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 absorption[121] and alteration of metabolism of several hormones, including calcitropic hormone,[122] estradiol,[123–125] adrenal corticol 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' 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 to 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 antithrombin 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 loss[182] 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 *Prescrire 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 enterodiol 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.

DISCLOSURE OF INTERESTS

Dr. J.E. Pizzorno reports personal fees from Bioclinic Naturals for dietary supplements, outside the submitted work. Dr. Karan Baucom and Dr. Lara Pizzorno have nothing to disclose.

REFERENCES

1. *National Osteoporosis Foundation* (http://www.nor.org). Accessed November 1, 2013.
2. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int*. 2006;17:1726–33.
3. Becker DJ, Kilgore ML, Morrisey MA. The societal burden of osteoporosis. *Curr Rheumatol Rep*. 2010;12:186–91.
4. Burge R, Dawson-Hughes B, Solomon DH, Wong JB, King A, Tosteson A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005–2025. *J Bone Miner Res*. 2007;22:465–75.
5. Budhia S, Mikyas Y, Tang M, Badamgarav E. Osteoporotic fractures: a systematic review of U.S. healthcare costs and resource utilization. *Pharmacoeconomics*. 2012;30:147–70.
6. Chrischilles EA, Butler CD, Davis CS, Wallace RB. A model of lifetime osteoporosis impact. *Arch Intern Med*. 1991;151:2026–32.
7. Braithwaite RS, Col NF, Wong JB. Estimating hip fracture morbidity, mortality and costs. *J Am Geriatr Soc*. 2003;51:364–70.
8. Dolan MM, Hawkes WG, Zimmerman SI, *et al.* Delirium on hospital admission in aged hip fracture patients: prediction of mortality and 2-year functional outcomes. *J Gerontol A Biol Sci Med Sci*. 2000;55:M527–34.
9. Lenze EJ, Munin MC, Skidmore ER, *et al.* Onset of depression in elderly persons after hip fracture: implications for prevention and early intervention of late-life depression. *J Am Geriatr Soc*. 2007;55:81–6.
10. Munch S, Shapiro S. The silent thief: osteoporosis and women's health care across the life span. *Health Soc Work*. 2006;31:44–53.

11. Bliuc D, Nguyen ND, Milch VE, Nguyen TV, Eisman JA, Center JR. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. *J Am Med Assoc*. 2009;301:513–21.

12. Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: an observational study. *Lancet*. 1999;353:878–82.

13. Cooper C. The crippling consequences of fractures and their impact on quality of life. *Am J Med*. 1997;103:12S–7S.

14. Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. *Lancet*. 2002;359:1761–7.

15. Wiktorowicz ME, Goeree R, Papaioannou A, Adachi JD, Papadimitropoulos E. Economic implications of hip fracture: health service use, institutional care and cost in Canada. *Osteoporos Int*. 2001;12:271–8.

16. Siris ES. Patients with hip fracture: what can be improved? *Bone*. 2006;38:S8–12.

17. Pizzorno L, Wright JV. *Your Bones*, 2nd edn. Edinburgh, VA: Praktikos Books; 2013.

18. Rizzoli R, Brandi ML, Dreinhofer K, Thomas T, Wahl DA, Cooper C. The gaps between patient and physician understanding of the emotional and physical impact of osteoporosis. *Arch Osteoporos*. 2010;5:145–53.

19. Satterfield T, Johnson SM, Slovic P, Neil N, Schein JR. Perceived risks and reported behaviors associated with osteoporosis and its treatment. *Women Health*. 2000;31:21–40.

20. Curtis JR, McClure LA, Delzell E, *et al.* Population-based fracture risk assessment and osteoporosis treatment disparities by race and gender. *J Gen Intern Med*. 2009;24:956–62.

21. Adler RA. Osteoporosis in men: recent progress. *Endocrine*. 2013;44(1):40–6.

22. Adler RA, Gill RS. Clinical utility of denosumab for treatment of bone loss in men and women. *Clin Interv Aging*. 2011;6:119–24.

23. Glüer CC, Marin F, Ringe JD, *et al.* Comparative effects of teriparatide and risedronate in glucocorticoid-induced osteoporosis in men: 18-month results of the EuroGIOPs trial. *J Bone Miner Res.* 2013;28(6):1355–68.

24. Mosekilde L, Vestergaard P, Rejnmark L. The pathogenesis, treatment and prevention of osteoporosis in men. *Drugs*. 2013;73(1):15–29.

25. Saggese G, Baroncelli GI, Bertelloni S. Osteoporosis in children and adolescents: diagnosis, risk factors, and prevention. *J Pediatr Endocrinol Metab*. 2001;14:833–59.

26. Campion JM, Maricic MJ. Osteoporosis in men. *Am Fam Physician*. 2003;67:1521–6.

27. Seeman E. Pathogenesis of bone fragility in women and men. *Lancet*. 2002;359:1841–50.

28. Orwig DL, Chan J, Magaziner J. Hip fracture and its consequences: differences between men and women. *Orthop Clin North Am*. 2006;37:611–22.

29. Fitzpatrick LA. Secondary causes of osteoporosis. *Mayo Clin Proc*. 2002;77:453–68.

30. Heaney RP, Abrams S, Dawson-Hughes B, *et al.* Peak bone mass. *Osteoporos Int*. 2000;11:985–1009.

31. Lippuner K. The future of osteoporosis treatment – a research update. *Swiss Med Wkly*. 2012;142:w13624.

32. Brown JP, Josse RG. 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. *Can Med Assoc J*. 2002;167:S1–34.

33. Cashman KD. Vitamin D in childhood and adolescence. *Postgrad Med J.* 2007;83(978):230–5.

34. Cashman KD. Vitamin K status may be an important determinant of childhood bone health. *Nutr Rev.* 2005;63(8):284–9.

35. Tsugawa N, Uenishi K, Ishida H, *et al.* A novel method based on curvature analysis for estimating the dietary vitamin K requirement in adolescents. *Clin Nutr.* 2012;31(2):255–60.

36. "Vitamin K: another reason to eat your greens" January 2000, *Agricultural Research Magazine* (http://www.ars.usda.gov/is/ar/archive/jan00/green0100.htm?pf=1). Accessed September 13, 2013.

37. Lussana FM, Zighetti ML, Bucciarelli P, *et al.* Blood levels of homocysteine, folate, vitamin B6 and B12 in women using oral contraceptives compared to non-users. *Thromb Res*. 2003;112(1–2):37–41.

38. McLean RR, Jacques PF, Selhub J, *et al.* Plasma B vitamins, homocysteine, and their relation with bone loss and hip fracture in elderly men and women. *J Clin Endocrinol Metab.* 2008;93(6):2206–12.

39. Isley MM, Kaunitz AM. Update on hormonal contraception and bone density. *Rev Endocr Metab Disord.* 2011;12(2):93–106.

40. Seifert-Klauss V, Schmidmayr M, Hobmaier E, Wimmer T. Progesterone and bone: a closer link than previously realized. *Climacteric*. 2012;15(Suppl 1):26–31.

41. Bahamondes MV, Monteiro I, Castro S, *et al.* Prospective study of the forearm bone mineral density of long-term users of the levonorgestrel-releasing intrauterine system. *Hum Reprod.* 2010;25(5):1158–64.

42. Pérez-López FR, Brincat M, Erel CT, *et al.* EMAS position statement: vitamin D and postmenopausal health. *Maturitas*. 2012;71(1):83–8.

43. Luz Rentero M, Carbonell C, Casillas M, *et al.* Risk factors for osteoporosis and fractures in postmenopausal women between 50 and 65 years of age in a primary care setting in Spain: a questionnaire. *Open Rheumatol J.* 2008;2:58–63.

44. Bolton JM, Targownik LE, Leung S, *et al.* Risk of low bone mineral density associated with psychotropic medications and mental disorders in postmenopausal women. *J Clin Psychopharmacol.* 2011;31(1):56–60.

45. Bolton JM, Metge C, Lix L, *et al.* Fracture risk from psychotropic medications: a population-based analysis. *J Clin Psychopharmacol.* 2008;28(4):384–91.

46. Damsa C, Bumb A, Bianchi-Demicheli F, *et al.* "Dopamine-dependent" side effects of selective serotonin reuptake inhibitors: a clinical review. *J Clin Psychiatry.* 2004;65(8):1064–8.

47. O'Keane V. Antipsychotic-induced hyperprolactinaemia, hypogonadism and osteoporosis in the treatment of schizophrenia. *J Psychopharmacol.* 2008;22(Suppl 2): 70–5.

48. O'Keane V, Meaney AM. Antipsychotic drugs: a new risk factor for osteoporosis in young women with schizophrenia? *J Clin Psychopharmacol.* 2005; 25(1):26–31.

49. Loke YK, Singh S, Furberg CD. Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. *Can Med Assoc J*. 2009;180(1):32–9.

50. Dormuth CR, Carney G, Carleton B, *et al.* Thiazolidinediones and fractures in men and women. *Arch Intern Med.* 2009;169(15):1395–402.

51. Douglas IJ, Evans SJ, Pocock S, *et al.* The risk of fractures associated with thiazolidinediones: a self-controlled case-series study. *PLoS Med.* 2009; 6(9):e1000154.

52. Aubert RE, Herrera V, Chen W, *et al.* Rosiglitazone and pioglitazone increase fracture risk in women and men with type 2 diabetes. *Diabetes Obes Metab.* 2010;12(8):716–21.

53. Bodmer M, Meier C, Kraenzlin ME, *et al.* Risk of fractures with glitazones: a critical review of the evidence to date. *Drug Saf.* 2009;32(7):539–47.

54. Bruedigam C, Eijken M, Koedam M, *et al.* A new concept underlying stem cell lineage skewing that explains the detrimental effects of thiazolidinediones on bone. *Stem Cells.* 2010;28(5):916–27.

55. Daniell HW. Opioid endocrinopathy in women consuming prescribed sustained-action opioids for control of nonmalignant pain. *J Pain.* 2008;9(1):28–36.

56. Rhodin A, Stridsberg M, Gordh T. Opioid endocrinopathy: a clinical problem in patients with chronic pain and long-term oral opioid treatment. *Clin J Pain.* 2010;26(5):374–80.

57. Colameco S. Opioid-induced endocrinopathy: diagnosis and screening. *J Pain Palliat Care Pharmacother.* 2012;26:73–5.

58. Elliott JA, Horton E, Fibuch EE. The endocrine effects of long-term oral opioid therapy: a case report and review of the literature. *Opioid Manag.* 2011; 7(2):145–54.

59. Adler RA, Curtis JR, Saag K, *et al.* Glucocorticoid-induced osteoporosis. In: Marcus R, Feldman D, Nelsen DA, Rosen CJ, eds. *Osteoporosis*, 3rd edn. San Diego, CA: Elsevier Academic Press; 2008. pp. 1135–66.

60. Van Staa TP, Laan RF, Barton IP, *et al.* Bone density threshold and other predictors of vertebral fracture in patients receiving oral glucocorticoid therapy. *Arthritis Rheum*. 2003;48:3224–9.

61. Steinbuch M, Youket TE, Cohen S. Oral glucocorticoid use is associated with an increased risk of fracture. *Osteoporos Int*. 2004;15:323–8.

62. Weinstein RS. Clinical practice. Glucocorticoid-induced bone disease. *N Engl J Med.* 2011;365(1):62–70.

63. Weinstein RS. Glucocorticoid-induced osteoporosis. In: Rosen C, ed. *The ASBMR Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*, 7th edn. Washington, DC: ASBMR; 2008. pp. 267–72.

64. Wright JV, Lenard L. *Why Stomach Acid is Good for You, Natural Relief from Heartburn, Indigestion, Reflux & GERD*. Lanham, MD: M. Evans; 2001. pp. 25–8.

65. Mackay JD, Bladon PT. Hypomagnesaemia due to proton-pump inhibitor therapy: a clinical case series. *QJM.* 2010;103(6):387–95.

66. http://www.niams.nih.gov/Health_Info/Bone/Osteoporosis/bone_mass.asp.

67. Jarvinen TL, Kannus P, Sievanen H. Estrogen and bone – a reproductive and locomotive perspective. *J Bone Miner Res*. 2003;18:1921–31.

68. Peacock M, Koller DL, Lai D, Hui S, Foroud T, Econs MJ. Bone mineral density variation in men is influenced by sex-specific and non sex-specific quantitative trait loci. *Bone*. 2009;45:443–8.

69. Looker AC, Melton LJ III, Harris TB, Borrud LG, Shepherd JA. Prevalence and trends in low femur bone density among older US adults: NHANES 2005–2006 compared with NHANES III. *J Bone Miner Res.* 2010;25:64–71.

70. Robitaille J, Yoon PW, Moore CA, *et al.* Prevalence, family history, and prevention of reported osteoporosis in U.S. women. *Am J Prev Med*. 2008;35:47–54.

71. http://www.gdx.net/core/one-page-test-descriptions/Osteo-Genomic-Test-Description.pdf. (Note that this profile is being discontinued but the SNPs are evaluated via other profiles available at Genova Diagnostics.)

72. Holick MF. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. *Am J Clin Nutr*. 2004;79:362–71.

73. Lips P, Hosking D, Lippuner K, *et al.* The prevalence of vitamin D inadequacy amongst women with osteoporosis: an international epidemiological investigation. *J Intern Med*. 2006;260:245–54.

74. Feskanich D, Willett WC, Colditz GA. Calcium, vitamin D, milk consumption, and hip fractures: a prospective study among postmenopausal women. *Am J Clin Nutr*. 2003;77:504–11.

75. Chapuy MC, Arlot ME, Duboeuf F, *et al.* Vitamin D3 and calcium to prevent hip fractures in the elderly women. *N Engl J Med.* 1992;327(23):1637–42.

76. Meunier PJ, Chapuy MC, Arlot ME, *et al.* Can we stop bone loss and prevent hip fractures in the elderly? *Osteoporos Int.* 1994;4(Suppl 1):71–6.

77. Chapuy MC, Meunier PJ. Prevention of secondary hyperparathyroidism and hip fracture in elderly women with calcium and vitamin D3 supplements. *Osteoporos Int.* 1996;6(Suppl 3):60–3.

78. Chapuy MC, Pamphile R, Paris E, *et al.* Combined calcium and vitamin D3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: the Decalyos II study. *Osteoporos Int.* 2002;13(3):257–64.

79. Lilliu H, Pamphile R, Chapuy MC, *et al.* Calcium-vitamin D3 supplementation is cost-effective in hip fractures prevention. *Maturitas*. 2003;44(4):299–305.

80. Chapuy MC, Arlot ME, Delmas PD, *et al.* Effect of calcium and cholecalciferol treatment for three years on hip fractures in elderly women. *Brit Med J.* 1994;308(6936):1081–2.

81. Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. *J Am Med Assoc*. 2005;293:2257–64.

82. Grimnes G, Joakimsen R, Figenschau Y, Torjesen PA, Almas B, Jorde R. The effect of high-dose vitamin D on bone mineral density and bone turnover markers in postmenopausal women with low bone mass – a randomized controlled 1-year trial. *Osteoporos Int*. 2012;23:201–11.

83. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, *et al.* Effect of vitamin D on falls: a meta-analysis. *J Am Med Assoc*. 2004;291:1999–2006.

84. http://www.vitamindcouncil.org/about-vitamin-d/testing-for-vitamin-d/. Accessed September 12, 2013.

85. Mundy GR, Guise TA. Hormonal control of calcium homeostasis. *Clin Chem*. 1999;45:1347–52.

86. Trivedi R, Mithal A, Chattopadhyay N. Anabolics in osteoporosis: the emerging therapeutic tool. *Curr Mol Med.* 2010;10(1):14–28.

87. Brixen KT, Christensen PM, Ejersted C, *et al.* Teriparatide (biosynthetic human parathyroid hormone 1–34): a new paradigm in the treatment of osteoporosis. *Basic Clin Pharmacol Toxicol.* 2004;94(6):260–70.

88. Kim BJ, Seo M, Huh JK, *et al.* Associations of plasma homocysteine levels with arterial stiffness in prehypertensive individuals. *Clin Exp Hypertens*. 2011;33:411–7.

89. LeBoff MS, Narweker R, LaCroix A, *et al.* Homocysteine levels and risk of hip fracture in postmenopausal women. *J Clin Endocrinol Metab*. 2009;94:1207–13.

90. van Meurs JB, Dhonukshe-Rutten RA, Pluijm SM, *et al.* Homocysteine levels and the risk of osteoporotic fracture. *N Engl J Med*. 2004;350:2033–41.

91. Herrmann M, Peter SJ, Umanskaya N, *et al.* The role of hyperhomocysteinemia as well as folate, vitamin B_6 and B_{12} deficiencies in osteoporosis: a systematic review. *Clin Chem Lab Med*. 2007;45:1621–32.

92. Kuyumcu ME, Yesil Y, Ozturk ZA, *et al.* The association between homocysteine (hcy) and serum natural antioxidants in elderly bone mineral densitometry (BMD). *Arch Gerontol Geriatr*. 2012;55:739–43.

93. Tucker KL, Hannan MT, Qiao N, *et al.* Low plasma vitamin B12 is associated with lower BMD: the Framingham Osteoporosis Study. *J Bone Miner Res*. 2005;20:152–8.

94. Maggio D, Barabani M, Pierandrei M, *et al.* Marked decrease in plasma antioxidants in aged osteoporotic women: results of a cross-sectional study. *J Clin Endocrinol Metab*. 2003;88:1523–7.

95. Gerdhem P, Ivaska KK, Isaksson A, *et al.* Associations between homocysteine, bone turnover, BMD, mortality, and fracture risk in elderly women. *J Bone Miner Res*. 2007;22:127–34.

96. Zhu K, Beilby J, Dick IM, Devine A, Soos M, Prince RL. The effects of homocysteine and MTHFR genotype on hip bone loss and fracture risk in elderly women. *Osteoporos Int*. 2009;20:1183–91.

97. Bozkurt N, Erdem M, Yilmaz E, *et al.* The relationship of homocyteine, B12 and folic acid with the bone mineral density of the femur and lumbar spine in Turkish postmenopausal women. *Arch Gynecol Obstet*. 2009;280:381–7.

98. Saito M. [Biochemical markers of bone turnover. New aspect. Bone collagen metabolism: new biological markers for estimation of bone quality]. *Clin Calcium.* 2009;19(8):1110–7.

99. Petramala L, Acca M, Francucci CM, *et al.* Hyperhomocysteinemia: a biochemical link between bone and cardiovascular system diseases? *J Endocrinol Invest.* 2009;32(Suppl 4):10–4.

100. Yilmaz N, Eren E. Homocysteine oxidative stress and relation to bone mineral density in post-menopausal osteoporosis. *Aging Clin Exp Res.* 2009;21(4–5):353–7.

101. Haliloglu B, Aksungar FB, Ilter E, *et al.* Relationship between bone mineral density, bone turnover markers and homocysteine, folate and vitamin B12 levels in postmenopausal women. *Arch Gynecol Obstet.* 2010;281(4):663–8.

102. Selhub J, Jacques PF, Wilson PW, Rush D, Rosenberg IH. Vitamin status and intake as primary determinants of homocysteinemia in an elderly population. *J Am Med Assoc*. 1993;270:2693–8.

103. Jacques PF, Selhub J, Bostom AG, Wilson PW, Rosenberg IH. The effect of folic acid fortification on plasma folate and total homocysteine concentrations. *N Engl J Med*. 1999;340:1449–54.

104. ACOG Practice Bulletin N. 129. Osteoporosis. *Obstet Gynecol*. 2012;120:718–34.

105. Seifert-Klauss V, Prior JC. Progesterone and bone: actions promoting bone health in women. *J Osteoporos.* 2010;2010:845180.

106. Manolagas SC. From estrogen-centric to aging and oxidative stress: a revised perspective of the pathogenesis of osteoporosis. *Endocr Rev*. 2010;31:266–300.

107. Katagiri T, Takahashi N. Regulatory mechanisms of osteoblast and osteoclast differentiation. *Oral Dis.* 2002;8(3):147–59.

108. Lange U, Teichmann J, Schett G, *et al.* [Osteoimmunology: how inflammation influences bone metabolism]. *Dtsch Med Wochenschr.* 2013;138(37):1845–9 (in German).

109. Cauley JA, Robbins J, Chen Z, *et al.* Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *J Am Med Assoc*. 2003;290:1729–38.

110. Jackson RD, Wactawski-Wende J, LaCroix AZ, *et al.* Effects of conjugated equine estrogen on risk of fractures and BMD in postmenopausal women with hysterectomy: results from the Women's Health Initiative randomized trial. *J Bone Miner Res*. 2006;21:817–28.

111. Holtorf K. The bioidentical hormone debate: are bioidentical hormones (estradiol, estriol, and progesterone) safer or more efficacious than commonly used synthetic versions in hormone replacement therapy? *Postgrad Med.* 2009;121(1):73–85.

112. Khosla S, Amin S, Orwoll E. Osteoporosis in men. *Endocr Rev*. 2008;29:441–64.

113. Mellstrom D, Vandenput L, Mallmin H, *et al.* Older men with low serum estradiol and high serum SHBG have an increased risk of fractures. *J Bone Miner Res*. 2008;23:1552–60.

114. Vanderschueren D, Vandenput L, Boonen S, Lindberg MK, Bouillon R, Ohlsson C. Androgens and bone. *Endocr Rev*. 2004;25:389–425.

115. Behre HM, Kliesch S, Leifke E, Link TM, Nieschlag E. Long-term effect of testosterone therapy on bone mineral density in hypogonadal men. *J Clin Endocrinol Metab*. 1997;82:2386–90.

116. Crawford BA, Liu PY, Kean MT, Bleasel JF, Handelsman DJ. Randomized placebo-controlled trial of androgen effects on muscle and bone in men requiring long-term systemic glucocorticoid treatment. *J Clin Endocrinol Metab*. 2003;88:3167–76.

117. Jones G, Scott FS. A cross-sectional study of smoking and bone mineral density in premenopausal parous women: effect of body mass index, breastfeeding, and sports participation. *J Bone Miner Res*. 1999;14:1628–33.

118. Hollenbach KA, Barrett-Connor E, Edelstein SL, Holbrook T. Cigarette smoking and bone mineral density in older men and women. *Am J Public Health*. 1993;83:1265–70.

119. Holmberg T, Bech M, Curtis T, Juel K, Gronbaek M, Brixen K. Association between passive smoking in adulthood and phalangeal bone mineral density: results from the KRAM study – the Danish Health Examination Survey 2007–2008. *Osteoporos Int*. 2011;22:2989–99.

120. Ward KD, Klesges RC. A meta-analysis of the effects of cigarette smoking on bone mineral density. *Calcif Tissue Int*. 2001;68:259–70.

121. Krall EA, Dawson-Hughes B. Smoking increases bone loss and decreases intestinal calcium absorption. *J Bone Miner Res*. 1999;14:215–20.

122. Rapuri PB, Gallagher JC, Balhorn KE, Ryschon KL. Smoking and bone metabolism in elderly women. *Bone*. 2000;27:429–36.

123. Michnovicz JJ, Hershcopf RJ, Haley NJ, Bradlow HL, Fishman J. Cigarette smoking alters hepatic estrogen metabolism in men: implications for atherosclerosis. *Metabolism*. 1989;38:537–41.

124. Barbieri RL, Gochberg J, Ryan KJ. Nicotine, cotinine, and anabasine inhibit aromatase in human trophoblast in vitro. *J Clin Invest*. 1986;77:1727–33.

125. Cassidenti DL, Vijod AG, Vijod MA, Stanczyk FZ, Lobo RA. Short-term effects of smoking on the pharmacokinetic profiles of micronized estradiol in postmenopausal women. *Am J Obstet Gynecol*. 1990;163:1953–60.

126. Tang TH, Fitzsimmons TR, Bartold PM. Effect of smoking on concentrations of receptor activator of nuclear factor kappa B ligand and osteoprotegerin in human gingival crevicular fluid. *J Clin Periodontol*. 2009;36:713–8.

127. Lappin DF, Sherrabeh S, Jenkins WM, Macpherson LM. Effect of smoking on serum RANKL and OPG in sex, age and clinically matched supportive-therapy periodontitis patients. *J Clin Periodontol*. 2007; 34:271–7.

128. Sorensen LT, Toft BG, Rygaard J, *et al.* Effect of smoking, smoking cessation, and nicotine patch on wound dimension, vitamin C, and systemic markers of collagen metabolism. *Surgery*. 2010;148:982–90.

129. Ma L, Zheng LW, Sham MH, Cheung LK. Uncoupled angiogenesis and osteogenesis in nicotine-compromised bone healing. *J Bone Miner Res*. 2010;25:1305–13.

130. Kazantzis G. Cadmium, osteoporosis and calcium metabolism. *Biometals*. 2004;17(5):493–8.

131. Rothem DE, Rothem L, Soudry M, *et al.* Nicotine modulates bone metabolism-associated gene expression in osteoblast cells. *J Bone Miner Metab.* 2009;27(5):555–61.

132. Kamer AR, El-Ghorab N, Marzec N, *et al.* Nicotine induced proliferation and cytokine release in osteoblastic cells. *Int J Mol Med.* 2006;17(1):121–7.

133. Op. cit., Holtorf K. The bioidentical hormone debate: are bioidentical hormones (estradiol, estriol, and progesterone) safer or more efficacious than commonly used synthetic versions in hormone replacement therapy? *Postgrad Med.* 2009;121(1):73–85.

134. *International Society for Clinical Densitometry* (http://www.iscd.org).

135. Cauley JA, Hochberg MC, Lui LY, *et al.* Long-term risk of incident vertebral fractures. *J Am Med Assoc*. 2007;298:2761–7.

136. Lafleur J, McAdam-Marx C, Kirkness C, Brixner DI. Clinical risk factors for fracture in postmenopausal osteoporotic women: a review of the recent literature. *Ann Pharmacother*. 2008;42:375–86.

137. Huber F, Traber L, Roth HJ, *et al.* Markers of bone resorption – measurement in serum, plasma or urine? *Clin Lab.* 2003;49(5–6):203–7.

138. Genuis SJ, Bouchard TP. Combination of Micronutrients for Bone (COMB) Study: bone density after micronutrient intervention. *J Environ Public Health.* 2012;2012:354151.

139. Ross AC, Taylor CL, Yaktine AL, Del Valle HB, eds. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington, DC: The National Academies Press; 2010.

140. Body JJ. How to manage postmenopausal osteoporosis? *Acta Clin Belg*. 2011;66:443–7.

141. http://www.vitamindcouncil.org/about-vitamin-d/how-do-i-get-the-vitamin-d-my-body-needs/. Accessed September 12, 2013.

142. Bailey RL, Dodd KW, Goldman JA, *et al.* Estimation of total usual calcium and vitamin D intakes in the United States. *J Nutr*. 2010;140:817–22.

143. Ervin RB, Wang CY, Wright JD, Kennedy-Stephenson J. Dietary intake of selected minerals for the United States population: 1999–2000. *Adv Data*. 2004;1–5.

144. Brown LM. *Helicobacter pylori*: epidemiology and routes of transmission. *Epidemiol Rev.* 2000;22(2):283–97.

145. Fox J, Sheh A. The role of the gastrointestinal microbiome in *Helicobacter pylori* pathogenesis. *Gut Microbes.* 2013;4(6):43–68.

146. Hannan MT, Felson DT, Dawson-Hughes B, *et al.* Risk factors for longitudinal bone loss in elderly men and women: the Framingham Osteoporosis Study. *J Bone Miner Res*. 2000;15:710–20.

147. Shea MK, Booth SL, Massaro JM, *et al.* Vitamin K and vitamin D status: associations with inflammatory markers in the Framingham Offspring Study. *Am J Epidemiol.* 2008;167(3):313–20.

148. Binkley N, Harke J, Krueger D, *et al.* Vitamin K treatment reduces undercarboxylated osteocalcin but does not alter bone turnover, density, or geometry in healthy postmenopausal North American women. *J Bone Miner Res*. 2009;24:983–91.

149. Pizzorno L. Vitamin K2: optimal levels essential for the prevention of age-associated chronic disease. August 2011. *Longevity Medicine Review.* (http://www.lmreview.com/articles/view/Vitamin-K2-Essential-for-Prevention-of-Age-Associated-Chronic-Disease/). Accessed September 14, 2013.

150. Booth SL, Broe KE, Gagnon DR, *et al.* Vitamin K intake and bone mineral density in women and men. *Am J Clin Nutr*. 2003;77:512–6.

151. Booth SL, Tucker KL, Chen H, *et al.* Dietary vitamin K intakes are associated with hip fracture but not with bone mineral density in elderly men and women. *Am J Clin Nutr*. 2000;71:1201–8.

152. Cheung AM, Tile L, Lee Y, *et al.* Vitamin K supplementation in postmenopausal women with osteopenia (ECKO trial): a randomized controlled trial. *PLoS Med*. 2008;5:e196.

153. Braam LA, Knapen MH, Geusens P, *et al.* Vitamin K1 supplementation retards bone loss in postmenopausal women between 50 and 60 years of age. *Calcif Tissue Int*. 2003;73:21–6.

154. Op. cit., Pizzorno L. Vitamin K2: optimal levels essential for the prevention of age-associated chronic disease. August 2011. *Longevity Medicine Review*. (http://www.lmreview.com/articles/view/Vitamin-K2-Essential-for-Prevention-of-Age-Associated-Chronic-Disease/). Accessed September 14, 2013.

155. Feskanich D, Weber P, Willett WC, Rockett H, Booth SL, Colditz GA. Vitamin K intake and hip fractures in women: a prospective study. *Am J Clin Nutr*. 1999;69:74–9.

156. van Summeren MJ, van Coeverden SC, Schurgers LJ, *et al.* Vitamin K status is associated with childhood bone mineral content. *Br J Nutr*. 2008;100:852–8.

157. Inoue T, Fujita T, Kishimoto H, *et al.* Randomized controlled study on the prevention of osteoporotic fractures (OF study): a phase IV clinical study of 15-mg menatetrenone capsules. *J Bone Miner Metab*. 2009;27:66–75.

158. Iwamoto J, Sato Y. Menatetrenone for the treatment of osteoporosis. *Expert Opin Pharmacother*. 2013;14:449–58.

159. Bunyaratavej N, Kittimanon N, Jitivirai T, Tongthongthip B. Highly recommended dose of MK4 for osteoporosis. *J Med Assoc Thai*. 2009;92(Suppl 5):S4–6.

160. Shearer MJ, Newman P. Metabolism and cell biology of vitamin K. *Thromb Haemost.* 2008;100(4):530–47.

161. Koitaya N, Ezaki J, Nishimuta M, *et al.* Effect of low dose vitamin K2 (MK-4) supplementation on bioindices in postmenopausal Japanese women. *J Nutr Sci Vitaminol (Tokyo)*. 2009;55:15–21.

162. Schurgers LJ, Vermeer C. Differential lipoprotein transport pathways of K-vitamins in healthy subjects. *Biochim Biophys Acta.* 2002;1570(1):27–32.

163. Schurgers LJ, Teunissen KJ, Hamulyák K, *et al.* Vitamin K-containing dietary supplements: comparison of synthetic vitamin K1 and natto-derived menaquinone-7. *Blood.* 2007;109(8):3279–83.

164. Knapen MH, Drummen NE, Smit E, Vermeer C, Theuwissen E. Three-year low-dose menaquinone-7 supplementation helps decrease bone loss in healthy postmenopausal women. *Osteoporos Int.* 2013;24(9):2499–507.

165. Westenfeld R, Krueger T, Schlieper G, *et al.* Effect of vitamin K2 supplementation on functional vitamin K

deficiency in hemodialysis patients: a randomized trial. *Am J Kidney Dis.* 2012;59(2):186–95.

166. Knapen MH, Schurgers LJ, Vermeer C. Vitamin K(2) supplementation improves hip bone geometry and bone strength indices in postmenopausal women. *Osteoporos Int.* 2007;18(7):963–72.

167. Ishida Y. [Vitamin K2]. *Clin Calcium.* 2008;18(10):1476–82.

168. Cockayne S, Adamson J, Lanham-New S, *et al.* Vitamin K and the prevention of fractures: systematic review and meta-analysis of randomized controlled trials. *Arch Intern Med.* 2006;166(12):1256–61.

169. Adams J, Pepping J. Vitamin K in the treatment and prevention of osteoporosis and arterial calcification. *Am J Health Syst Pharm.* 2005;62(15):1574–81.

170. Bügel S. Vitamin K and bone health in adult humans. *Vitam Horm.* 2008;78:393–416.

171. Kanellakis S, Moschonis G, Tenta R, *et al.* Changes in parameters of bone metabolism in postmenopausal women following a 12-month intervention period using dairy products enriched with calcium, vitamin D, and phylloquinone (vitamin K(1)) or menaquinone-7 (vitamin K (2)): the Postmenopausal Health Study II. *Calcif Tissue Int.* 2012;90(4):251–62.

172. Op. cit., Knapen MH, Drummen NE, Smit E, Vermeer C, Theuwissen E. Three-year low-dose menaquinone-7 supplementation helps decrease bone loss in healthy postmenopausal women. *Osteoporos Int.* 2013;24(9):2499–507.

173. Bolland MJ, Grey A, Avenell A, *et al.* Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. *Brit Med J.* 2011;342:d2040.

174. Wallace RB, Wactawski-Wende J, O'Sullivan MJ, *et al.* Urinary tract stone occurrence in the Women's Health Initiative randomized clinical trial of calcium and vitamin D supplements. *Am J Clin Nutr.* 2011;94(1):270–7.

175. Pizzorno L. Vitamin D and vitamin K team up to lower CVD risk. *Longevity Medicine Review*, 2009 (http://www.lmreview.com/articles/view/vitamin-d-and-vitamin-k-team-up-to-lower-cvd-risk-part-II/).

176. Price PA, Faus SA, Williamson MK. Warfarin-induced artery calcification is accelerated by growth and vitamin D. *Arterioscler Thromb Vasc Biol.* 2000;20(2):317–27.

177. Spronk HM, Soute BA, Schurgers LJ, *et al.* Tissue-specific utilization of menaquinone-4 results in the prevention of arterial calcification in warfarin-treated rats. *J Vasc Res.* 2003;40(6):531–7.

178. Theuwissen E, Teunissen K, Spronk H, *et al.* Effect of low-dose supplements of menaquinone-7 [vitamin K2(35)] on the stability of oral anticoagulant treatment: dose-response relationship in healthy volunteers. *J Thromb Haemost.* 2013;11(6):1085–92.

179. Tahir F, Riaz H, Riaz T, *et al.* The new oral anti-coagulants and the phase 3 clinical trials – a systematic review of the literature. *Thromb J.* 2013;11(1):18.

180. Scaglione F. New oral anticoagulants: comparative pharmacology with vitamin K antagonists. *Clin Pharmacokinet.* 2013;52(2):69–82.

181. Pfeilschifter W, Luger S, Brunkhorst R, *et al.* The gap between trial data and clinical practice – an analysis of case reports on bleeding complications occurring under dabigatran and rivaroxaban anticoagulation. *Cerebrovasc Dis.* 2013;36(2):115–9.

182. Rude RK, Singer FR, Gruber HE. Skeletal and hormonal effects of magnesium deficiency. *J Am Coll Nutr*. 2009;28:131–41.

183. Kanazawa I, Yamamoto M, Yamaguchi T, Yamauchi M, Yano S, Sugimoto T. A case of magnesium deficiency associated with insufficient parathyroid hormone action and severe osteoporosis. *Endocr J*. 2007;54:935–40.

184. Sahota O, Mundey MK, San P, Godber IM, Hosking DJ. Vitamin D insufficiency and the blunted PTH response in established osteoporosis: the role of magnesium deficiency. *Osteoporos Int*. 2006;17:1013–21.

185. Reginster JY, Strause L, Deroisy R, Lecart MP, Saltman P, Franchimont P. Preliminary report of decreased serum magnesium in postmenopausal osteoporosis. *Magnesium*. 1989;8:106–9.

186. Rude RK, Olerich M. Magnesium deficiency: possible role in osteoporosis associated with gluten-sensitive enteropathy. *Osteoporos Int*. 1996;6:453–61.

187. Rude RK, Adams JS, Ryzen E, *et al.* Low serum concentrations of 1,25-dihydroxyvitamin D in human magnesium deficiency. *J Clin Endocrinol Metab.* 1985;61(5):933–40.

188. Chou HF, Schwartz R, Krook L, Wasserman RH. Intestinal calcium absorption and bone morphology in magnesium deficient chicks. *Cornell Vet*. 1979;69:88–103.

189. Sader MS, Legeros RZ, Soares GA. Human osteoblasts adhesion and proliferation on magnesium-substituted tricalcium phosphate dense tablets. *J Mater Sci Mater Med*. 2009;20:521–7.

190. National Academy of Sciences. *A Report of the Panel on Micronutrients. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. Washington, DC: National Academy Press; 2001.

191. Tranquilli AL, Lucino E, Garzetti GG, Romanini C. Calcium, phosphorus and magnesium intakes correlate with bone mineral content in postmenopausal women. *Gynecol Endocrinol.* 1994;8:55–8.

192. Tucker KL, Hannan MT, Chen H, Cupples LA, Wilson PW, Kiel DP. Potassium, magnesium, and fruit and vegetable intakes are associated with greater bone-mineral density in elderly men and women. *Am J Clin Nutr.* 1999;69:727–36.

193. Stendig-Lindberg G, Tepper R, Leichter I. Trabecular bone density in a two year controlled trial of peroral magnesium in osteoporosis. *Magnes Res*. 1993;6:155–63.

194. Freeland-Graves JH, Turnlund JR. Deliberations and evaluations of the approaches, endpoints and paradigms for manganese and molybdenum dietary recommendations. *J Nutr*. 1996;126:2435S–40S.

195. Strause L, Saltman P, Glowacki J. The effect of deficiencies of manganese and copper on osteoinduction and on resorption of bone particles in rats. *Calcif Tissue Int*. 1987;41:145–50.

196. Strause LG, Hegenauer J, Saltman P, Cone R, Resnick D. Effects of long-term dietary manganese and copper deficiency on rat skeleton. *J Nutr*. 1986;116:135–41.

197. Strause L, Saltman P, Smith KT, Bracker M, Andon MB. Spinal bone loss in postmenopausal women supplemented with calcium and trace minerals. *J Nutr*. 1994;124:1060–4.

198. Meunier PJ, Slosman DO, Delmas PD, *et al.* Strontium ranelate: dose-dependent effects in established postmenopausal vertebral osteoporosis – a 2-year randomized placebo controlled trial. *J Clin Endocrinol Metab*. 2002;87:2060–6.

199. Marie PJ, Ammann P, Boivin G, Rey C. Mechanisms of action and therapeutic potential of strontium in bone. *Calcif Tissue Int*. 2001;69:121–9.

200. Li C, Paris O, Siegel S, *et al.* Strontium is incorporated into mineral crystals only in newly formed bone during strontium ranelate treatment. *J Bone Miner Res*. 2010;25:968–75.

201. Boivin G, Doublier A, Farlay D. Strontium ranelate – a promising therapeutic principle in osteoporosis. *J Trace Elem Med Biol*. 2012;26:153–6.

202. Saidak Z, Marie PJ. Strontium signaling: molecular mechanisms and therapeutic implications in osteoporosis. *Pharmacol Ther*. 2012;136:216–26.

203. Roux C, Fechtenbaum J, Kolta S, Isaia G, Andia JB, Devogelaer JP. Strontium ranelate reduces the risk of vertebral fracture in young postmenopausal women with severe osteoporosis. *Ann Rheum Dis*. 2008;67:1736–8.

204. Seeman E, Devogelaer JP, Lorenc R, *et al.* Strontium ranelate reduces the risk of vertebral fractures in patients with osteopenia. *J Bone Miner Res*. 2008;23:433–8.

205. Reginster JY, Seeman E, De Vernejoul MC, *et al.* Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study. *J Clin Endocrinol Metab*. 2005;90:2816–22.

206. Audran M, Jakob FJ, Palacios S, *et al.* A large prospective European cohort study of patients treated with strontium ranelate and followed up over 3 years. *Rheumatol Int*. 2013;33:2231–9.

207. Kaufman JM, Audran M, Bianchi G, *et al.* Efficacy and safety of strontium ranelate in the treatment of osteoporosis in men. *J Clin Endocrinol Metab*. 2013;98:592–601.

208. Osborne V, Layton D, Perrio M, *et al.* Incidence of venous thromboembolism in users of strontium ranelate: an analysis of data from a prescription-event monitoring study in England. *Drug Saf.* 2010;33(7):579–91.

209. Le Merlouette M, Adamski H, Dinulescu M, *et al.* [Strontium ranelate-induced DRESS syndrome]. *Ann Dermatol Venereol.* 2011;138(2):124–8.

210. Jonville-Bera AP, Autret-Leca E. [Adverse drug reactions of strontium ranelate(Protelos® in France]. *Presse Med.* 2011;40(10):e453–62.

211. Anonymous. Strontium: new drug. Postmenopausal osteoporosis: too many unknowns. *Prescrire Int.* 2005;14(80):207–11.

212. Anonymous. Strontium ranelate: too many adverse effects (continued) Do not use. *Prescrire Int.* 2012;21(125):72.

213. Protelos, INN-Strontium ranelate – European Medicines (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000560/WC500045522.pdf). Accessed September 14, 2013.

214. Neufeld EB, Boskey AL. Strontium alters the complexed acidic phospholipid content of mineralizing tissues. *Bone.* 1994;15(4):425–30.

215. Ozgur S, Sumer H, Kocoglu G. Rickets and soil strontium. *Arch Dis Child.* 1996;75(6):524–6.

216. Centers for Disease Control's Agency for Toxic Substances and Disease Registry Health Effects of Strontium report (http://www.atsdr.cdc.gov/ToxProfiles/tp159-c3.pdf).

217. Garrett IR, Boyce BF, Oreffo RO, Bonewald L, Poser J, Mundy GR. Oxygen-derived free radicals stimulate osteoclastic bone resorption in rodent bone *in vitro* and *in vivo*. *J Clin Invest*. 1990;85:632–9.

218. Yang S, Madyastha P, Bingel S, Ries W, Key L. A new superoxide-generating oxidase in murine osteoclasts. *J Biol Chem*. 2001;276:5452–8.

219. Sontakke AN, Tare RS. A duality in the roles of reactive oxygen species with respect to bone metabolism. *Clin Chim Acta*. 2002;318:145–8.

220. Mody N, Parhami F, Sarafian TA, Demer LL. Oxidative stress modulates osteoblastic differentiation of vascular and bone cells. *Free Radic Biol Med*. 2001;31:509–19.

221. Fatokun AA, Stone TW, Smith RA. Responses of differentiated MC3T3-E1 osteoblast-like cells to reactive oxygen species. *Eur J Pharmacol*. 2008;587:35–41.

222. Welch A, Macgregor A, Jennings A, Fairweather-Tait S, Spector T, Cassidy A. Habitual flavonoid intakes are positively associated with bone mineral density in women. *J Bone Miner Res*. 2012;27:1872–8.

223. Hardcastle AC, Aucott L, Reid DM, Macdonald HM. Associations between dietary flavonoid intakes and

bone health in a Scottish population. *J Bone Miner Res*. 2011;26:941–7.

224. Hooshmand S, Arjmandi BH. Viewpoint: dried plum, an emerging functional food that may effectively improve bone health. *Ageing Res Rev*. 2009;8:122–7.

225. Muraki S, Yamamoto S, Ishibashi H, *et al.* Diet and lifestyle associated with increased bone mineral density: cross-sectional study of Japanese elderly women at an osteoporosis outpatient clinic. *J Orthop Sci*. 2007;12:317–20.

226. Hegarty VM, May HM, Khaw KT. Tea drinking and bone mineral density in older women. *Am J Clin Nutr*. 2000;71:1003–7.

227. Devine A, Hodgson JM, Dick IM, Prince RL. Tea drinking is associated with benefits on bone density in older women. *Am J Clin Nutr*. 2007;86:1243–7.

228. Chen Z, Pettinger MB, Ritenbaugh C, *et al.* Habitual tea consumption and risk of osteoporosis: a prospective study in the women's health initiative observational cohort. *Am J Epidemiol*. 2003;158:772–81.

229. Hamdi KI, Aydin S, Gemalmaz A, *et al.* Habitual tea drinking and bone mineral density in postmenopausal Turkish women: investigation of prevalence of postmenopausal osteoporosis in Turkey (IPPOT Study). *Int J Vitam Nutr Res*. 2007;77:389–97.

230. Kyriazopoulos P, Trovas G, Charopoulos J, Antonogiannakis E, Galanos A, Lyritis G. Lifestyle factors and forearm bone density in young Greek men. *Clin Endocrinol (Oxf)*. 2006;65:234–8.

231. Saitoglu M, Ardicoglu O, Ozgocmen S, Kamanli A, Kaya A. Osteoporosis risk factors and association with somatotypes in males. *Arch Med Res*. 2007;38:746–51.

232. Holzer N, Braun KF, Ehnert S, *et al.* Green tea protects human osteoblasts from cigarette smoke-induced injury: possible clinical implication. *Langenbecks Arch Surg*. 2012;397:467–74.

233. Shen CL, Cao JJ, Dagda RY, *et al.* Green tea polyphenols benefits body composition and improves bone quality in long-term high-fat diet-induced obese rats. *Nutr Res*. 2012;32:448–57.

234. Shen CL, Yeh JK, Cao JJ, Chyu MC, Wang JS. Green tea and bone health: evidence from laboratory studies. *Pharmacol Res*. 2011;64:155–61.

235. Atmaca A, Kleerekoper M, Bayraktar M, Kucuk O. Soy isoflavones in the management of postmenopausal osteoporosis. *Menopause*. 2008;15:748–57.

236. Zhang X, Shu XO, Li H, *et al.* Prospective cohort study of soy food consumption and risk of bone fracture among postmenopausal women. *Arch Intern Med*. 2005;165:1890–5.

237. Brink E, Coxam V, Robins S, Wahala K, Cassidy A, Branca F. Long-term consumption of isoflavone-enriched foods does not affect bone mineral density, bone metabolism, or hormonal status in early postmenopausal women: a randomized, double-blind, placebo controlled study. *Am J Clin Nutr*. 2008;87:761–70.

238. Alekel DL, Van Loan MD, Koehler KJ, *et al.* The soy isoflavones for reducing bone loss (SIRBL) study: a 3-y randomized controlled trial in postmenopausal women. *Am J Clin Nutr*. 2010;91:218–30.

239. Levis S, Strickman-Stein N, Ganjei-Azar P, Xu P, Doerge DR, Krischer J. Soy isoflavones in the prevention of menopausal bone loss and menopausal symptoms: a randomized, double-blind trial. *Arch Intern Med*. 2011;171:1363–9.

240. Kenny AM, Mangano KM, Abourizk RH, *et al.* Soy proteins and isoflavones affect bone mineral density in older women: a randomized controlled trial. *Am J Clin Nutr*. 2009;90:234–42.

241. Vupadhyayula PM, Gallagher JC, Templin T, Logsdon SM, Smith LM. Effects of soy protein isolate on bone mineral density and physical performance indices in postmenopausal women – A 2-year randomized, double-blind, placebo-controlled trial. *Menopause*. 2009;16:320–8.

242. Morabito N, Crisafulli A, Vergara C, *et al.* Effects of genistein and hormone-replacement therapy on bone loss in early postmenopausal women: a randomized double-blind placebo-controlled study. *J Bone Miner Res*. 2002;17:1904–12.

243. Marini H, Minutoli L, Polito F, *et al.* Effects of the phytoestrogen genistein on bone metabolism in osteopenic postmenopausal women: a randomized trial. *Ann Intern Med*. 2007;146:839–47.

244. Ma DF, Qin LQ, Wang PY, Katoh R. Soy isoflavone intake increases bone mineral density in the spine of menopausal women: meta-analysis of randomized controlled trials. *Clin Nutr*. 2008;27:57–64.

245. Liu J, Ho SC, Su YX, Chen WQ, Zhang CX, Chen YM. Effect of long-term intervention of soy isoflavones on bone mineral density in women: a meta-analysis of randomized controlled trials. *Bone*. 2009;44:948–53.

246. Marini H, Bitto A, Altavilla D, *et al.* Breast safety and efficacy of genistein aglycone for postmenopausal bone loss: a follow-up study. *J Clin Endocrinol Metab*. 2008;93:4787–96.

247. Taylor CK, Levy RM, Elliott JC, Burnett BP. The effect of genistein aglycone on cancer and cancer risk: a review of in vitro, preclinical, and clinical studies. *Nutr Rev*. 2009;67:398–415.

248. Hooper L, Madhavan G, Tice JA, Leinster SJ, Cassidy A. Effects of isoflavones on breast density in pre- and post-menopausal women: a systematic review and meta-analysis of randomized controlled trials. *Hum Reprod Update*. 2010;16:745–60.

249. Dong JY, Qin LQ. Soy isoflavones consumption and risk of breast cancer incidence or recurrence: a meta-analysis of prospective studies. *Breast Cancer Res Treat*. 2011;125:315–23.

250. Andres S, Abraham K, Appel KE, Lampen A. Risks and benefits of dietary isoflavones for cancer. *Crit Rev Toxicol*. 2011;41:463–506.

251. Lethaby AE, Brown J, Marjoribanks J, Kronenberg F, Roberts H, Eden J. Phytoestrogens for vasomotor menopausal symptoms. *Cochrane Database Syst Rev*. 2007;CD001395.

252. Prior JC. Perimenopause: the complex endocrinology of the menopausal transition. *Endocr Rev*. 1998;19:397–28.

253. Scheven BA, Damen CA, Hamilton NJ, Verhaar HJ, Duursma SA. Stimulatory effects of estrogen and progesterone on proliferation and differentiation of normal human osteoblast-like cells *in vitro*. *Biochem Biophys Res Commun*. 1992;186:54–60.

254. Schmidmayr M, Magdolen U, Tubel J, Kiechle M, Gurgkart R, Seifert-Klauss V. Progesterone enhances differentiation of primary human osteoblasts in long-term cultures. The influence of concentration and cyclicity of progesterone on proliferation and differentiation of human osteoblasts *in vitro*. *Geburtshilfe Frauenheilk*. 2008;68:722–8.

255. Franck F, Ehle A, Wimmer T, Kiechler M, Seifert-Klauss V. Zum Einfluss von Ernahrung und Aktivitat auf die Knochendichte perimenopausaler Frauen - die Perimenopausale Knochendichte und Ovulation (PEKNO)-Studie. *Geburtshilfe Frauenheilk*. 2011;71:409.

256. Ehle A, Muller D, Boppel K, Kiechle M, Siefert-Klauss V. Cycle-evaluation and cycle patterns in peri-menopausal women: the PEKNO study. *Geburtshilfe Frauenheilk*. 2008;2008:S182.

257. Prior JC. Progesterone as a bone-trophic hormone. *Endocr Rev*. 1990;11:386–98.

258. Anonymous. Effects of hormone therapy on bone mineral density: results from the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial. The Writing Group for the PEPI. *J Am Med Assoc*. 1996;276:1389–96.

259. Lindsay R, Gallagher JC, Kleerekoper M, Pickar JH. Effect of lower doses of conjugated equine estrogens with and without medroxyprogesterone acetate on bone in early postmenopausal women. *J Am Med Assoc*. 2002;287:2668–76.

260. Leowattana W. DHEA(S): the fountain of youth. *J Med Assoc Thai*. 2001;84(Suppl 2):S605–12.

261. Ghebre MA, Hart DJ, Hakim AJ, *et al.* Association between DHEAS and bone loss in postmenopausal women: a 15-year longitudinal population-based study. *Calcif Tissue Int*. 2011;89:295–302.

262. Papierska L, Rabijewski M, Kasperlik-Zaluska A, Zgliczynski W. Effect of DHEA supplementation on serum IGF-1, osteocalcin, and bone mineral density in postmenopausal, glucocorticoid-treated women. *Adv Med Sci*. 2012;57:51–7.

263. Hart DJ, Spector TD. The relationship of obesity, fat distribution and osteoarthritis in women in the general population: The Chingford Study. *J Rheumatol*. 1993;20:331–5.

264. Zhai G, Hart DJ, Valdes AM, *et al.* Natural history and risk factors for bone loss in postmenopausal Caucasian women: a 15-year follow-up population-based study. *Osteoporos Int*. 2008;19:1211–7.

265. Tok EC, Ertunc D, Oz U, Camdeviren H, Ozdemir G, Dilek S. The effect of circulating androgens on bone mineral density in postmenopausal women. *Maturitas*. 2004;48:235–42.

266. Villareal DT, Holloszy JO, Kohrt WM. Effects of DHEA replacement on bone mineral density and body composition in elderly women and men. *Clin Endocrinol (Oxf)*. 2000;53:561–8.

267. Martel C, Sourla A, Pelletier G, *et al.* Predominant androgenic component in the stimulatory effect of dehydroepiandrosterone on bone mineral density in the rat. *J Endocrinol*. 1998;157:433–42.

268. Tucker KL, Morita K, Qiao N, Hannan MT, Cupples LA, Kiel DP. Colas, but not other carbonated beverages, are associated with low bone mineral density in older women: The Framingham Osteoporosis Study. *Am J Clin Nutr*. 2006;84:936–42.

269. Heaney RP. Effects of caffeine on bone and the calcium economy. *Food Chem Toxicol*. 2002;40:1263–70.

270. Howe TE, Shea B, Dawson LJ, *et al.* Exercise for preventing and treating osteoporosis in postmenopausal women. *Cochrane Database Syst Rev*. 2011;CD000333.

271. Engelke K, Kemmler W, Lauber D, Beeskow C, Pintag R, Kalender WA. Exercise maintains bone density at spine and hip EFOPS: a 3-year longitudinal study in early postmenopausal women. *Osteoporos Int*. 2006;17:133–42.

272. Kranz S, Lin PJ, Wagstaff DA. Children's dairy intake in the United States: too little, too fat? *J Pediatr*. 2007;151:642–6.

273. Moore LL, Singer MR, Qureshi MM, Bradlee ML, Daniels SR. Food group intake and micronutrient adequacy in adolescent girls. *Nutrients*. 2012;4:1692–708.

274. Holick MF. Vitamin D deficiency. *N Engl J Med*. 2007;357:266–81.

275. Whiting SJ, Healey A, Psiuk S, Mirwald R, Kowalski K, Bailey D. Relationship between carbonated and other low nutrient dense beverages and bone mineral content of adolescents. *Nutr Res*. 2001;21:1107–15.

276. McGartland C, Robson PJ, Murray L, *et al.* Carbonated soft drink consumption and bone mineral density in adolescence: The Northern Ireland Young Hearts project. *J Bone Miner Res*. 2003;18:1563–9.

277. Seeman E, Compston J, Adachi J, *et al.* Non-compliance: the Achilles' heel of anti-fracture efficacy. *Osteoporos Int*. 2007;18:711–9.

278. Siris ES, Selby PL, Saag KG, Borgstrom F, Herings RM, Silverman SL. Impact of osteoporosis treatment adherence on fracture rates in North America and Europe. *Am J Med*. 2009;122:S3–13.

279. Baxter-Jones AD, Faulkner RA, Forwood MR, Mirwald RL, Bailey DA. Bone mineral accrual from 8 to 30 years of age: an estimation of peak bone mass. *J Bone Miner Res*. 2011;26:1729–39.

280. Cvijetic S, Colic BI, Keser I, Cecic I, Satalic Z, Blanusa M. Peak bone density in Croatian women: variations at different skeletal sites. *J Clin Densitom*. 2008;11:260–5.

281. Lorentzon M, Mellstrom D, Ohlsson C. Age of attainment of peak bone mass is site specific in Swedish men – The GOOD study. *J Bone Miner Res*. 2005;20:1223–7.

282. Matkovic V, Jelic T, Wardlaw GM, *et al.* Timing of peak bone mass in Caucasian females and its implication for the prevention of osteoporosis. Inference from a cross-sectional model. *J Clin Invest*. 1994;93:799–808.