condition, such as hyperthyroidism or Cushing's disease. Type II includes bone loss due to any specific condition, including marrow disorders, endocrine disorders, cancer, gastrointestinal or renal disorders, and side effects of medications.²⁹

Although the highest incidence of disease actually appears in menopause and later life stages, prevention best occurs during the adolescent stage when the foundation is laid for bone growth and development. During adolescent years, the skeletal system is highly active in the body, absorbing dietary calcium and providing for the bone mass that will be required for life; 90% of adult bone mass is acquired during adolescence. Although 60–80% of the amount of peak bone mass achieved is predetermined by genetics,³⁰ the final amount is influenced by environmental, health, and lifestyle factors.

BONE REMODELING AND REPAIR

Bone is a dynamic system involving remodeling and repair. These continuous processes are facilitated through resorption and formation directed by specific cell types within the bone. The purpose of resorption and formation is to regulate calcium homeostasis, and repair mechanical load-induced micro-fractures, preventing accumulation of excess old bone. Resorption is controlled by osteoclasts, and formation is controlled by osteoblasts. Parathyroid hormone (PTH) and PTH-related protein are influenced by the presence of nutritional calcium and its absorption via the effects of vitamin D, and control the lifespan of osteoblasts.³¹ The

rate of bone formation is dependent on individual osteoblast activity, lifespan of the osteoblasts, and number of precursor cells recruited. Expression of receptor activator of nuclear factor κ -B (RANK) ligand (RANKL) by osteoblasts activates RANK on osteoclast cells, which leads to their proliferation, maturation, activation, and lifespan, ultimately resulting in bone resorption.^{31, 32}

Osteocytes, the cell type into which osteoblasts develop when they become trapped in the bone matrix they have secreted, are the most common cell in bone tissue. Although their specific role and mechanisms of action are not yet fully understood, it appears that they play a key role in regulating phosphate metabolism and perhaps control bone remodeling.³¹

RISK FACTORS

Numerous risk factors for osteoporosis have been identified (Table 1) and include gender (with females being at greater risk than males); smoking; a number of prescription and over-the-counter medications; family history of osteoporosis; ethnicity; nutrient insufficiencies, particularly inadequate calcium, magnesium, vitamin D, and vitamin K2 intake; low estrogen or progesterone levels in women and low testosterone levels in men. Sufficiency of vitamin D, vitamin K2, calcium, and magnesium; healthy digestive function; and regular weight-bearing exercise are key factors in achieving optimal skeletal health.

THE SEEDS OF OSTEOPOROSIS ARE SOWN IN ADOLESCENCE

Osteoporosis is a preventable, potentially crippling disease characterized by low bone density and increased bone fragility that affects millions of people. The seeds of this pernicious disease are sown during adolescence, when the skeleton is most active in absorbing dietary calcium and building up nearly all the bone mass that will carry the teenager throughout life. Dietary intake of calcium is critical during this life stage for optimal bone growth; unfortunately, the majority of adolescents in the USA do not consume adequate amounts. Along with calcium, both vitamin D and vitamin K (particularly

Table 1: Major and minor risk factors for osteoporosis.³²

Major risk factors	Minor risk factors
Vertebral compression fracture	Rheumatoid arthritis
Fragility fracture after age 40 years	Past history of hyperthyroidism
Family history of osteoporotic fracture	Chronic anticonvulsant therapy
Systemic glucocorticoid therapy lasting >3 months	Low dietary calcium intake
Malabsorption syndrome	Smoking
Primary hyperparathyroidism	Excessive alcohol intake
Propensity to fall	Excessive caffeine intake
Osteopenia apparent on X-ray film	Weight <57 kg
Hypogonadism	Weight loss >10% of weight at age 25 years
Early menopause (before age 45 years)	Chronic heparin therapy

vitamin K2) are essential for bone formation. A number of recent investigations have shown a high prevalence of low vitamin D status in the US population, especially in adolescents, during the winter.³³ Little research has been done to evaluate adolescents' vitamin K requirements for optimal bone development, but recent papers indicate that vitamin K status plays an important role in children's bone health,³⁴ and that bone metabolism requires significantly more vitamin K than blood coagulation.³⁵ Given the abysmally low intake of foods rich in vitamin K in the US population, for example, broccoli, leafy greens, and unhydrogenated vegetable oils (hydrogenation detrimentally changes the chemical structure of vitamin K), vitamin K insufficiency in adolescents is very high. Research evaluating vitamin K intake found that only half the females age 13 and over and less than half the males got the recommended daily allowance of vitamin K, which recent evidence suggests is not sufficient for maximizing the function of vitamin K in bones.³⁶

In addition, many adolescents are now using oral contraceptives. Whether a combination of a patented version of estradiol plus progestin or a progestogen-only "mini-pill" is taken, either form of birth control pill inhibits follicular development and prevents ovulation, thus inhibiting production of progesterone, which is primarily produced as a result of ovulation and is required for the development of osteoblasts. Oral contraceptives also lower blood levels of vitamins B6 and B12, both of which are necessary to prevent elevated

levels of homocysteine. Homocysteine interferes with collagen crosslinking, and its impact on bone can be significant. In the elderly, elevated levels of homocysteine have been found to increase risk of hip fracture by 70%.^{37, 38} One of the most recently developed contraceptives, now being used in women as young as 14 years of age, is an intrauterine device containing a progestin (levonorgestrel) marketed under the trade name, Mirena®. Mirena® not only prevents ovulation but also causes amenorrhea in the majority of the young, premenopausal and perimenopausal women in whom it has been inserted. A recent meta-analysis has estimated a BMD increase of 0.5% per year in women with normal ovulation, but a decrease in BMD of 0.7% per year in young women with ovulatory disturbances (anovulation or short luteal phase). The use of progestins inhibits ovulation. Because the span of years from adolescence when menstruation begins through to the early 30s are the years when women are supposed to be building up peak bone mass, use of progestins may be setting up this generation of young women for early and severe osteoporosis.³⁹⁻⁴¹

COMMONLY PRESCRIBED MEDICATIONS

Many commonly prescribed medications disrupt normal bone remodeling and promote osteoporosis. These include benzodiazepines used to manage epilepsy, anxiety, insomnia, depression, schizophrenia, and restless leg syndrome; selective serotonin reuptake inhibitors and atypical antipsychotics used to manage anxiety and depression;

thiazolidinediones prescribed to manage type 2 diabetes; opioids (e.g., morphine, codeine, hydrocodone, oxycodone, methadone, tramadol) used to manage chronic pain; glucocorticoids (e.g., prednisone, prednisolone, kenalog, dexamethasone) used to manage allergies, asthma and autoimmune diseases; and antacids, histamine H₂-receptor blockers, proton-pump inhibitors used to manage indigestion and gastroesophageal reflux disease (GERD).^{42–65}

GENDER

Up to 90% of peak bone mass is acquired by age 18 in girls and by age 20 in boys, but bone mass continues to accrue until around age 30. At that point, bones have reached their maximum strength and density, that is, peak bone mass.⁶⁶ Sex steroids, especially during puberty, play an important role in bone growth and maintenance. During puberty, hormone activity plays an important role in bone growth. It has been suggested that females gain more bone mineral content per lean body mass than males during puberty to compensate for declines during pregnancy and lactation.⁶⁷

During adolescence, there is greater formation than resorption, leading to increased bone mineral content. In early adult years, there is minimal net gain or loss of bone mineral content. Mid-life, a shift occurs towards greater resorption than formation, which results in a net loss of bone mineral content. In women, the most rapid loss is observed with the rapid decline in estrogen associated with onset of menopause. This occurs 1 year prior to the final menses and lasts for approximately 3 years. The decrease in estrogen levels results in increased bone resorption and decreased deposition of new bone mineral in these women. The combination of early bone mineral loss and increased life expectancy in women compared with men puts women at increased risk of osteoporosis over men.

The genetic determinants appear to vary between men and women. One study identified possible sex-specific quantitative trait loci in men and found that loci on chromosomes 7, 14, and 21 were specific to men, whereas chromosomes 4, 19, and 22 were shared between the genders, suggesting a complex role for genetics in BMD.⁶⁸

ETHNICITY

In the National Health and Nutrition Examination Survey (NHANES; 2005–2006), it was reported that ethnic background is a factor related to BMD. BMD was found to be highest in African American women, lower in Mexican American women, and lowest in Caucasian American women.⁶⁹ These differences may, in part, be due to cultural differences with respect to dietary patterns, environmental factors, and lifestyle.

FAMILY HISTORY OF OSTEOPOROSIS

The NHANES (1999–2004) collected information on osteoporosis in first-degree relatives and grandparents. This study found that there was a significant, independent association of family history and risk of osteoporosis in women age 35 years and older. Risk was found to increase with an increasing number of family relatives having osteoporosis.⁷⁰ This is not surprising because a number of single nucleotide polymorphisms (SNPs) that impact peak bone mass accrual and susceptibility to excessive bone loss have been identified. For example, bone formation is impacted by SNPs in genes that affect the synthesis of collagen (COL1A1), the metabolic actions of the hormones calcitonin (CALCR, calcitonin receptor), and vitamin D₃ (VDR, vitamin D₃ receptor). Bone resorption increases in response to chronic inflammation and is therefore affected by SNPs that result in increased production of the inflammatory cytokines, interleukin-6 (IL-6) and tumor necrosis factor (TNF)- α .⁷¹

DIETARY VITAMIN D AND CALCIUM INTAKE

Nutritional intake plays a role in the rate of bone loss and overall bone mass. Among the various nutrients believed to play a role in bone metabolism are vitamin D, vitamin K (particularly K₂, but also K₁), vitamin C, B vitamins, essential fatty acids, calcium, magnesium, and numerous trace minerals. In the body, vitamin D is involved in the absorption of calcium from the intestine, regulation of calcium metabolism,⁷² and utilization of calcium by bone.

As such, vitamin D deficiency is a significant risk factor for development of osteoporosis.⁷³ Numerous studies published over the past 20 years have shown that risk of osteoporotic fracture is lessened in postmenopausal women given supplemental calcium and vitamin D.^{74–79}

Most of the research has been done using both calcium and vitamin D, but even studies using vitamin D3 alone have found that supplementation reduces the risk of hip fracture. In one such study, 700 IU/day of vitamin D3 alone reduced the rate of hip fracture in elderly women (average age 84 years) by nearly 60% – from 1.3% to 0.5%.⁸⁰ A meta-analysis found that supplementation with 700–800 IU/day of vitamin D lowered the risk of hip and non-vertebral fractures. This appeared to be dose-dependent, as 400 IU/day did not offer this protection.⁸¹ However, a recent study found that supplementation with a high dose of vitamin D (6,500 IU/day) provided no additional benefits to BMD when compared with 800 IU/day in vitamin D-replete postmenopausal women.⁸² This may have been due to the fact that these women were given no supplemental vitamin K, specifically, vitamin K2 (discussed below). In brief, vitamin D increases the absorption of calcium but does nothing to regulate its use in the body. This is the purview of osteocalcin and matrix Gla protein, both of which require vitamin K2 for their carboxylation (activation).

In addition to its effect on BMD, vitamin D supplementation has been shown to reduce the risk of falls by 22%, possibly by improving body sway and lower body strength.⁸³ Preventing falls is key in protecting at-risk patients from fractures.

Optimal circulating levels of 25-hydroxyvitamin D [25(OH)D] for prevention of falls and reduced risk of fracture are now thought to be ≥ 125 nmol/L to 200 nmol/L (this is the equivalent of 60 ng/mL to 80 ng/mL). Levels at the higher end of this range are warranted in the summer to allow for decreases associated with reduced amounts obtained from sunlight in the winter months in the Northern hemisphere. Deficiency is defined as blood levels of < 75 nmol/L (30 ng/mL) by the Vitamin D Council, as < 20 ng/mL by the Endocrine Society, and as < 11 ng/mL by the Food and Nutrition Board.⁸⁴

Calcium is an essential mineral for a wide range of bodily functions, including vascular contraction,

vasodilation, hormone secretion, and intracellular signaling, among others. These processes require $< 1\%$ of the total amount of calcium found in the body. The remainder is stored in bone tissue where it supports the structure and function of bones and teeth.

When calcium excretion exceeds calcium absorption, an imbalance leading to low calcium levels in the blood occurs. Hormones play an important role in regulating blood calcium homeostasis. The three major hormones involved are PTH, calcitonin, and 1,25-dihydroxyvitamin D3 [1,25(OH)2D3]. The parathyroid gland is stimulated to secrete PTH in response to a decrease in blood calcium levels. The increase in PTH prompts a release of calcium from the skeletal system, kidneys, and intestines. Increases in PTH levels in the blood stimulate osteoclasts to release calcium from the bone, which, if chronic, leads to bone loss over time. Once blood calcium levels are restored, PTH decreases, resulting in closure of the feedback loop.⁸⁵ (It should be noted that one of the concerns regarding the use of teriparatide is that this medication, a fragment of human parathyroid hormone, is injected daily to cause intermittent elevations in PTH, which also increase osteoblast activity. It is hypothesized that the osteoblast activation caused by teriparatide will outpace osteoclast activation resulting in a net anabolic effect on bone; however, use of this medication is limited to 2–3 years because of its adverse effects and concerns that it may promote later development of osteosarcoma.)^{86, 87}

HOMOCYSTEINE

Elevated plasma homocysteine levels are associated with oxidative stress, increased bone turnover, and increased risk of fractures.^{88–91} Patients with osteoporosis have an imbalance in oxidative and antioxidative markers.⁹² Antioxidants protect the body from free radical-mediated receptor damage, and their protective effects are well documented.^{93, 94} Consensus has not been reached regarding the effects of high homocysteine plasma concentrations on BMD. Whereas some researchers have found no relationship between homocysteine and BMD,⁹⁰ others have suggested an association between homocysteine and BMD,^{92, 95–97} and BMD has been shown

to be negatively affected by homocysteine in a number of studies.^{89, 98–101} Riboflavin (vitamin B2), pyridoxine (vitamin B6), folic acid (vitamin B9), and cobalamin (vitamin B12) are cofactors or substrates involved in homocysteine metabolism and may play a beneficial role in regulating plasma homocysteine levels.^{102, 103}

LOW LEVELS OF ESTROGEN AND PROGESTERONE IN WOMEN

Estrogen appears to be one of the main hormones associated with bone health in both males and females, and is a critical factor in bone maturation. The decline of estrogen in later life stages, especially the rapid drop that occurs during menopause, is associated with a decline in BMD. Declines in estrogen and BMD have also been associated with anorexia, lactation, and prolonged use of certain medications.¹⁰⁴

Estrogen acts through several mechanisms on different cell types in order to regulate BMD. Estrogen decreases osteoclastogenic cytokines and induces osteoclast apoptosis, thereby reducing the negative effects of osteoclasts. Although the beneficial effects of estrogen on bone are not completely understood, there are several hypotheses on how estrogen controls osteoclastogenic cytokines. Furthermore, estrogen also collaborates with progesterone to increase osteoblast activity, promoting bone formation. The differentiation of human osteoblasts is dependent on progesterone, and estrogen increases osteoblast activity.^{40, 105}

The drop in estrogen production that accompanies menopause is only part of the pathophysiology of osteoporosis. Reactive oxygen species (ROS)¹⁰⁶ also play a role in increasing the rate of resorption and decreasing the formation of osteoblasts. Recent studies have shown that lipopolysaccharide and inflammatory cytokines, such as TNF receptor- α and IL-1, directly regulate osteoclast differentiation and function. In other words, not just the lessening of the anti-inflammatory actions of estrogen that occurs with menopause but also all factors that promote chronic inflammation increase osteoclast differentiation and activity.^{107, 108} Further research is required to elucidate the role of ROS in the pathogenesis of osteoporosis.

The Women's Health Initiative (WHI) study found that hormone replacement therapy (HRT) prevented bone fractures.^{109, 110} However, increased awareness of serious side effects such as breast cancer, heart disease, and stroke, associated with prolonged use of HRT have led to their decreased use. The conjugated equine estrogens (CEEs) and progestins used in HRT, however, have significantly different chemical structures from human bioidentical estrogens and progesterone. A recent review of published papers identified from PubMed/MEDLINE, Google Scholar, and Cochrane databases that compared the effects of bioidentical and synthetic hormones, including clinical outcomes and *in vitro* results, revealed that physiological data and clinical outcomes demonstrate that bioidentical hormones are associated with lower risks, including the risk of breast cancer and cardiovascular disease, and are more efficacious than their synthetic and animal-derived counterparts. Bioidentical HRT should be considered in women at high risk of osteoporotic fracture.¹¹¹

SEX HORMONES IN MEN

The most predominant factors contributing to osteoporosis in men include genetic factors; alterations in sex hormone levels, with fracture risk attributable to estradiol and sex hormone binding globulin (SHBG) levels; failure of timely and complete pubertal development; and diseases causing secondary osteoporosis.^{112, 113} Other major causes of secondary osteoporosis include smoking, alcohol abuse, glucocorticoid excess (endogenous or exogenous), and hypogonadism (often due to hormone suppression therapy). Osteoporosis in men can also occur due to hypogonadism before puberty and failure of timely and complete pubertal development, leading to reduced bone mass and size as a result of insufficient exposure to androgens and estrogens. However, this can be reversed through restoration of serum testosterone levels. Acquired hypogonadism in adults is associated with increased bone turnover and acceleration of bone loss. Testosterone substitution is usually indicated in all cases of hypogonadism and is reported to decrease bone turnover and prevent additional bone loss, and, perhaps, increase BMD in some patients.^{112, 114–116} As

it is well established that estradiol plays a key role in regulating bone homeostasis, and treatment with testosterone has not yet been linked to decreased risk of fracture, treatment should include established treatments with or without testosterone.

SMOKING

Studies have suggested that smoking, including passive smoking, is a risk factor for low BMD.^{117–119} The effect of smoking is directly related to the amount smoked (or the amount of second-hand exposure) and body weight, with more frequent users and those with lower body weight having greatest loss of BMD.^{117, 120} The mechanisms involved in pathogenesis of osteoporosis in smokers involve multiple changes within the body, including decreased intestinal calcium absorption¹²¹ and alteration of metabolism of several hormones, including calcitropic hormone,¹²² estradiol,^{123–125} adrenal corticoid hormone, or effects on the RANK-RANKL-osteoprotegerin (OPG) system,^{126, 127} collagen metabolism,¹²⁸ and bone angiogenesis.¹²⁹ The effects of two key components in cigarette smoke, cadmium and nicotine, provide insight into smoking and is so detrimental to bone. Cadmium stimulates the formation and activity of osteoclasts and inhibits inactivation of cortisol (chronically elevated cortisol destroys osteocytes). Nicotine depresses osteoblast activity and increases hepatic clearance of estrogen; women who smoke enter menopause up to 2 years earlier than their non-smoking peers.^{120, 130–132}

DIAGNOSTIC PROCEDURES FOR DETERMINING BONE DENSITY AND FUTURE FRACTURE RISK

BONE MINERAL DENSITY MEASUREMENT

BMD measurement is a clinical tool that can diagnose osteoporosis or bone weakness before the first fracture occurs. It is most effective in determining risk when clinical risk factors are also taken into account. Ideally, BMD should be evaluated around age 35 years, the age at which peak bone mass

should be present, both to establish a reference point and to identify those who have not built up adequate reserves to safely transition through menopause. It is important that BMD measurement is performed in women at onset of menopause and at regular intervals thereafter to monitor changes in bone density. During the transition through menopause, estrogen levels decline rapidly, and bone loss is greatest. Although osteoporosis is generally associated with postmenopausal women, it also affects men. However, owing to the later onset of andropause and shorter life span in men, the risk for lifetime fracture is greater in women than in men. Bioidentical HRT should be considered in both men and women at high risk of excessive bone loss, particularly in those using medications that promote bone loss.¹³³

Generally there are no visible symptoms of osteoporosis until the time of fracture. BMD measurement is the most widely recommended clinical tool for diagnosing patients at high risk of fracture before the first fracture occurs. Dual-energy X-ray absorptiometry (DXA) is the “gold standard” for measuring BMD because there is a strong correlation between BMD and bone strength, the test has a high degree of accuracy and precision, and radiation exposure is very low. Currently, DXA is the only validated method for diagnosing osteoporosis.

The use of DXA to measure BMD involves ionizing radiation with photon beams of two different energy levels. The differences in attenuation of the beams passing through body tissues of variable composition allow the instrument to provide a quantitative measurement of bone density. Other technologies, such as quantitative ultrasound (QUS), measure properties of bone strength at peripheral skeletal sites (e.g., the calcaneus). Although QUS-derived values correlate well with fracture risk, at this time they cannot be used with the World Health Organization (WHO) criteria for diagnosing osteoporosis and are not clinically useful for monitoring changes in response to therapy.

Anyone at risk for fracture should be considered for BMD measurement, provided the results are likely to influence patient management decisions. Of the many guidelines for ordering BMD measurement, those of the International Society for Clinical Densitometry (ISCD) are the most comprehensive.¹³⁴ Most guidelines are in agreement that

women over the age of 65 years and those under 65 years with risk factors should be considered for BMD measurement.

Results of DXA testing are reported as standardized values expressed as T-scores and Z-scores. Both of these rely on standard deviation (SD) variability, that is, the patient's BMD compared with the mean BMD of a young adult reference (T-score) and an age-matched population (Z-score). The T-score is then used with the WHO criteria to classify the patient as having a normal BMD, low bone mass (osteopenia), osteoporosis, or severe osteoporosis. The ISCD recommends that patients undergoing DXA be routinely measured at the lumbar spine and hip, and at the non-dominant forearm if indicated (e.g., obesity exceeding the weight limit of table, hyperparathyroidism, and spine or hip invalid for measuring BMD). The lowest T-score of the lumbar spine, total proximal femur, femoral neck, or 33% radius (if measured) should be used for diagnostic calculation.

The prediction of fracture risk is greatly enhanced by combining BMD results with clinical risk factors for fracture. Many clinical risk factors for hip fracture have been identified, including personal history of any type of fracture after age 50 years, maternal history of hip fracture, self-rated fair or poor health, and difficulty rising from a chair. The best validated risk factors for vertebral fractures are low BMD, advanced age, and previous fracture of any type.^{135, 136} Methodologies are currently under development to combine T-scores with clinical risk factors to provide an estimate of the 10-year probability of fracture, which may then be considered with DXA findings to help determine whether the patient is likely to benefit from pharmacological therapy.

Risk should be assessed using the fracture risk algorithms (FRAX) scoring system. FRAX is more accurate at predicting the risk of hip fracture than bone density alone and is used to predict risk of occurrence in the next 10 years. FRAX is a validated algorithm incorporating clinical risk factors which include gender, age, body mass index, previous fragility fracture, parental hip fracture, corticosteroid use, alcohol intake (>3 drinks per day), smoking status, rheumatoid arthritis, and other secondary causes of osteoporosis. In the USA, FRAX is most often used to make decisions

regarding treatment course when a patient's BMD scores indicate low bone mass (osteopenia). Current clinical guidelines suggest treatment initiation when there is a 3% risk of hip fracture or 20% risk of major fracture (i.e., fracture of forearm, hip, shoulder, or spine) in the next 10 years.¹⁰⁴

VERTEBRAL FRACTURE ASSESSMENT

Vertebral fracture assessment (VFA) is a spinal image that can be obtained by DXA at the same time as BMD is measured. Compared with standard spinal radiography, it exposes the patient to a lower dose of ionizing radiation, has lower associated costs, is more convenient for the patient, and offers good diagnostic sensitivity and specificity. Interpretation of VFA requires special training – especially for non-radiologists – which is provided by organizations such as the ISCD. Previously unrecognized vertebral fractures may be detected by VFA, possibly altering the patient's diagnostic classification, fracture risk level, and management.

BONE TURNOVER MARKERS

Bone turnover markers (BTMs) are byproducts of bone resorption and bone formation that can be assessed in the blood and urine. Although they are not useful in the diagnosis of osteoporosis, they are helpful in the research setting to provide a better understanding of the pathogenesis of osteoporosis and the mechanism of action of therapeutic agents. In clinical practice, BTMs potentially play a role in the assessment of fracture risk and in monitoring the effects of therapy on bone remodeling. BTM changes can be detected earlier than changes in BMD.

The BTMs most commonly used in clinical practice are markers of bone resorption, N-telopeptide (NTx), and C-telopeptide (CTX), which can be measured in serum or urine. CTX, specifically the newer serum test, has been shown to be the most accurate of currently available tests.¹³⁷ The preferred method for measuring NTx is with a fasting serum specimen, which is easier to collect

than a time urine specimen and has less variability. Procollagen type 1 intact N-terminal peptide is a serum marker of bone formation that may have clinical utility in predicting BMD response to treatment with the anabolic agent teriparatide.

Elevated BTM values suggest a high bone turnover rate, which is a risk factor for fracture independent of BMD. Failure to suppress BTMs with antiresorptive drugs suggest poor patient compliance, inadequate drug absorption, or the presence of a disorder/disease that is increasing bone turnover and overwhelming the effect of the drug. Failure to elicit a positive response to antiresorptive medications could also indicate that the patient is deficient in one or more nutrients required for bone remodeling, that their digestive function is impaired or that they are highly inflammatory for other reasons, such as heavy metal toxicity or environmental chemical exposures. In the recently published Combination of Micronutrients for Bone (COMB) study, patients who had “failed” antiresorptive drug therapy were able to build bone with a natural approach supplying key nutrients, a healthy diet, and weight bearing exercise.¹³⁸

CLINICAL RECOMMENDATIONS

Three key lifestyle changes may help reduce the risk of osteoporosis and resulting fractures. These include: proper nutrition (eating as well as dietary supplementation), exercise, and monitoring and awareness of bone health.

NUTRITION AND SUPPLEMENTATION FOR HEALTHY BONES

Calcium, Vitamin D, and Vitamin K2

Calcium, vitamin D, and vitamin K2 are three key nutrients required for maintaining healthy bones. The Food and Nutrition Board identify daily requirements for calcium of 1300 mg/day for children and adolescents aged 9–18 years, and 1,000 mg/day for 19–50 year olds.¹³⁹ Daily requirements for men continue to be 1,000 mg/day until age 70 years. For women over 50 years of age, daily requirements increase to 1,200 g/day. After age 70 years, the male requirement equals that of women at 1200 mg/day.

It is essential that calcium be taken with both vitamin D and vitamin K2 for fracture prevention. Vitamin D increases absorption of calcium from the intestines but does nothing to regulate where that calcium will be deposited; this is the purview of vitamin K2, which is required for the carboxylation of the vitamin K-dependent proteins, including osteocalcin and matrix Gla protein. Osteocalcin pulls calcium into bone; matrix Gla protein prevents the deposition of calcium in soft tissue, for example, arteries, kidneys, brain, breasts. Daily requirements for vitamin D are 600 IU/day from age 1 through to age 70 years, with an increase to 800 IU/day after age 70 years.¹³⁹ These recommendations differ slightly to those suggested by the National Osteoporosis Foundation, who suggest that after the age of 50 years, vitamin D should be increased to 1,000 IU/day. Beneficial effects on risk of fracture have been seen with vitamin D supplementation of at least 800 IU/day and total daily intake of calcium of 1 g/day.¹⁴⁰ Other authorities suggest that vitamin D intake be significantly higher: at least 2,000 IU per day (2500–5000 IU for maintenance of ideal D3 range of 60–80; if D3 less than 10, then recommend using 10,000–20,000 IU for 3–6 months until optimal range obtained, then use maintenance dose). The only way to accurately identify the individual patient’s requirements for vitamin D is to check serum levels of 25(OH)D and supplement accordingly. Optimal levels of 25(OH)D are 60–80 ng/mL. The Vitamin D Council recommends prescribing 5,000 IU/day of D3 and retesting after 3 months.¹⁴¹

One should aim to obtain the recommended amounts of calcium from the diet, but where this cannot be achieved, supplements offer a viable alternative. Calcium is readily abundant in dairy products, broccoli, kale, tofu, and canned salmon with bones. Additionally, many juices and cereals are now fortified with calcium to promote consumption of this important mineral. A diet rich in these foods along with fruit and vegetables high in calcium is important for promoting bone health.

To maintain adequate intake of calcium and prevent osteoporosis, supplementation is often required, as the modern North American diet provides inadequate levels of calcium.^{142, 143} In addition, particularly in the elderly, digestive function may be impaired. Calcium must be solubilized by stomach acid for absorption. Not only does hydrochloric

acid production lessen with age but also approximately 50% of the world's population is infected with *Helicobacter pylori*, which is commonly associated with hypochlorhydria and gastritis.^{144, 145} Furthermore, frequent use of antacids, H-2 blockers, or proton-pump inhibitors is not uncommon.

As calcium can interfere with iron absorption, timing of these supplements should be separated. In addition to vitamin D and calcium, the Framingham Osteoporosis Study found that vitamin B6 and vitamin B12 are also important in reducing the risk of bone fractures.^{38, 146}

Vitamin K

There are two major forms of vitamin K, phylloquinone (vitamin K1) and menaquinone (vitamin K2). Leafy green vegetables contain vitamin K1, whereas vitamin K2 is present in significant amounts in the fermented soybean product, natto, and in miniscule amounts in meat, eggs, and dairy products. In addition to its well-known role in coagulation, vitamin K1 is important for bone health as it greatly lessens the body's production of a wide range of proinflammatory agents, including IL-6, TNF, and C-reactive protein.¹⁴⁷ Insufficiency of vitamin K2 results in decreased carboxylation of osteocalcin, a vitamin K-dependent protein required for the deposition of calcium in bone,¹⁴⁸ and matrix Gla protein, a vitamin K-dependent protein that prevents and reverses calcium deposition in soft tissues, for example, the vasculature, kidneys, breasts, and brain.¹⁴⁹

Reports of vitamin K supplementation in the literature have been controversial, with some studies, utilizing vitamin K1, showing no effect on BMD,^{150–152} whereas others, utilizing vitamin K2 as either menatetrenone, a synthetic version of the short chain menaquinone-4 (MK-4), or MK-7, the long-chain menaquinone derived from natto, have had positive effects on hip BMD.^{153, 154}

Low vitamin K1 (phylloquinone) intake has been clearly associated with low BMD in women.¹⁵⁰ Further low serum vitamin K has been found in patients with osteoporosis, whereas high intake is associated with greater bone health.^{150, 151, 155} In healthy, peripubertal children, a better vitamin K status was associated with a more pronounced increase in bone mass.¹⁵⁶ There are two reasons

for the beneficial effects of vitamin K1 on bone: (1) as noted above, vitamin K1 has significant anti-inflammatory effects, and (2) when supplied in excess of the amount needed for carboxylation of clotting proteins, the remaining K1 will be converted to MK-4 and sent into the systemic circulation where it will activate vitamin K-dependent proteins, including osteocalcin and matrix Gla protein.

Menatetrenone (synthetic MK-4) has been shown in a large Phase IV clinical study to have a positive effect on BMD; however, smaller randomized controlled trials have failed to show similar effects.^{157, 158} The recommended dosage of MK-4 varies in the literature, with most studies using a dose of 45 mg/day,¹⁵⁹ (more precisely, 15 mg/tid, because MK-4 is incorporated into triglycerides and cleared within 8 h),¹⁶⁰ and others suggesting that low doses of menatetrenone positively influence serum osteocalcin concentrations, suggesting a role for low-dose therapy in bone health in postmenopausal women.¹⁶¹

In contrast to the rapid clearance of K1 and MK-4, the longer chain menaquinones are incorporated into low-density lipoprotein (LDL) cholesterol in the liver before being sent into the systemic circulation, giving these forms of K2 several day half-lives during which they can be used to build and maintain a reserve that promotes continuous availability for activation of the extrahepatic vitamin K-dependent proteins. Expressed as AUC (area under the concentration time curve) over 24 h, the availability of MK-7 is 2.5-fold better than that of K1; expressed as AUC over 96 h, it is 6-fold better. This greatly extended availability is what enables the long-chain MKs to optimize activation of extrahepatic vitamin K-dependent proteins at a dose that could feasibly be supplied by the diet (a serving of natto provides as much as 400 µg/day of MK-7) rather the pharmaceutical dose (15 mg tid, i.e., 45 mg/day) required to provide continuous availability of MK-4.^{162, 163}

Because MK-7 is incorporated into cholesterol and therefore remains available far longer (~3 days), a much lower dosage taken once daily is effective. Typical doses showing benefit in the research range from 100 µg/day to 180 µg/day, the amount used in the most recent studies on postmenopausal

osteoporosis,¹⁶⁴ to 360 µg/day, the dose showing benefit in clinical trials of hemodialysis patients.¹⁶⁵

Numerous studies have now shown that vitamin K2, as MK-4 and as MK-7, exerts beneficial effects on BMD.^{158, 166–171} The most recent relevant study was the 3-year clinical trial noted above in which low dose vitamin K2 in the form of MK-7 (180 µg/day) significantly attenuated bone loss in 244 postmenopausal women.¹⁷² Research is ongoing to clarify the most effective treatment protocol for vitamin K. As both phylloquinone and menaquinone exert separate beneficial effects on bone, both should be utilized as a prevention and therapy for osteoporosis.

Patients should be encouraged to eat a diet rich in both vitamin K1 and vitamin K2. The variation in study results is likely to be due to supplementation with varied dosages of vitamin K or the type of vitamin K (vitamin K1 vs. vitamin K2) supplemented; however, the totality of the evidence indicates a positive role for vitamin K in bone health.

Finally, the importance of adequate vitamin K2 in patients supplementing with calcium and vitamin D cannot be overemphasized. Two studies published in April 2011 underscore the importance to patient outcomes of an awareness of the role of K2 in regulating calcium deposition, and the requirement for K2 sufficient to balance the increased absorption of calcium that occurs when supplemental vitamin D is given. Both studies reported significant increased risk of adverse outcomes in women taking calcium supplements with or without vitamin D.

The first study, published in the *British Medical Journal*, was a 7-year, randomized, placebo-controlled trial of daily supplementation with calcium (1 g) and vitamin D (400 IU) in 36,282 postmenopausal women in the Women's Health Initiative (WHI) study. Meta-analysis of three placebo-controlled trials found that calcium and vitamin D increased risk of myocardial infarction by 24% and the composite of myocardial infarction or stroke by 15%. The following conclusion was drawn by Bolland *et al.*: "A reassessment of the role of calcium supplements in osteoporosis management is warranted."¹⁷³ The second paper, published in the *American Journal of Clinical Nutrition*, analyzed data collected on the same 36,282 postmenopausal women participating in the WHI study, this time in relation to whether calcium plus vitamin D

supplements increased risk of kidney stone formation. Unsurprisingly, a 17% excess in urinary tract stone incidence was noted in the women taking both supplements.¹⁷⁴ Had awareness of the role of vitamin K in regulating calcium been utilized, these highly negative outcomes could have easily been predicted – and, more importantly, avoided.

It is well known that vitamin D boosts the absorption of calcium from the intestines and its reabsorption from the kidneys, thus greatly enhancing levels of available calcium within the body. Less widely known is that vitamin D upregulates the expression of the vitamin K-dependent Gla proteins, whose activation depends on vitamin K-mediated carboxylation. Vitamin D thus increases both the demand for vitamin K and the potential for benefit from K-dependent proteins, including osteocalcin in bone and matrix Gla protein in the vasculature.¹⁷⁵

One potentially adverse repercussion of this is that by increasing the need for vitamin K2, increased levels of vitamin D may actually induce a functional vitamin K2 deficiency, with the result that levels of uncarboxylated osteocalcin (ucOC) and uncarboxylated matrix Gla protein (ucMGP) increase in the circulation and vasculature. In this case, not only is calcium not delivered to the bones, which become porous, but also it is deposited in the arteries, which become calcified, and overloads the kidneys, promoting stone formation. Vitamin D toxicity has been proposed to be the result of precisely such induction of vitamin K2 deficiency.¹⁶⁹ As vitamin D induces levels of Gla proteins to increase, the pool of available vitamin K available to carboxylate them becomes depleted, and thus vitamin K-dependent processes that retain minerals in the bone matrix that protect soft tissues from calcification can no longer be performed. The fact that warfarin, a coumadin derivative that induces a functional vitamin K deficiency, has definitively been shown to produce extensive hypervitaminosis D-like calcification of soft tissues, and to exert toxicity synergistically with vitamin D when the two are combined, supports this hypothesis. In addition, vitamin K alone has been shown to fully reverse the calcification induced by warfarin, both confirming that the drug's inhibition of vitamin K is directly responsible for its induction of calcification and also adding to the likelihood that vitamin D toxicity is due to the same or a similar mechanism.^{176, 177}

It is important to note that even very low dose MK-7 supplementation is inadvisable in patients on warfarin. In a recent small study ($n=18$), daily intakes of 10 and 20 μg of MK-7 were independently judged by two hematologists to cause a clinically relevant lowering of the INR (international national ratio) in at least 40% and 60% of subjects, respectively, and to significantly increase ETP (endogenous blood clot formation) by 20% and 30%, respectively. Even worse, these tiny doses of MK-7 had no beneficial effect on increasing carboxylation of circulating ucOC and desphospho-ucMGP. Virtually all the MK-7 was triaged to carboxylate prothrombin. The result was increased risk for blood clot formation with no benefit. Use of MK-7 supplements should be avoided in patients on vitamin K antagonist (VKA; warfarin) therapy.¹⁷⁸

A potential option is switching patients on warfarin to a recently approved class of anticoagulant drug called Xa inhibitors that act directly upon Factor X in the coagulation cascade, without using anti-thrombin as a mediator, and thus vitamin K does not lessen their anticlotting effects. The drawback for these drugs is that if the patient is unable to form clots when needed, giving vitamin K (which is used when needed to restore clotting in those on warfarin) will not be effective; thus, the Xa inhibitors carry a significant risk of mortality if excessive bleeding occurs. Xa inhibitor drugs, for example, rivaroxaban and apixaban, are taken orally, are well absorbed from the gut, and maximum inhibition of factor Xa occurs 4 h after a dose. The effects last 8–12 h, but factor Xa activity does not return to normal within 24 h, so once-daily dosing is possible. Unlike with warfarin, however, there is no safety net: no specific way to reverse the anticoagulant effect of rivaroxaban in the event of a major bleeding event. Nonetheless, because vitamin K insufficiency is certain to promote cardiovascular calcification and bone loss, the risk associated with Xa inhibitors is one that many are likely to find acceptable.^{179–181}

Magnesium

In vivo experiments have shown that insufficient magnesium intake is associated with bone loss¹⁸² and osteoporosis.^{183–186} This may be due to the role of magnesium in regulating calcium absorption [specifically, magnesium is a required co-factor in

350 enzymes, one of which is needed for the conversion of vitamin D in the kidneys into its most active, hormonal form, 1,25(OH)₂D₃]¹⁸⁷ and PTH secretion.^{188, 189} Magnesium deficiency leads to impairment of PTH release, which can lead to suppression of bone remodeling. Dietary recommendations for magnesium are 310–420 mg/day for adults; however, studies have indicated that less than half of the US population consumes adequate magnesium in their diet.¹⁹⁰ A few population studies have shown that osteoporotic postmenopausal women have low magnesium intake^{185, 191} and intake is associated with greater BMD.¹⁹² Few studies have investigated the role of magnesium in preventing osteoporosis and its role in bone health in humans. In one study in osteoporotic women, BMD was significantly increased with dietary magnesium supplementation (250 mg/day) compared with a placebo control group.¹⁹³

Manganese

Manganese is an important mineral required for bone matrix formation, as well as acting as a cofactor for bone tissue enzymes. Decreased plasma manganese has been associated with osteoporosis.¹⁹⁰ In a recent animal study, manganese supplementation resulted in increased BMD and increased bone formation, as documented by increased serum concentrations of osteocalcin. Although human clinical studies have not evaluated manganese alone as a supplement for bone health, a 2-year study on postmenopausal women found that manganese in combination with other minerals, including calcium, copper, and zinc, resulted in greater gains in bone compared with calcium alone.^{194–196} Gains in BMD are reported with daily intakes of 1.8 mg/day for women and 5 mg/day for men.¹⁹⁷ Men require more manganese as they do not absorb the trace mineral as well as women, which may be dependent on serum ferritin levels.

Strontium

Although oral strontium ranelate has not yet been approved by the US Food and Drug Administration (FDA) for the treatment of osteoporosis, it has received approval in Europe and several other countries. Several studies have shown that strontium ranelate increases BMD.¹⁹⁸ Preclinical studies have

shown that strontium ranelate reduces bone resorption by osteoclasts and increases the bone formation activity of osteoblasts.¹⁹⁹ It has been shown that treatment with strontium ranelate results in heterogeneous distribution of strontium in new bone tissue, which is incorporated at a rate of 0.5 strontium ions per 10 calcium ions in postmenopausal women.^{199,200} Furthermore, bone mineral quality is maintained post-treatment with strontium ranelate.²⁰¹ Improvements in bone strength from strontium ranelate treatment may be due, in part, from its effects on bone cells, bone mass, microarchitecture, and overall changes in bone matrix properties.²⁰² In the past few years, advances have been made in understanding the mechanisms of action of strontium and this area of research continues to be investigated to fully understand its pharmacological effects.

Strontium ranelate has shown efficacy in younger postmenopausal women (50–65 years of age).²⁰³ The first osteoporotic fracture indicates greater increased risk mortality in this age group, yet few treatments are available for women of <65 years of age. Recent studies have demonstrated that strontium ranelate reduces risk of vertebral fracture incidence in women with lumbar spine osteopenia,^{203,204} and non-vertebral fractures (including hip)²⁰⁵ with what is said to be a good safety profile.^{206,207}

However, data collected on risk of adverse effects in a number of studies are of concern.^{208–210} A review of the research on strontium ranelate published in 2005 states that, “Strontium [ranelate] caused a 50% increase in the risk of venous thromboembolism (including pulmonary embolism).”²¹¹ The most recent review of the evidence indicating that strontium ranelate may cause potentially lethal adverse effects was published in *Prescribe International*, March 21, 2012. The title of this review was: “Strontium ranelate: too many adverse effects: Do not use”.²¹² Because strontium is the active agent in strontium ranelate (“Ranelic acid is an organic, highly polar molecule without pharmacological activity”) and at least 93% of ranelic acids are said to be excreted unchanged,²¹³ it seems reasonable to consider that natural forms of strontium would offer comparable benefit.

Although natural forms of strontium salts are available (e.g., strontium citrate), long-term safety and efficacy has only been evaluated for strontium

ranelate, with, as noted above, questionable results for the latter. No adverse effects have been associated with the natural forms of strontium when calcium and vitamin D are also supplied. The only negative effects seen with natural strontium occurred in one animal study conducted in 1994 and one human study conducted in 1996.^{214,215} In the animal study, immature laboratory rats (i.e., animals whose bones were still developing) were given a low calcium diet and supplemented with high doses of strontium. Not surprisingly, because calcium is the major mineral found in normal bone, and these animals were calcium-deprived, the rats developed ricket-like bone deformities. The human study was conducted in Turkey in 1996. Before complete data analysis, it appeared that there was a higher incidence of bone malformations (i.e., rickets) in young children in areas of Turkey with very high strontium concentrations in the soil. However, when the question of whether the children had been breastfed was taken into account, the risk for rickets no longer differed between people living in high strontium areas compared with those with low strontium. Calcium and strontium compete for absorption, and calcium will be preferentially absorbed. Breast milk had provided adequate calcium to prevent excessive incorporation of strontium into bone. Patients supplemented with any form of strontium should be consuming twice as much calcium as strontium.

According to the Centers for Disease Control’s Agency for Toxic Substances and Disease Registry, which published a 161-page report on the health effects of natural forms of strontium,²¹⁶ “There is no direct evidence that strontium is toxic to humans, but there is suggestive epidemiological evidence that the oral toxicity observed at high doses in juvenile laboratory animals may pertain to humans under special circumstances [here, they are referring to the two studies discussed immediately above, which is why their following sentence emphasizes the importance of adequate calcium, phosphorus, and vitamin D]. At low exposure levels, ingestion of stable strontium poses no harm to organisms with access to adequate calcium, phosphorus, and vitamin D. At higher exposure levels, especially under conditions of inadequate calcium, phosphorus, and vitamin D, stable strontium will interfere with normal bone development, causing ‘strontium rickets’ of variable severity.”

Natural forms of strontium may be a useful adjunctive therapy for osteoporosis prevention and reversal. Future studies with natural salt forms, including bioequivalence studies, are warranted.

Flavonoids and Phytoestrogens

Flavonoids are a diverse group of phytochemicals found in many foods including fruits, vegetables, herbs, grains, tea, and wine, and include anthocyanins, favanols, flavan-3-ols, flavones, and isoflavones. It is hypothesized that the beneficial effects of flavonoids on skeletal health may be due to their antioxidant properties countering oxidative stress and ROS. Oxidative stress has been associated with pathogenesis of osteoporosis, playing a key role in osteoclast differentiation and function.²¹⁷ ROS are involved in bone resorption^{218, 219} and inhibit osteoblast differentiation.^{220, 221}

Some flavonoids and flavonoid-rich foods have been associated with increased BMD.^{222–224} Clinical studies on tea consumption and skeletal health offer conflicting data. Whereas some researchers have reported positive effects of tea consumption on BMD,^{225–229} others have found no association.^{230, 231} There are several confounding factors that may lead to varying results between studies, including alcohol intake, smoking, intake of other nutrients, type of exercise, and amount of tea consumed, and lack of quantitative biomarkers for tea ingestion. Several *in vitro* and *in vivo* studies support green tea polyphenols for bone health.^{232–234} Furthermore, after 6 months of supplementation with green tea polyphenols (500 mg/day), increases in serum bone-specific alkaline phosphatase, a biomarker of bone formation, were observed in postmenopausal women.²³⁴ However, owing to the short nature of this study, BMD was not assessed. Well-designed, randomized, controlled clinical studies are warranted to clarify the effects of green tea and/or green tea polyphenols on BMD and bone microarchitecture in postmenopausal women.

Some flavonoids are classified as phytoestrogens due to their structural similarities to 17- β -estradiol. Three major types of phytoestrogens – isoflavones, lignans, and coumestans – have been identified in plants and function as estrogen agonist-antagonists. Isoflavones are primarily found in soybeans, soy products, and legumes and include genistein, daidzein, and glycitein; enterolactone and enterodiols are lignans

found in oilseeds such as flax, bran, and legumes; and coumestrol is a coumestan found in alfalfa and clover. The majority of research on BMD and phytoestrogens has been focused on soy isoflavones.

The effects on skeletal health vary between different phytoestrogens. There are several mechanisms of action that have been postulated for phytoestrogens in the improvement of skeletal health, including the ability to alter the receptor activator for the RANKL/OPG pathway, induce osteoblast apoptosis, inhibit inflammation, and enhance antioxidant enzymes and modulate insulin-like growth factor levels.²³⁵ The effects of soy isoflavones on bone health are inconsistent in the literature, possibly due to dose, study design, or population studied. A large, 4.5-year observational study of 24,403 postmenopausal Chinese women found that high dietary soy intake reduced fracture risk by 36% over women with low dietary soy intake.²³⁶ However, data from randomized, controlled trials have reported either no effect on BMD or improved BMD.^{235, 237–243} In a meta-analysis of 10 studies, reduction of vertebral bone loss was found when intake of isolated soy isoflavones was >90 mg/day.²⁴⁴ Another meta-analysis reported that doses of >80 mg/day of soy isoflavones had a weak effect on spine BMD.²⁴⁵ Studies of genistein aglycone at a dose of 54 mg/day have produced gains in vertebral and hip BMD equivalent to hormone therapy and produced modest increases in bone formation markers and decreases in bone resorption markers,^{242, 243, 246} suggesting a positive role for soy isoflavone supplements to support bone health. Soy isoflavones have a good safety profile; side effects include mild gastrointestinal effects, which are minimized if supplements are taken with food.^{247–251}

Progesterone

The role of estradiol in bone health is well characterized. Progesterone works together with estradiol in the normal physiology of women. When estradiol concentrations decrease, progesterone behaves in a similar manner. When estrogen levels are low, progesterone levels should be evaluated as well. Sometimes the level of concentration of estradiol may correlate with progesterone as well. During perimenopause, low progesterone levels precede drops in estradiol.²⁵² *In vitro* studies have shown that progesterone increases the number of osteoblasts, promotes

osteoblast differentiation, and works together with estradiol to achieve peak bone mass.^{253, 254} There is growing evidence for the role of ovulation and progesterone in bone loss during menopause. The PEKNO [Perimenopausale Knochendichte (bone density) und Ovulation] study is a 2-year prospective observational study in perimenopausal women with a primary goal of investigating whether perimenopausal women with anovulatory cycles have increased BMD loss. This study is expected to add to the body of evidence that bone loss seen during and after menopause is not solely due to changes in estrogen levels but also due to changes in progesterone levels and ovulation. Data on menstrual cycles, hormone concentrations, changes in BMD and bone turnover marker values will be collected during the luteal phase. Interim data suggest that over 82% of participants show a decrease in BMD.²⁵⁵ It has also been suggested that the decrease in BMD correlates with a decrease in ovulation.⁴⁰ Preliminary results of this study have also shown that progesterone levels decrease prior to women experiencing common anovulatory cycles.²⁵⁶ Understanding the link between ovulation and bone physiology is key to understanding the viability of progesterone therapy and its potential effects on BMD.

As a therapy, progesterone appears to have a role in osteoporosis in postmenopausal women when combined with antiresorptive therapy. Progesterone has been shown to have a dose-dependent effect on osteoblast differentiation and may increase BMD by 0.4% when administered with estrogen therapy.^{40, 254} However, higher than physiological amounts suggest a potential risk of increased rate of bone loss in women receiving progestogens.²⁵⁴ It has also been suggested that progesterone therapy may be beneficial to pre- and perimenopausal women who experience irregular menstrual cycles.²⁵⁷ It has also been suggested that the efficacy of progesterone therapy may be greater when an antiresorptive agent is also provided.^{258, 259} Further studies are warranted to determine the effectiveness of progesterone in preventing fractures in postmenopausal women in combination with antiresorptive agents.

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS) are hormones secreted by the adrenal glands. The level of these hormones decreases with

increasing age; they have been associated with osteoporosis and may protect against BMD loss.²⁶⁰ High levels of circulating DHEAS have been associated with decreased femoral neck and lumbar spine bone loss.²⁶¹ DHEA replacement therapy increases blood concentrations of DHEAS, androstenedione, and testosterone.²⁶² Several studies have demonstrated a beneficial effect of DHEA replacement therapy on bone mass.^{262–265} Animal models have shown that DHEA increases insulin-like growth factor (IGF)-1 level, increasing activity of osteoblasts, thus stimulating bone formation.^{266, 267} Although it is well known that the physiology is different between non-primate mammals and humans, a recent study confirmed these effects in postmenopausal women, suggesting this may be the mechanism of action for DHEA therapy in the prevention of osteoporosis.²⁶²

Reduce Carbonated Beverage Intake

Increased intake of carbonated beverages has been seen in recent years. Several studies have investigated the effects of carbonated beverages on BMD and have reported mixed results. Data from over 2,500 men and women who participated in the Framingham Osteoporosis Study were examined and it was found that cola, but not other carbonated beverages, was associated with low BMD in women, but not in men.²⁶⁸ The mechanisms by which this occurs are not fully understood, but it has been hypothesized that the content of phosphoric acid may play a role.

Caffeinated carbonated drinks have stronger associations than decaffeinated beverages with low BMD,²⁶⁸ possibly due to the effect caffeine has on calcium absorption. Caffeine intake can inhibit the uptake of calcium,²⁶⁹ therefore reduction of caffeine intake is recommended and should at least be separated from intake of sources of calcium.

Weight-Bearing Exercise with Resistance and Strengthening

In addition to proper nutrition, current recommendations for the prevention of osteoporosis include weight-bearing exercise of at least 30 min/day for bone health and fracture prevention.²⁷⁰ Weight-bearing exercises include intense walking, jogging up and down stairs, dancing, playing tennis, and

running. Furthermore, rowing is an excellent way to build bone mass in the spine.

Weight-bearing exercise means that muscles and bones work against gravity. A walking program is an excellent choice provided it is intense. To ramp up walks, bursts of fast walking up hills, going up and down stairs, or wearing a weighted vest are recommended.

Resistance and strengthening exercises are important as they build power and coordination, and prevent falls by working the core muscles, which help maintain balance. Weight lifting with free weights or machines, push-ups, pull-ups, and resistance bands all qualify. The literature supports the benefits of weight-bearing exercise in maintaining bone density in postmenopausal women, with the amount of exercise required being dependent on intensity.²⁷¹ Non-weight-bearing, progressive resistance strength training of the lower limbs is effective for BMD of the neck and femur, and combination programs are effective for the spine.²⁷⁰

Starting Young to Prevent Osteoporosis

It is important to raise awareness that prevention of osteoporosis starts in the adolescent years when the body is creating the majority of bone mass that will be required for life. It is of great importance that the nutritional needs of our youths are met to ensure their health in the future. Current dietary habits in North America warrant more attention, particularly with respect to ensuring recommended nutritional requirements are being met and habits such as cola and caffeine consumption is minimized, which puts bone health at risk in future years.

For lifelong bone health, it is essential for teenagers – particularly girls – to consume enough calcium, vitamin D, and vitamin K (particularly vitamin K2) while they are young to achieve their maximum bone density. By the mid-20s the critical window period for calcium absorption starts to close, as a woman's ability to stock pile this mineral in her bones is greatly reduced.

Calcium and dairy intake in the USA is inadequate in 4–18 year olds, with calcium intake reported to be approximately 500 mg/day among this population.²⁷² Today, few teenage girls in America are meeting the recommended dietary guidelines for

calcium intake during this period of peak bone mass accrual.²⁷³ The decreased consumption of dairy products has been associated with vitamin D deficiency and increased consumption of carbonated beverages and/or sweetened beverages.^{274–276}

Soft drinks are problematic, not only because they have displaced calcium-rich milk as a source of refreshment but also as caffeine (which most sodas contain) impairs absorption and thereby increases the excretion of calcium in the urine, further reducing the calcium available for bone development. As such, soda consumption, especially colas, should be reduced and teenagers should be encouraged to increase intake of low-fat milk and other healthy sources of calcium such as dairy products, fortified juices, and vegetables.

Other ways to increase exposure to healthy foods may be to set higher nutritional standards for the foods sold in school vending machines and stores to provide healthier options. Notably, the Kansas legislature has been considering a new statute that would do just that. Senate Bill 499 would require every school district in the state to follow the same “exemplary” guidelines for the sale of so-called “competitive foods” in schools that a minority of Kansas districts now follows voluntarily. These guidelines restrict beverages sold in schools to water, low-fat milk, and 100% juice. Parents, educators, and health professionals are rallying around the bill as a first step in assuring not only healthy bone development but also better oral health, reduced obesity, and improved academic performance.

CONCLUSIONS

Regular weight-bearing exercise, adequate intake of calcium, vitamin D and vitamin K, and avoidance of cigarette smoking, excess alcohol, and carbonated beverage intake are recommended to minimize the adverse skeletal effects of estrogen deficiency and aging. It is also important to monitor BMD, especially around menopause in women during which time estrogen levels decline sharply and greatest bone loss occurs. Baseline scans at menopause provide physicians with information to determine osteoporosis risk. Such tests should be carried out regardless of insurance coverage as it

is important to take measures in preventing osteoporosis in those who are at greatest risk. BMD measurement combined with clinical risk factors provide the best estimation of fracture risk.

If BMD findings and clinical evaluation suggest that a patient is at high risk for fracture, insufficiencies of nutrients essential for healthy bone remodeling should be addressed, weight-bearing exercise recommended, and, as a last resort, pharmacological therapy may be indicated. Although many agents have been approved for treatment and/or prevention of osteoporosis, long-term adherence to therapy is typically poor for the reasons discussed above, with <50% of patients still using the drug 1 year after starting.^{277, 278} Strategies to improve adherence include the development of agents with longer intervals between dosing and injectable administration.^{279–282} Perhaps the best clinical approach to optimizing adherence is regular contact with a healthcare professional to reinforce the importance of a healthy diet supplemented where needed with key bone building nutrients, weight-bearing exercise, and, where indicated, continuing to take medication correctly. Repeat BMD measurement 1–2 years after starting therapy with the goal of stabilizing or increasing BMD, and

follow-up measurement of BTMs in some patients may also help to improve compliance. A significant loss of BMD during therapy is a cause for concern and warrants investigation for factors that could produce a suboptimal response.

Unfortunately, prevention occurs at an early age when many are not worried about bone health later in life. Although the importance of calcium and vitamin D intake is well understood in the medical community, fewer physicians are aware of the importance of vitamin K2, and little has changed with respect to dietary intake. Public awareness of calcium, vitamin D and vitamin K deficiency, and programs to increase intake of these key nutrients and to decrease poor dietary habits during adolescent years is crucial to reducing the prevalence of osteoporosis and decreasing the burden on the healthcare system in future generations. Improving dietary habits during mid-life, menopause, and after menopause is of equal importance in promoting bone health and should include incorporation of dietary sources of calcium, vitamin D, vitamin K, polyphenols, and phytoestrogens. Supplementation with specific isoflavones, strontium, DHEA, magnesium, and manganese may also be warranted to improve BMD.

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