

## Osteoporosis

Osteoporosis is “a disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk.”<sup>1,2</sup> It is asymptomatic; it is an important public health issue because of its clinical expression in age-related fractures.<sup>3</sup> Of these fractures (hip, spine and distal forearm), hip fractures are the most serious, leading to an reduction in survival of 10-20% in women and 30% in men.<sup>4</sup>

The importance of recognition and treatment of osteoporosis while it is asymptomatic is even more important due to increased life expectancy around the globe and the increased number of elderly individuals in every region.<sup>5</sup> The estimated 323 million individuals in the world age 65 years or over at present is expected to rise to 1555 million by the year 2050.<sup>6</sup> These demographic changes alone can be expected to cause the number of hip fractures throughout the world to increase to epidemic proportions--from about 1.7 million in 1990 to 6.3 million in 2050—with no intervention.<sup>6</sup>

A postmenopausal woman has a 50% chance of sustaining an osteoporotic fracture during the remainder of her lifetime;<sup>7</sup> while a 60 year old man has a 25% lifetime risk.<sup>8</sup> For women of all ages, the one-in-six risk of hip fracture for Caucasians is greater than their one-in-nine risk of developing breast cancer, and the death rate associated with hip fracture is higher as well.<sup>9,10</sup>

It is important to identify men and women with osteoporosis because effective treatments can reduce fracture risk by about half. Additionally, since it is probably not possible to restore bone strength fully once an individual has developed osteoporosis, interventions should ideally be started when bone density is in the lower range of normal, before it falls into the range of osteoporosis.<sup>11-14</sup>

### ***Pathophysiology***

Bone is an active tissue that undergoes remodeling throughout the lifespan. The remodeling occurs as the result of opposing actions of two cell types: osteoclasts and osteoblasts. Osteoclasts are attracted to an area of microdamage; once they have resorbed the bone, osteoblasts are recruited to synthesize replacement bone.<sup>15</sup> Osteoporosis results from an imbalance in the process due to the failure of osteoblasts to repair the bone removed by the osteoclasts.<sup>16,17</sup>

Substances thought to affect this balance include parathyroid hormone, prostaglandins, growth factors, acidosis, corticosteroids, calcium, vitamin D, and estrogen, among others. Clinically, this pathophysiology is related to secondary causes of osteoporosis. (See Table 1) In research, biochemical markers associated with the processes of bone turnover help estimate bone turnover rate and are used in clinical trials as secondary endpoints of treatment efficacy.<sup>18</sup>

## ***PREDISPOSING FACTORS***

### ***Female gender***

Women have a higher prevalence of osteoporosis than men due to the accelerated bone loss from the estrogen deficient state of menopause. During the 5-7 years of menopause, women lose 5-7% of their bone strength. This accelerated loss is in addition the age-related 0.5-1% per year loss that men and women experience beginning around age 40.

### ***Caucasian race***

Caucasian race carries an increased risk for osteoporosis, albeit not as much as weight or age. According to the Third National Health and Nutrition Examination Survey (NHANES III), the prevalence of osteoporosis in women over 50 years of age is 20%; Caucasians (non-Hispanic whites) have the highest prevalence at 21%; African-Americans have the lowest prevalence at 10% and Mexican-Americans have an intermediate prevalence at 16%.<sup>19</sup> The prevalence among Asian women is in a similar range to that of Caucasians. Further elucidation regarding race/ethnicity should be forthcoming with the release of the data from the NHANES IV.

### ***Family history of fracture***

Genetics and heredity account for 50-80% of the variability in BMD.<sup>14, 20</sup> Osteoporosis is thought to be a disorder involving not one single gene, but rather components of several genes.<sup>21</sup> Although a number of genes have been associated with osteoporosis, the research is still in its infancy and the discoveries have not yet resulted in a clinical application in the diagnosis or treatment. When discussing osteoporosis in the context of family history, many patients will not know whether their ancestors had osteoporosis, *per se*. The clinically important aspect of the heritability of osteoporosis lies in the acquisition of a complete family history that includes fracture history in parents and grandparents. Elderly women with a positive family history of fracture are at increased risk for hip fracture.<sup>22</sup>

### ***Increased age***

Peak bone mass is attained by age 25; age-related bone loss of 0.5-1% per year begins at age 40 in both men and women. Women lose an additional 5-7% of bone during menopause. The risk of increased age is shown by prevalence data indicating that at 50 years of age, about 40% of women have low bone mineral density (osteoporosis and osteopenia) at the femur, but by the time women reach 80 years of age, the prevalence is more than 80%.<sup>19, 23</sup> Osteoporosis in men has not been studied to the extent it has in women, but increased age increases risk for them as well. Since men have larger bones and experience the only age-related “slow” phase of bone loss (0.5-1% per year), but not the accelerated bone loss associated with menopause, men have a lower prevalence rate for both osteoporosis and fracture than women.

### ***Low body weight***

Low body weight has also been shown to increase the risk of osteoporosis in men and women.<sup>24, 25</sup> In a study of 1346 menopausal women, those weighing 135 lbs. (61 kg.) or

less had a 36.4% prevalence of osteoporosis-- twice that of their counterparts who weighed between 151-165 lbs. (69-75 kg.) and five times that of those who weighed 181 lbs. (82 kg.) and above.<sup>23</sup> Men have been studied less, but low body weight was also associated with an increased risk for osteoporosis and fracture.<sup>26</sup> Two mechanisms that may influence the positive relationship between heavier weight and stronger bones are: a direct route of increased mechanical stress and load from the weight itself; and an indirect route of peripheral aromatization of androgen to estrogen that occurs in the adipose and skeletal muscle tissue.

### ***Lifestyle factors***

In the 1980s and early 1990s, case control studies and prospective studies suggested lower body weight, cigarette smoking, caffeine intake, use of long-acting sedatives and inactivity as potential risk factors for hip fractures.<sup>27-33</sup> Other studies suggested additional risks factors including: previous history of minimal trauma fracture (fracture from a simple fall); early menopause (prior to 40 or 45 years of age); first-degree relative with osteoporosis; and heavy alcohol usage of more than 7 drinks per week (women) or 14 drinks per week (men).

In 1995, a large prospective study of 9516 white women 65 years of age and older identified sixteen independent risk factors for hip fracture *besides* bone density. These factors included (in descending order of relative risk): 1) current use of anticonvulsant drugs, 2) inability to rise from a chair, 3) history of maternal hip fracture, 4) resting pulse rate >80 beats/minute, 5) previous hyperthyroidism, 6) poor self-rated health, 7) on feet <4 hours/day, 8) current use of long-acting benzodiazepines, 9) increased age (per five years), 10) lowest quartile for depth perception, 11) current caffeine intake (per 190 mg/day), 12) low-frequency contrast sensitivity, and 13) increased height (per 6 cm).<sup>22</sup>

### ***Screening***

Recent recommendations published by the North American Menopause Society (NAMS)<sup>34</sup> the Scientific Advisory Council of the Osteoporosis Society of Canada<sup>14</sup> and U.S. Preventive Services Task Force (USPSTF) recommends that all women 65 years of age and older be screened for osteoporosis with dual energy x-ray absorptiometry (DXA).<sup>7</sup> The USPSTF also recommends screening women 60-64 years of age with risk factors of low weight, low body mass index or nonuse of hormone replacement therapy. These guidelines are based on a number needed to screen (NNS) of 732 for women over age 65, meaning that 732 women would have to be screened to prevent one hip fracture in five years. The NNS for the 60-64 year age group is 1092. These recommendations suggest that for osteoporosis, a NNS of approximately 1000 has a favorable risk/benefit and cost ratio, based on current evidence.<sup>7, 14</sup>

### **Technological Assessment**

#### ***Dual energy x-ray absorptiometry (DXA)***

Bone mineral density (BMD) measurement by dual energy x-ray absorptiometry (DXA) is the gold standard for the diagnosis of osteoporosis, because it measures BMD at the

important sites of osteoporotic fractures, especially the hip.<sup>35</sup> BMD measurements include an absolute value (gm/cm<sup>2</sup>) as well as a standard deviation (t-score) value comparing an individual's bone density to that of peak bone mass according to reference standards established in the Third National Health and Nutritional Examinations Survey (NHANES III) in women ages 20-29.<sup>2</sup> Extensive work to standardize variation in BMD values due to DXA machines of differing manufacturers and to account for bone mass differences in race/ethnicity has been accounted for in the calculation of the standard deviation.<sup>35, 36</sup>

The World Health Organization (WHO) set four diagnostic categories of osteoporosis in 1994 by defining fracture risk by bone mineral density (BMD). Bone density is considered normal when BMD is within 1 standard deviation (SD) of the young adult reference mean. Osteopenia is characterized by a BMD of more than 1 SD below the young adult mean but less than 2.5 SD below this norm (t-score >-1 to -2.49). A BMD of more than or equal to 2.5 SD below the mean for a young person (t-score = <-2.5) is indicative of osteoporosis. Severe osteoporosis is characterized by a BMD score of more than 2.5 SD below the young adult mean, which is also accompanied by one or more fragility fractures.<sup>2, 37</sup>

This definition is based on a correlation of fracture risk with BMD. Each 1 SD decline in BMD is associated with a 2.0-3.6-fold increase in the age-adjusted risk of hip fracture.<sup>5, 18, 38</sup> Therefore, a woman with a "t-score" of -2 (deemed the fracture threshold by some experts<sup>39-42</sup> and the "treatment threshold" by the National Osteoporosis Foundation)<sup>43</sup> has at least a 4-fold increase in risk for hip fracture.

### ***Ultrasound***

The role of quantitative ultrasound (QUS) in the screening and treatment of osteoporosis remains unclear. Ultrasound measurements at the heel have been shown in large longitudinal studies to predict future fractures in postmenopausal women over age 65 years of age.<sup>14, 44-47</sup> However, evidence for the use of these devices in men and younger women is limited. Additionally, discordance between the measures of strength of the peripheral heel ultrasound and central DXA scans has emerged as a major problem causing misclassification of individuals.<sup>48, 49</sup>

### **Prevention and Treatment**

#### ***Conventional therapy***

A comprehensive discussion of conventional pharmacological approaches to osteoporosis are beyond the scope of this report, but excellent therapeutic reviews include an 2003 article by Follin and Hansen,<sup>50</sup> the 2002 Canadian clinical practice guidelines,<sup>14</sup> and the American Association of Clinical Endocrinologists Guidelines.<sup>51</sup>

Briefly, the bisphosphonates are first-line therapies in the prevention and treatment of osteoporosis (in both the hip and spine) for women and men, including those patients requiring prolonged glucocorticoid therapy.<sup>14</sup> They inhibit bone resorption through their effects on osteoclasts, interfering with osteoclast recruitment, differentiation and action as well as enhancing osteoclast apoptosis.<sup>52</sup> Raloxifene is a good option for the prevention and treatment of spine (only) osteoporosis.<sup>14</sup> It is a selective estrogen receptor modulator that has estrogen-agonist effects on bone, but antagonistic effects in the breast and uterus. Nasal calcitonin is most appropriate for pain relief in acute spinal compression fracture; it also is a consideration for women with proven osteoporosis that is limited to the spine. In the context of osteoporosis prevention, estrogen therapy alone (or with a progestational agent in women with an intact uterus) is most appropriate for women suffering from other menopausal symptoms,<sup>50</sup> those who experience menopause before age 45<sup>14</sup> and/or those unable to tolerate first-line therapies. (See Table 2)

## ***PHARMACEUTICALS OF SPECIAL INTEREST***

### ***Fluoride***

Fluoride has had a controversial role in osteoporosis treatment. In 1966, Bernstein et al reported that the incidence of osteoporosis was lower in an area where fluoride was naturally high in the water.<sup>53</sup> However, clinical trials conducted with high dose fluoride (75 mg/day) administered for four years failed to show efficacy. Although an increase in vertebral BMD was demonstrated, there was no decrease in vertebral fractures; additionally, there was an increase in non-vertebral fractures.<sup>54, 55</sup> Both studies were criticized for using high levels of fluoride supplementation.<sup>56</sup>

More recently, studies of low dose (20 mg/day) fluoride and low dose intermittent therapy have shown decreased vertebral fracture rates and increased BMD, with effects more pronounced for the spine than hip.<sup>57-59</sup> Fluoride is also being studied in combination with other conventional agents with good results. FDA approval for fluoride as an osteoporosis therapy in the US is still pending, and it is not recommended for prevention or treatment by the 2002 Canadian practice guidelines.<sup>14</sup>

### ***Statins***

Statins are the mainstay in the treatment of hyperlipidemia, and in some studies, statins have shown to produce a reduction in bone turnover thought to be due to decreased bone resorption. The effect of statins is modest compared to the effect of other antiresorptive agents (e.g. estrogen, bisphosphonates) and did not translate to a change in BMD.<sup>60</sup> Two different case-control studies involving large numbers of patients from the United Kingdom-based General Practice Research Database to determine if lipid-lowering agents were associated with a reduction in the risk of bone fractures resulted in conflicting conclusions.<sup>61, 62</sup>

In women with ischemic heart disease in the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study<sup>63</sup> and postmenopausal women in the Women's Health Initiative Observational Study (WHI-OS)<sup>64, 65</sup> statin use did not improve fracture risk. However, women in the WHI-OS who took statins for greater than three years showed

statistically significant higher BMD of the total hip and spine, and those who were taking higher potency drugs (atorvastatin and simvastatin) were found to have a higher BMD of the total hip than non-users.

### ***PHYSICAL MODALITIES***

***Exercise*** plays a useful role in cardiorespiratory, circulatory, and psychological functions as well as balance and overall stamina.<sup>66</sup> Finding a single “optimal formula” of exercises for osteoporosis has been elusive probably due to the fact that animal studies have shown that a variety of brief bouts of strenuous activity are osteogenic.<sup>66</sup>

Survey data indicates that active lifestyles are associated with a 50% reduction of hip fracture risk,<sup>67</sup> even though walking (by itself) has not been shown to be very effective in increasing BMD. However, any increase in physical activity may have a positive effect on bone mass who have been sedentary.<sup>68</sup> One American study suggests that a brisk 5 minute walk daily confers as much improvement in BMD than longer walks, so even the frail elderly and their caretakers should be encouraged to do this.<sup>66</sup>

A Cochran database systematic review of eighteen randomized controlled trials of exercise as a preventive tool for osteoporosis concluded that aerobics, weight bearing and resistance exercises were all effective on the BMD of the spine and that walking was effective for BMD of spine and hip.<sup>69</sup>

In younger, premenopausal women, jumping for 60 seconds per day was shown to increase BMD in the hip by nearly 4% after five months. Jogging has been shown to increase vertebral BMD and reduce loss of BMD in the femur.<sup>70</sup> Additionally, exercise to music that involves stepping and jumping are helpful in persons over 50 years of age. However when the jumping protocol described previously was repeated in post-menopausal women, no effect was found, suggesting that older women need a more than a minute of jumping to affect bone.<sup>66</sup>

Resistance training (weight-training or strength training) is most effective with slow lifts and heavy weights (above 70% of an individual's maximum) for men and women.<sup>66</sup> One interesting trial in which one side of the body did the weight-lifting while the other side served as the control showed increases of 3-4% in the BMD of the radius and hip after 12 months of exercise.<sup>71</sup> This study confirmed the site-specific nature of osteogenic loading. This form of exercise need not be demanding in cardio-respiratory terms and when introduced gradually, can be safe for men and women of all ages.

Regarding the selection of exercise machines at a gym or for home use, priority should be given to devices that provide some form of weight-bearing or impact-loading activity. Treadmills and stair-climbers off a lot of impact to the bone, whereas ski machines, exercise bicycles and rowing machines provide little or no impact.<sup>72</sup> Additionally, non-weight bearing exercises such as swimming and cycling are not effective in osteoporosis prevention.

Exercises to be avoided in persons with osteoporosis include, sit-ups or crunches as they are associated with a dramatically increased rate of vertebral fracture and straight-leg toe touches which carry an increased risk of retinal detachment.<sup>66</sup>

**Tai Chi Chuan** is a low-weight-bearing exercise and a major physical exercise regularly practiced worldwide by elder populations of Chinese origin. It has been shown effective for elderly people in maintaining neuromuscular coordination, muscle strength, flexibility, functions of cardio respiratory and immunoendocrine systems.<sup>73</sup>

A 2002 study by Qin *et al* conducted in Hong Kong was the first case-control study to show that regular Tai Chi Chuan exercise may help retard bone loss in the weight-bearing bones of postmenopausal women age 50-59 years. Regular Tai Chi Chuan exercisers and an age-matched control group of non-exercisers were followed for four years. At baseline, the women who participated in regular Tai Chi Chuan exercise had a significantly higher BMD (10-14%); in follow-up, although both groups experienced bone loss, the exercise group also had less bone loss as measured by DXA. Tai Chi may be an effective exercise for osteoporosis prevention.

**Vibration** High frequency vibration training as a potential treatment to increase BMD is in the developmental phase. In an Italian study, participants standing on a ground-based oscillating platform for six minutes, twice weekly for 6 months showed improvement in muscle power, but did not show changes in BMD or in biomarkers of bone turnover,<sup>74</sup> suggesting that either increased frequency or increased vibration may be necessary to effect bone. Studies by Rubin and associates showed more promising results in a prospective, randomized, double-blind, placebo-controlled pilot study involving 67 postmenopausal women followed for one year. As measured by DXA, significant prevention of bone loss in both spine and hip was reported after one year of two ten-minute sessions per day. This promising therapy is deserving of future studies.<sup>75, 76</sup>

**Electromagnetic fields.** The effect of electromagnetic fields on bones has been studied in animal models since the late 1980s. In animal models, use of pulsed electromagnetic fields (PEMF), induced at a physiological frequency and intensity, was shown to prevent both disuse osteoporosis<sup>77, 78</sup> and post-menopausal osteoporosis.<sup>79, 80</sup> An osteogenic dose-response was observed. The authors suggested that there is an effective window of induced electrical power in which bone mass can be controlled in the absence of mechanical loading. Additionally, an observed increase in bone marrow blood flow seemed to be related with this increase of bone volume and bone formation activity. Clinically, pulsed electromagnetic field therapy has been shown to aid in the treatment of delayed fracture union and has potential clinical application for osteoporosis.<sup>81</sup>

## **DIETARY CONSIDERATIONS**

Diets higher in fruits, vegetables, potassium and magnesium have been shown to result in higher bone mineral density in the hip for both older men and women.<sup>82</sup>

The issue of vegetable versus animal protein does not seem to be significant, as many epidemiological studies report no differences in BMD between vegetarians and non-vegetarians.<sup>56</sup> A few studies report a greater rate of bone loss after age 50 in lacto-ovo vegetarians<sup>83, 84</sup> or lower bone BMD at the hip.<sup>85</sup>

**Tea** drinkers have higher BMD than non-drinkers, but tea drinking has not been shown to be associated with a reduced fracture risk. The positive affect on BMD is thought to be due to the flavinoids found in tea. British researchers studying community dwelling women in Cambridge found a 5% mean difference in BMD, most notably in the spine.<sup>86</sup> In one Chinese study, persons who reported tea drinking for more than ten years showed an increase in BMD.<sup>87</sup> However, in the Women's Health Initiative Observational Study conducted from 1994-1998, the effect of habitual tea drinking on bone density was small and did not alter the risk of fractures among US postmenopausal women.<sup>88</sup> Tea can be recommended as part of a bone-healthy diet.

**Caffeine** was initially thought to simply increase urinary loss of calcium and as such, was considered a risk for bone loss. However, its effect is probably more complex, including affecting intestinal calcium absorption from endogenous sources. Each 6 fl. oz. of caffeinated coffee results in 40 mg of calcium lost. This can be offset by adding two tablespoons of milk to each serving of coffee.<sup>56, 89</sup>

**Carbonated beverages** are frequently associated with potential adverse effect on bone metabolism. Some studies have shown decreased bone mass and elevated fracture rates with the consumption of carbonated beverages, while others have not shown such a relationship.<sup>56</sup> A possible explanation for the adverse effect of carbonated beverages on bones could be due to the resulting acid load caused by the ingestion of phosphoric acid. However, other available studies do not differentiate between the beverages made with phosphoric acid or other acidulants. The reported adverse effect of carbonated beverages on bones may be due to the displacement of milk by carbonated beverages leading to lower calcium intake as well.<sup>56</sup> Nonetheless, carbonated beverages have no nutritional value.

**Alcohol** in moderation may have a positive impact on bone in elderly men and women. Evaluation of the 1,154 members of the Framingham Heart Study revealed that women who drank at least 7 oz. Of alcohol had higher bone densities at most sites. Men who were heavy alcohol drinkers (14 oz. or more/week) also had higher bone density than light drinkers.<sup>90</sup> An observational study of 489 women ages 65-77 resulted in similar conclusions.<sup>91</sup> Large European population studies on alcohol consumption and hip fracture risk indicated that moderate intake had no influence on fracture rate, but heavy drinking increased the risk of hip fracture, especially in men.<sup>92</sup>

**Dried plums**, a rich source of phenolic and flavonoid compounds, have been shown to have positive effects on bone metabolism in animal models. In a 2002 study, 58 women post-menopausal not on estrogen therapy were randomly assigned to consume either 100 g dried plums (about 18 dried plums) or 75 g dried apples daily for 3 months. Biochemical markers associated with bone formation were higher in the women who

consumed dried plums, suggesting that they may exert positive effects on bone in postmenopausal women. Longer duration studies are needed to confirm the beneficial effects of dried plum on BMD.<sup>93</sup>

### ***VITAMINS, SUPPLEMENTS AND HERBS (SEE TABLE 3)***

Adequate *calcium* intake is the most basic building block and best studied in the armamentarium in osteoporosis prevention. Adequate calcium is necessary for peak bone mass during the twenties; it continues to offer benefit even into the seventies. It also has increased effectiveness when given in combination with vitamin D, bisphosphonates, estrogens and soy. Despite the evidence supporting the positive effect of calcium on bone, national dietary surveys indicate that calcium intake in girls and women is below current recommendations (1000 mg in adult, premenopausal women and 1200 mg in postmenopausal women). Variations in calcium nutrition early in life can account for as much as a 5-10% difference in peak adult bone mass, which could potentially contribute more than 50% to the hip-fracture rates later in life.<sup>94</sup>

Bone is lost at such a rapid pace during early menopause that calcium alone is ineffective in preventing bone loss except in calcium-deficient women.<sup>95</sup> In late menopause, however, dietary calcium is more effective.<sup>56</sup> However, reports on the effectiveness of calcium supplementation for fracture prevention all show a substantial decrease in fractures with calcium supplementation. The data suggest that long-term calcium supplementation of 1000mg daily can affect a 24-30% reduction in fractures.<sup>56</sup> Calcium citrate is absorbed best in individuals on acid blockers and in the elderly with low gastric acidity, otherwise, the type of calcium supplement can be adjusted to individual preferences as long as adequate elemental calcium is attained. Adequate dietary calcium can be obtained by including three to four servings of dairy products each day.

*Vitamin D* facilitates calcium absorption in the intestine and is involved directly in bone turnover. It is most effective when given in conjunction with calcium. The Study of Osteoporotic Fractures (SOF) showed no benefits of vitamin D supplements (alone) to fractures rates.<sup>96</sup> When 500 mg of calcium is added to vitamin D, 700 IU and given daily to community dwelling men and women over age 65, nonvertebral fractures were reduced by more than 50% over a three year study period.

Vitamin D levels in the body decrease greatly with age, due to a combination of decreased sun exposure, diminished absorption from food, decreased ability to produce an activated product by various processes in the skin, kidney and liver. Hospitalized and homebound elderly persons are at highest risk for vitamin D deficiency.<sup>97, 98</sup> In 1997 requirements for vitamin D were decreased to 200 IU for those up to 50 years in age, while they were doubled or even tripled for the aged (400IU for those 51-70 years to 600 IU for those over 70 years).<sup>56, 99</sup>

### ***Soy and Isoflavones***

Isoflavones are naturally occurring sterols found in plants—some are called “phytoestrogens” because they have weak estrogenic activity. Genistein and daidzein, isoflavones found in soy and red clover, are probably the most commonly studied.

In a randomized, double blind placebo-controlled clinical trial of 208 women for conducted in Southern California,<sup>100</sup> borderline significance was noted in total isoflavone consumption and total spine BMD. **Red clover** containing 40mg of isoflavones/day in pre and perimenopausal women showed some evidence of reduction of bone loss of spinal bone mineral density in pre- and peri-menopausal women, but not in postmenopausal women. It had no effect on hip BMD.<sup>101</sup> Another red clover study involving 46 postmenopausal women followed for six months showed increased BMD of the radius and ulna with doses of 57mg/day or higher. The response with 28.5mg of isoflavones was not significant, suggesting a dose-dependent response.<sup>102</sup>

Another substantial evaluation of dietary isoflavones and BMD came from the Study of Women’s Health across the Nation (SWAN).<sup>103</sup> This US community-based multi-center study followed a longitudinal cohort of 1,927 women aged 42-52 years throughout menopause. Ethnic composition consisted of 497 African-Americans, 1003 Caucasians, 200 Chinese and 227 Japanese. The African-Americans and Caucasians had too low of dietary intake of the isoflavone genistein, to analyze; however, there was a substantial, positive, dose-response between BMD and genistein intake from premenopausal Japanese women. There was no relationship between BMD and genistein intake in postmenopausal Japanese women and for all Chinese women. The authors noted that the common Japanese form was more potent than the usual Chinese form, again suggesting a dose-response effect.

Studies suggest that 40 grams of soy protein containing 80-90 mg of isoflavones is the minimal dose needed to prevent osteoporosis.<sup>99</sup> The evidence for a positive relationship of dietary soy and isoflavones is suggestive.

***Dehydroepiandrosterone (DHEA)***—Given topically, DHEA shows promise, although the studies to date are small. The effect of 12-month dehydroepiandrosterone (DHEA) therapy was evaluated in 14 women, ages 60 to 70-yrs. The women received daily applications of a 10% DHEA cream. Most interesting, the bone mineral density significantly increased at the hip from 0.744 +/- 0.021 to 0.759 +/- 0.025 g/cm<sup>2</sup> after 12 months of treatment (P < 0.05). A 2.1-fold increase over the control value in plasma osteocalcin was also observed, suggesting that DHEA stimulated bone formation.<sup>104</sup>

***Magnesium*** has a positive association with BMD as demonstrated by population studies, including the Framingham Heart Study cohort.<sup>82</sup> Good sources of magnesium are whole grains, broccoli, squash, nuts and seeds, dairy products, meats and chocolate. Except in cases of proven deficiency, supplements are not recommended.<sup>99</sup>

Numerous studies have been done ***Vitamin K*** and its relationship to bone health.<sup>105-107</sup> Vitamin K is a necessary coenzyme that promotes enhanced incorporation of calcium into

bone. The usual diet contains more than enough Vitamin K. Vegetables, especially cabbage, cauliflower, spinach, cereals, and soybeans can be recommended as good dietary sources. Additional supplementation with Vitamin K is not recommended for prevention or treatment of osteoporosis by the 2002 Canadian practice guidelines.<sup>14</sup>

**Folate** levels were lower in osteoporotic women than in women with normal BMD in a recent Italian study by Cagnacci *et al.*<sup>108</sup> Additionally, in the 161 women, only serum folate levels and weight were independently related to BMD. The authors did not find a relationship between BMD and homocysteine levels or B12 levels. Further research needed to understand the relationship of folate to bone health, and vegetables rich in folate can be recommended.

**Ipriflavone** is a semi-synthetic isoflavone manufactured from the isoflavone, daidzein. It enhances osteoblastic function and inhibits bone resorption, mainly by inhibiting recruitment of osteoclasts. Ipriflavone has been tested extensively in clinical trials in Italy, Japan and Hungary. It has been shown to prevent bone loss in postmenopausal osteoporosis and to increase BMD when administered with calcium or estrogen.<sup>99</sup> It has also shown to be helpful in the management of pain from osteoporosis and compression fractures.

However, Ipriflavone use has been found to adversely affect lymphocyte counts, especially in first six months of use. Ipriflavone is not recommended for prevention or treatment in the 2002 Canadian guidelines.<sup>14</sup>

### **Herbs**

To date, evaluation of the potency of herbal supplements in the area of bone health has been limited to animal models or *in vitro*. Traditional Chinese medicines (different combinations of herbs in various Kampo Formulae) show similar effects to estrogen in preventing bone loss in ovariectomized rats<sup>109</sup> or inhibiting bone resorption *in vitro*.<sup>110</sup> A Japanese herbal medicine Chujo-to<sup>111</sup> and Chinese Guizhou epimedium<sup>112</sup> both show improvements in bone parameters in ovariectomized rats. Research in this area is in its infancy and before any official recommendations can be given for the herbal effects on bone, controlled clinical trials have to be performed.<sup>56</sup>

### **Agents with no proven benefit**

Flaxseed has been shown to improve lipids, but has not been shown to alter biomarkers of bone metabolism in postmenopausal women.<sup>113</sup> Similarly, there are no studies to indicate any benefit from gelatin, don quai, ginseng, alfalfa or licorice. Additionally, without proven deficiency, there is insufficient evidence to recommend supplementation with vitamin K, magnesium, manganese, boron, zinc or copper as effective prevention or treatment for osteoporosis.<sup>99</sup> However, a multivitamin with minerals taken as directed should not contain excesses that would prove harmful for those patients who want to augment their diet.

### ***Conclusions***

Osteoporosis is a preventable condition; however, without a change toward increased screening and intervention, it will result in millions of unnecessary fractures annually. The initial step in this prevention should focus on improving screening with DXA. Once osteoporosis is identified, renewed emphasis on low-impact, weight bearing exercise including Tai-Chi Chuan, appropriate weight training prescriptions, healthy diets with increased proportions of fruits, vegetables, calcium and soy, and prudent use of supplements and pharmaceuticals has the potential to reduce fractures by half. Additionally, we must also continue to investigate thoroughly any regimen, including physical modalities, pharmaceuticals, vitamins, supplements and herbs to generate responsible recommendations for both prevention and treatment of osteoporosis. If we want our eldest patients to enjoy a fracture-free life, we must begin immediately to translate knowledge into action.

**Table 1: Common secondary causes of bone loss<sup>34</sup>**

Medications

- Glucocorticoids (e.g., prednisone @ 5mg/day) for > 6 months
- Excessive thyroxine doses
- Long-term uses of certain anticonvulsants (e.g., phenytoin)
- Anticoagulants (e.g., heparin, warfarin)
- Cytotoxic agents
- Gonadotropin-releasing hormones agonists or analogues
- Intramuscular medroxyprogesterone contraceptive (Depo-Provera)
- Immunosuppressives (e.g., cyclosporine)

Genetic disorders

- Hemophilia
- Thalessemia
- Hypophosphatasia
- Hemochromatosis

Disorders of calcium balance

- Hypercalciuria
- Vitamin D deficiency

Endocrinopathies

- Cortisol excess
- Cushing's syndrome
- Gonadal insufficiency (primary and secondary)
- Hyperthyroidism
- Type I diabetes mellitus
- Primary hyperparathyroidism

Gastrointestinal diseases

- Chronic liver disease (e.g., primary biliary cirrhosis)
- Malabsorption syndromes (e.g., celiac disease, Crohn's disease)
- Total gastrectomy
- Billroth I gastroenterostomy

Other disorders and conditions

- Multiple myeloma
- Lymphoma and leukemia
- Systemic mastocytosis
- Nutritional disorders (e.g., anorexia nervosa)
- Rheumatoid arthritis
- Chronic renal disease

**Table 2: Antifracture efficacy of the most frequently used treatments of postmenopausal osteoporosis in addition to the effects of calcium or vitamin D supplementation, or both, as derived from placebo controlled randomized trials Adapted from Delmas.<sup>114</sup>**

<i>Drug</i>	<i>Vertebral fractures</i>	<i>Non-vertebral Fractures (hip)</i>
Alendronate	+++	++
Calcitonin (nasal)	+	0
Etidronate	+	0
#Fluoride	±	-
Estrogen*	+	0
Parathyroid hormone $\tau$	+++	++
Raloxifene	+++	0
Risedronate	+++	++
Vitamin D derivatives	±	0

#Not FDA approved

+++ = strong evidence; ++ = good evidence; + = some evidence; ± = equivocal;

0 = no effects; - = negative effects.

\* Evidence derived mainly from observational studies.

$\tau$  Effect on hip fractures not documented in prospective controlled trials

**Table 3: Efficacy of Vitamins and Supplements for Osteoporosis**

<b>Agent</b>	<b>Dose range</b>	<b>Efficacy<sup>99</sup></b>	<b>Adverse Reactions</b>	<b>Special Notes</b>
<b>Calcium</b>	1000mg– 1200mg	Likely effective (++)	Constipation	Not effective in early menopause. Additive with other agents Calcium citrate for patients on acid blockers or elderly with low gastric acidity.
<b>Vitamin D</b>	5-15 µg/d (200-600 IU) dosage is age dependent	Effective (+++) in steroid induced osteoporosis  Possibly (+) in postmenopausal osteoporosis.		Ineffective alone. <sup>115</sup> Effective when added to Calcium
<b>Magnesium</b>		Possibly (+)		Effective only in those with magnesium deficiency
<b>Manganese</b>		Possibly (+) when used in combination with calcium, zinc, and copper		
<b>Vitamin K</b>	65mcg-80mcg	Investigational only		Dietary or multivitamin is adequate
<b>SOY</b>	40g/day	Possibly (+)		
<b>Isoflavones</b>	53.3-130 mg/d  90mg/d <sup>116</sup>	Likely (++)		Spinal only improvement <sup>117</sup>  Spinal only <sup>116</sup>
<b>Ipriflavone</b>	600mg/d	Likely (++) Not recommended <sup>118</sup>	Lymphocytopenia	No improvement <sup>118</sup>
<b>Fluoride<sup>54-56</sup></b>	20-75 mg	Under investigation	Increased fracture risk, bone pain, GI side affects	Not recommended. Lower doses show promise.

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