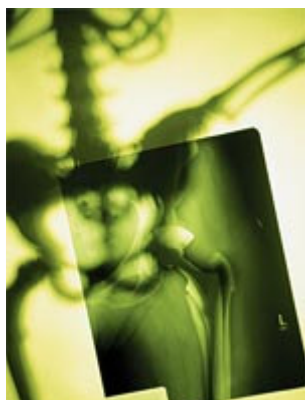


## Strategies for Preventing Osteoporosis in Men

By Julius G. Goepp, MD



Often overlooked, male osteoporosis is a rapidly growing health problem.<sup>1</sup> About 2 million US men have osteoporosis.<sup>2</sup> The annual cost of male osteoporosis has been estimated at about \$200 million in France alone.<sup>3</sup> Recent articles in the scientific literature have begun to recognize that osteoporosis and bone fractures in men pose “a significant public health problem,”<sup>4</sup> one that continues to be unrecognized by health care providers, insurers, and the public.<sup>5</sup> In a 2002 article in the journal *Urology*, Dr. Mark Moyad of the University of Michigan Medical Center noted that the impact of osteoporosis in men is “significant and noteworthy,” particularly in light of the growing use of androgen deprivation therapy (ADT) for prostate cancer.<sup>6</sup>

While osteoporosis has many different causes in both women and men, male osteoporosis generally differs in important ways from female osteoporosis. Men develop osteoporosis about a decade later in life than women,<sup>7</sup> and though men have fewer osteoporosis-related fractures than women, they are more likely to suffer serious complications or death as a result.<sup>2</sup> About one third of all osteoporotic fractures occur in men, and experts predict that with expected increases in life expectancy, the number of fractures in men will double by the year 2025.<sup>1</sup>

People often tend to think of hip fractures as a problem of older women. In fact, as many as one third of all hip fractures occur in men,<sup>5</sup> and elderly men have age-specific hip fracture rates that are nearly half those of women.<sup>8</sup> Moreover, the death rate after hip fracture is even higher in men than in women.<sup>2</sup> After the age of 80, spine fractures are equally common in men and women, and are associated with increased mortality.<sup>9</sup>

Women with osteoporosis tend to fracture their lower extremities more commonly than their arms, but men are more likely to have wrist fractures. In men, wrist fractures have been shown to be an important risk factor for having hip fractures later in life, whereas in women, a previous spine fracture is predictive of subsequent hip fractures.<sup>10</sup>

Millions of older adults around the world have neglected their bone health. The problem has become so important, in fact, that the decade between 2000 and 2010 has been designated as the “Bone and Joint Decade” by the United Nations, the World Health Organization, and 37 countries. This designation was made to encourage research into the burden of musculoskeletal disorders worldwide, in recognition of the rapid aging of the population.<sup>11</sup>

To prevent or overcome male osteoporosis, it is important to understand the many ways in which bone health is affected by growth, aging, the environment, and diet. In this article, we will look at normal bone structure and function, then examine the ways in which bone changes normally and abnormally over a lifetime. Finally, we will explore the many proven ways to maintain healthy bones that resist fractures and pain, and help maintain a vigorous and active lifestyle.

### Primary Osteoporosis: “Normal” Bone Loss with Aging

The human skeleton is the single largest organ system in the body. Composed of a complex mix of organic proteins and inorganic mineral crystals, bones are much more than just structural supports. Bones are the body’s only reservoir of important minerals such as calcium and phosphorus, which are critical for virtually every other organ system. Calcium, for example, is used in every nerve and muscle cell in the body as a chemical signal. Phosphorus is used in

every cell in the human body and is considered the universal energy “currency”; when fats, carbohydrates, and proteins are burned for energy, phosphate molecules move to or from carrier molecules to keep the energy flowing. Levels of calcium and phosphorus must be precisely maintained to keep tissues working properly. Because there is no other internal storage area for these minerals, the skeleton functions as a strategic reserve, absorbing or releasing minerals as required to keep blood levels virtually constant. Bones are able to fulfill this function due to their amazing complexity.

To a structural engineer, bone would be considered a “composite” material, part mineral and part living tissue. It is formed mostly of calcium phosphate arranged in crystals called hydroxyapatite, embedded in a protein matrix primarily made of collagen. This arrangement is very similar to reinforced concrete, in which strong steel bars are embedded in weaker cement. Like reinforced concrete, bone has remarkable strength when it is compressed (for example, when it supports the normal weight of a person standing or moving). Bone has relatively poor strength, however, when it is pulled or bent (such as in a fall). Dietary intake of calcium and phosphorus, as well as of protein (particularly structural proteins that go into the makeup of collagen), is critical in maintaining every element of healthy bone.



In a normal adult diet without supplementation, the amount of calcium entering the body just balances the amount that is excreted each day. This means that even a slight dietary deficiency in calcium itself, or in the vitamin D needed to absorb it, can result in a drop in total body calcium levels. Because blood levels must be maintained within a narrow range, this will result very rapidly in mobilization of calcium from bone to restore the balance. Although the entire skeleton contains large amounts of calcium, prolonged deficiency of vitamin D or calcium will rapidly deplete the stores, resulting in decreased bone mineral content and weaker bones.

Because it is living tissue, bone contains many different kinds of cells, each with a unique function in maintaining bone’s strength and shape. Osteoblasts are the body’s bone-forming cells. Living on or near the surface of bone, osteoblasts secrete protein to form the matrix in which hydroxyapatite crystals form. Osteoblasts are controlled by many different factors, including calcium and phosphorus levels and the sex hormones (estrogens in women and androgens in men). A different bone cell type, the osteoclast, is responsible for breaking down and absorbing bone, a function that is critical in allowing bones to adapt to changes in body size and shape. The overall state of a bone, then, is the result of a precise and delicate balance between the bone-forming work of the osteoblasts and the bone-resorbing osteoclasts. The combined process of production and resorption is called bone turnover, or remodeling.

During childhood and adolescence, bone formation is greater than bone resorption, with the result that bones grow in length, thickness, and strength. Sex hormones have a powerful impact on bone growth. At puberty, bone production increases dramatically, producing the growth spurt of the early teen years. This effect seems to be driven mostly by estrogens, the “female” hormones, in both boys and girls. Near the end of puberty, androgens, the “male” hormones, increase in both women and men. The androgen surge fuses the bone growth plates, with the result being that the bones can no longer elongate.

Young adults generally maintain a steady-state balance in which new bone formation is nearly equal to bone resorption. This process is essential in keeping the bones healthy and enabling them to respond to changes in weight, activity, and diet. Sex hormones also remain at steady levels throughout young adulthood and early middle age. After about the age of 35, however, the total amount of bone in the body begins to diminish. This is one reason that attention to diet and exercise is so important, even very early in life.

Because bone biology is so heavily influenced by sex hormones, it is not surprising that bones age differently in men and women. In aging women, bone is lost both from the inner and outer surfaces of bones, as bone resorption by osteoclasts exceeds new bone formation by osteoblasts. In men, however, new bone formation on the outer surface of bone keeps pace with resorption on the inner surface for much longer.<sup>12</sup> This may account for the fact that men begin to suffer fractures from osteoporosis about a decade later than women.<sup>7</sup>

After middle age, bone loss accelerates. In women, the process begins fairly sharply with the onset of menopause, when estrogen levels drop dramatically. This obvious connection probably accounts for the fact that osteoporosis was thought for so long to be a problem unique to women. Because bone density in men was thought to be related to androgen levels<sup>1</sup> and men did not appear to experience anything similar to menopause, doctors simply did not think of osteoporosis in men.

Over the past decade, a vastly different picture has emerged. Many experts now accept the reality of a male equivalent of menopause.<sup>1,4,13-17</sup> Some scientists refer to this change as “andropause,” though a more recent and accurate term is “androgen deficiency of the aging male.”<sup>18</sup> The distinction is important because, unlike the marked physical changes seen at menopause, the loss of androgens is more gradual and much more variable in terms of a man’s age at its onset.

Another way in which our understanding of the skeletal effects of aging has changed is the discovery that primary control of bone mineralization in both men and women is by estrogens.<sup>1</sup> This not only changes our understanding of how osteoporosis occurs in men, but also has dramatic implications for how we can prevent and treat it. Both estrogen and testosterone are produced in the body from androstenedione, which is itself formed from dehydroepiandrosterone (DHEA).<sup>8</sup>

## **Causes of Secondary Osteoporosis**

The previous discussion concerns “normal” bone loss with aging, or so-called primary osteoporosis. Bone loss frequently occurs due to other causes as well. Men are more likely than women to have so-called secondary osteoporosis<sup>2</sup> related to factors including:

**Corticosteroids.** The most common cause of secondary osteoporosis is treatment with glucocorticoids or corticosteroids, which are often used to treat cancer and many inflammatory conditions. Steroids suppress production of the sex hormones that maintain healthy bone. Bone loss during corticosteroid treatment is very rapid and occurs right at the beginning of treatment. Without supplementation, there will be less total body calcium available to restore the bone at the end of the corticosteroid treatment.<sup>19</sup> Even the very low doses of corticosteroids used in the inhaled form for treating asthma and other respiratory diseases have been shown to suppress serum levels of DHEA-S, the most important sex hormone building block.<sup>20</sup>

**Prostate cancer and its treatment.** Prostate cancer is the most common cancer in men, and major advances in early detection and treatment have made it a survivable condition for many men. Unfortunately, prostate cancer itself and its most effective treatment, androgen deprivation therapy, or ADT, both contribute to secondary osteoporosis.<sup>21</sup> These days, many men begin receiving ADT quite early in response to an elevated or rising prostate-specific antigen (PSA) test result. Because these men are likely to live for many years after starting treatment, they should have baseline bone mineral density measurements, which should be repeated periodically.

Even before ADT is started, many men with prostate cancer have pre-existing osteopenia and osteoporosis.<sup>22</sup> This finding has concerned experts because of the additional bone loss experienced during ADT, and has served to alert the medical community to the higher-than-expected frequency of osteoporosis in men overall.<sup>21,23</sup> It makes sense, then, for all men to

ensure the best possible degree of bone mineralization through regular intake of nutrients known to promote strong bone structure.

**Vitamin D deficiency.** Skin's exposure to sunlight is a critical element for activating vitamin D. As people age, their skin's ability to perform this crucial function diminishes, and less active people may not get out into the sun enough to promote the conversion. In fact, people who live in latitudes north of San Francisco may receive inadequate UVB radiation for several months of the year.<sup>24</sup> Because both the kidneys and liver are important in activating vitamin D, impairment in either of these organs makes less of the vitamin available.



**Miscellaneous causes.** There are a host of other causes of osteoporosis. Any condition or treatment that impairs calcium metabolism anywhere along the complex pathways that control it will make osteoporosis likely. These conditions include kidney disease, organ transplants, smoking, and anticoagulants.<sup>25-28</sup> Poor nutrition or the need for parenteral nutrition (intravenous “feeding”) are two possible causes of osteoporosis.<sup>29-31</sup> While the nature of the relationship is unclear, osteoporosis is also related to depression.<sup>32</sup> Interestingly, many of the things known to help prevent depression—such as good diet, regular exercise, and ample exposure to natural light—also help prevent osteoporosis.

#### WHICH TYPE OF BONE TEST IS BEST?



There are two tests used to measure bone mineral density. The **dual energy X-ray absorptiometry (DEXA)** test is most commonly used because there are more DEXA testing devices in doctors' offices than the more advanced **quantitative computed tomography (QCT)**.

In a report by Smith et al, osteoporosis was present in 63% of men at the time of diagnosis of prostate cancer, prior to any therapy.<sup>87</sup> In this landmark paper, the investigators evaluated DEXA bone mineral density testing and compared it to QCT bone mineral density testing in the same patients. **A**

**significantly greater percentage of men were found to have osteoporosis using the QCT methodology versus the DEXA approach.** DEXA bone mineral density evaluation detected osteoporosis in only 5% of men, whereas with QCT technology, **63%** of men were diagnosed with osteoporosis. Using QCT technology, total bone density abnormalities (osteopenia and osteoporosis) were found in 95% of men, compared to 34% of men evaluated with DEXA. This study corroborates the epidemic of bone loss faced by aging males.

Studies by prostate oncologists Drs. Stephen Strum and Mark Scholz have confirmed the results of Smith et al. Drs. Strum and Scholz found either osteoporosis (50%) or osteopenia (50%) in 100% of the men they studied with QCT. In the same men, using DEXA, they found only 5% with osteoporosis and 50% with osteopenia.<sup>88</sup> A reasonable question to ask is, “Why are there such differences in detection using the two techniques?” One answer is that the DEXA scan may pick up degenerative changes involving the bone and joint tissues, as well as calcium deposits within blood vessels, and read these as bone density, whereas the QCT reads only calcium deposits in bone itself.<sup>89-93</sup>

Although QCT testing exposes patients to more radiation than DEXA, the amount of radiation associated with QCT for determining bone density is roughly equivalent to that of

a dental series, and is roughly 50% less than that of a mammogram (depending on the technique used). Most important, QCT generates far less radiation exposure—orders of magnitude less—than a contrast-enhanced abdominal CT scan.

If you are going to have your bone density checked, the QCT test provides a more effective analysis than DEXA. First, it does not place the patient in harm's way due to the likelihood of underestimating bone density because of falsely high readings related to the reasons previously mentioned. Second, because QCT assesses the patient's status more accurately, this directs medical strategy to resolve the multiple medical problems encountered by the aging patient. Such problems may include bone aches and pain, vertebral compression fractures, and fractures of the hip, wrist, and other bones, as well as the problems commonly encountered by cancer patients at the time of diagnosis and during treatment.

## Tests, Treatments, and Supplements

Because of its slow and insidious nature, osteoporosis may not be diagnosed until after a serious fracture has occurred. For this reason, all modern guidelines recommend aggressive case-finding and screening programs.<sup>33</sup> The growing recognition that men are at much higher risk than previously believed means that men, too, should undergo regular screening. The sidebar on the previous page describes the best screening test to evaluate bone mineral density. Because prevention is much more effective than treatment, however, most experts recommend the use of nutritional supplements, even when early screening results are negative.

The main prescription medication for osteoporosis is a category of drugs called bisphosphonates—such as Fosamax®—that can prevent bone loss.<sup>34</sup> These drugs work by inhibiting osteoclasts, thereby slowing bone resorption. They have no significant effect on new bone formation, and may have significant side effects such as gastric ulcers or gastritis.<sup>35,36</sup> They are not currently recommended as preventive treatment.<sup>7</sup> Even when these drugs are used, adequate supplies of calcium and vitamin D may still be crucial for promoting bone health.<sup>37,38</sup>



According to Dr. Moyad of the University of Michigan, “complementary therapies, which may also have an impact on reducing osteoporosis risk, have not received attention.” He notes, “Dietary and supplemental calcium and vitamin D have been shown, in some preliminary investigations, to maintain bone density in women and men,” and “the supplemental doses required to impact risk have been moderate, appear to be safe, are of low cost, and thus may provide an additional route for reducing risk, especially if these interventions are initiated at the start of medical treatment.” According to Dr.

Moyad, “Simple, inexpensive, and potentially effective dietary and supplemental approaches to reduce the risk of osteoporosis in men exist, and they should be discussed with patients.”<sup>6</sup>

These supplemental approaches include mineral and vitamin supplements, hormone-like substances, protein supplements, and phyto-estrogens (including soy isoflavones). The mainstay of prevention and treatment for osteoporosis in men and women is to ensure adequate intake of calcium and vitamin D through dietary supplementation.

In a randomized, double-blind, placebo-controlled study published in 2000, daily supplementation with 750 mg of calcium reduced the loss of bone mineral density at the hip significantly more than placebo. Vitamin D alone had a similar, though smaller, effect.<sup>39</sup> This

study provided either calcium or vitamin D, but not the combination, and the authors point out that vitamin D is most effective in those who have insufficient calcium intake.

A 2005 randomized study found increased bone mineral density in patients who received 500 mg of calcium and 400 IU of vitamin D daily with or without the bisphosphonate drug etidronate (Didronel®). The drug-treated group had no greater improvement than the supplement-only group.<sup>40</sup> In another study, supplementation with the vitamin D derivative calcitriol and phosphate produced a larger increase in bone mineral density than etidronate.<sup>41</sup>

Recently, new synthetic versions of vitamin D have become available that offer more specific benefits directly to bone. One such product, ED-71, was shown to increase bone mass more than regular vitamin D3, while having a similar degree of effect on increasing intestinal calcium absorption.<sup>42</sup>

## Calcium: Not Just for Women

The recommendations above are general and apply to both men and women. As male osteoporosis becomes an increasingly important issue, new guidelines are appearing that specifically target men. Calcium and vitamin D supplements make up part of the so-called “bottom line” recommendations in a 2005 review of men’s health needs,<sup>43</sup> and ensuring adequate intakes has been called the “cornerstone of any regimen aimed at treating or preventing osteoporosis in men.”<sup>2</sup> Supplementation with calcium and vitamin D is at the top of all recent recommendations for treating

osteoporosis in men,<sup>44</sup> including guidelines issued by the American College of Rheumatology.<sup>45</sup> An expert meeting of the Belgian Bone Club concluded, “supplemental calcium and vitamin D should be considered as the first-line therapy.”<sup>46</sup> The same group determined that while combinations of anti-resorptive drugs should not be used, calcium and vitamin D in combination should be encouraged.

An expert panel convened by the World Health Organization Collaborating Center for Osteoporosis Prevention<sup>47</sup> issued the following statements about the use of oral supplements of calcium and vitamin D in preventing and treating osteoporosis:

1. When given in appropriate doses, calcium and vitamin D have been shown to be pharmacologically active, safe, and effective for the prevention and treatment of osteoporotic fractures in all patients (that is, those with and without adequate dietary calcium intake).
2. In patients with insufficient dietary intake of calcium and vitamin D, supplements are an essential but not sufficient component of an integrated management strategy for the prevention and treatment of osteoporosis.
3. Supplements are cost-effective in the prevention and treatment of osteoporosis.
4. Awareness of the efficacy of calcium and vitamin D supplementation is still low and further work needs to be done to increase awareness among patients, physicians, and people at risk. This lack of knowledge was borne out in a US study, in which an extensive review of the records of male veterans at risk for osteoporosis found that only 8% received the recommended calcium and vitamin D supplementation.<sup>45</sup>

## Calcium: How Much, How Often?

Calcium supplements come in various forms, as calcium carbonate, gluconate, citrate, or others.

### THE IMPORTANCE OF PREVENTION

Studies suggest that men may be less likely than women to implement preventive health strategies before they get sick.<sup>51</sup>

In the case of osteoporosis, this is a bad approach. In one study, men did not begin using valuable calcium supplements until after they had been diagnosed with low bone mineral density.<sup>52</sup> While we know it is never too late to start these simple supplements, it makes much more sense to start while bone density is normal.

It is important to remember that the amount of calcium used in these various studies is based only on the elemental calcium content of the supplement. Be sure to read the label of the supplement you are taking—the amount of elemental calcium should provide at least 1000 mg a day.

It may turn out that not only is supplementation vital to preventing and treating osteoporosis, but that the timing of the supplementation is important. For example, in a study of healthy volunteers, two doses of 500 mg of calcium and 400 IU of vitamin D taken six hours apart produced a more prolonged decrease in serum parathyroid hormone levels (low levels of which indicate adequate calcium levels) than a single dose with the same total amounts of calcium and vitamin D.<sup>48</sup>

Calcium can be paired with other bone-promoting supplements for an even greater benefit. Bone mineral density increased and fracture rate fell in men treated early with a fluoride-calcium regimen,<sup>49</sup> while salmon calcitonin and calcium produced significantly increased bone mineral density at multiple bone sites in men.<sup>50</sup>



## Other Vitamins and Minerals

Silicon, the second most common element in the Earth's crust, is an ultra-trace element that is vital for a large number of biological functions.<sup>53</sup> For more than two decades, it has been recognized that silicon plays a fundamental role in bone health<sup>54</sup> and may be protective against neurodegenerative conditions such as Alzheimer's disease.<sup>56</sup> The details of silicon's importance in preventing and treating osteoporosis in men are only now beginning to emerge.<sup>55-58</sup>

During new bone formation, silicon is essential for forming the protein cross-links in the organic matrix. In a rat model, bone formation in silicon-supplemented animals increased by 30% while bone resorption decreased by 31%.<sup>59</sup> Similar results were found more recently in rats and horses.<sup>60,61</sup>

In humans, higher silicon intake is associated with higher bone mineral density.<sup>62</sup> This effect has been found to be especially important in men and premenopausal women.<sup>56</sup> Because the primary dietary sources of silicon for men are beer and bananas,<sup>63</sup> supplemental silicon is likely to be required.

The most recent and exciting data on silicon supplements in humans come from a study presented at the American Society for Bone and Mineral Research meeting in September 2005.<sup>64</sup> The authors conducted a randomized, controlled trial of a highly bioavailable silicon supplement, choline-stabilized orthosilic acid (ch-OSA). While all the study subjects received both calcium and vitamin D3 supplements, the treatment groups also were given three different doses of ch-OSA. After 12 months, patients who took the silicon supplements at the two higher doses (6 mg and 12 mg of silicon) had significant improvements in markers of bone formation compared to controls. Bone mineral density also improved at the femoral neck in the 6-mg silicon group. The authors concluded that ch-OSA plus calcium and vitamin D3 is a safe, well-tolerated treatment with a potentially beneficial effect on bone turnover, especially bone collagen.

Oral magnesium supplementation has been shown to significantly reduce the bone turnover rate in men.<sup>65</sup> Because increased bone turnover rate is known to be an important factor in osteoporosis, magnesium supplementation may offer a natural approach to preventing and possibly managing this condition. While supplementing with magnesium and calcium at the same time may decrease the absorption of the respective minerals, this interaction has not been shown to be clinically significant.<sup>66</sup> Thus, consuming supplements that combine calcium and magnesium may be the most convenient way for individuals to acquire these crucial

minerals. Nutrition experts recommend obtaining calcium and magnesium in ratios ranging from 1:1 to 2:1.

Vitamin K, long known to be critical in the blood-clotting system, more recently has been found to be important in bone and mineral metabolism. Vitamin K2 is active and more powerful than vitamin K1 in both decreasing bone loss through resorption and enhancing the bone-building process. K2 was recently recommended for consideration in helping to prevent or treat osteoporosis in patients whose underlying conditions put them at risk for the disease.<sup>67</sup> Because vitamin K contributes to blood clotting, individuals who use warfarin should consult their physicians before taking vitamin K.

## Hormone Replacement Therapy

Conventional hormone replacement therapy with equine estrogens and synthetic progestins (medroxy progesterone acetate) has been used for years to prevent or mitigate osteoporosis in women, but recent reports of dangerous consequences, such as breast and uterine cancer, have cast doubts on its safety. Dehydroepiandrosterone (DHEA) may offer an alternative in people who do not have hormone-dependent cancers.

Both men and women manufacture DHEA throughout their lives as the common precursor to the sex hormones. DHEA levels, however, decline dramatically as men and women age. Restoring DHEA levels to the optimal range found in healthy young adults may enhance bone mineral density.<sup>68</sup> Importantly, and unlike prescription bisphosphonate drugs, DHEA appears to enhance new bone formation as well as inhibit bone resorption. This effect has been reported to be greater in women than in men, but a group of Italian researchers found that supplementation with 25 mg per day of DHEA in a group of aging men with partial androgen deficiency increased serum levels of DHEA, DHEA-S, androstenedione, total and free testosterone, progesterone, 17-hydroxyprogesterone, estrone, estradiol, and growth hormone.<sup>16</sup> These hormones all promote bone deposition and prevent bone resorption in the presence of adequate supplies of calcium, magnesium, and phosphorus. Importantly, supplementation with DHEA also lowered serum levels of the gonadotropin-releasing hormones follicle stimulating hormone (FSH) and luteinizing hormone (LH); this is the desirable effect obtained by many drugs used in treating prostate cancers, and may also help to reduce bone turnover and limit mineral losses.



Serum DHEA-S levels correlate strongly with bone mineral density in adults; DHEA-S is believed to convert to androstenedione and then to estrone within the osteoblast cell only.<sup>69</sup> This effect could explain how DHEA can augment bone density without producing unwanted feminizing effects on the body as a whole.

Most experts are calling for larger, placebo-controlled trials to fully define DHEA's benefits on bone mineral density.<sup>68</sup> Because DHEA is metabolized to estrogen and testosterone, it should not be used in people with known hormone-

dependent cancers such as breast or prostate cancer.

Hormone replacement therapy may benefit more than just bone mass and density. A small, randomized, double-blind, placebo-controlled trial in 2001 demonstrated improved performance on tests of spatial and verbal memory in older men who received testosterone injections compared to those who received placebo.<sup>15</sup> Because testosterone can be metabolized into estradiol, a female hormone, estradiol levels also rose in the treated men, and the authors raised the valid question of whether the observed improvement was due to higher estradiol levels

## Protein Supplements

Until recently, it was thought that high-protein diets may cause increased resorption of calcium from bone, because elevated calcium levels were found in the urine of those with a high intake of protein. More recent studies have demonstrated just the opposite: that the increased urine calcium levels seem to be the result of increased intestinal absorption of calcium, which of course means that there is more, not less, calcium available for bone mineralization. Lower-protein diets were found to decrease calcium absorption.<sup>30</sup> This may explain why people who habitually consume low-protein diets are known to have decreased bone density and increased bone loss.

Soy protein supplementation has been known to be protective of bone in women. In 2002, this finding was extended to men. A study of healthy older men (with an average age of 60) showed that those who supplemented daily with 40 grams of soy protein for three months significantly increased their levels of insulin-like growth factor 1 (IGF-1) compared to men who supplemented with milk protein. IGF-1 is associated with higher rates of bone formation. While markers of bone formation and resorption were not different between the two groups, the authors concluded that soy protein supplements may positively influence bone in men. They went on to suggest that a longer-duration study is warranted to demonstrate this effect.<sup>70</sup>

## **Phytoestrogens and Isoflavones**

There has been growing interest in how another soy component—the isoflavones—may help prevent and manage heart disease, osteoporosis, and cancer. Soy isoflavones are phytoestrogens, or plant-based compounds that resemble estrogen at the molecular level. Studies of traditional diets in large populations demonstrate that foods containing phytoestrogens may offer protection against many hormone-related cancers, and that adding phytoestrogen-rich foods to the diet helps maintain bone density in people with osteoporosis.<sup>71</sup> Particularly since the publication of the Women's Health Initiative warning against estrogen's use in hormone replacement therapy,<sup>14</sup> the importance of isoflavone phytoestrogens has grown.

Direct scientific evidence for isoflavones in osteoporosis is abundant. In 2001, a review of 74 major articles concluded that evidence for the health benefits of phytoestrogens was increasing.<sup>72</sup> A randomized, placebo-controlled clinical trial published in 2004 demonstrated a significant increase in lumbar-spine bone mineral density and a 37% reduction in urinary markers of bone turnover in patients with postmenopausal osteoporosis who supplemented with isoflavones.<sup>73</sup>

The beneficial effects of isoflavones on skeletal health have been attributed to their unique organic structures.<sup>74</sup> Isoflavones may act differently in different tissues, to the benefit of people who consume them. For example, in bone tissue, isoflavones act as weak estrogen-like hormones in the bone-building osteoblast cells, promoting new bone formation. The estrogen-like effect in bone also causes an increase in cell-signaling proteins that may inhibit the bone-absorbing activity of the osteoclast cells. In reproductive tissues, however, isoflavones function as weak estrogen antagonists, so they do not produce the feminizing effects of estrogen itself. Many of these molecular mechanisms closely resemble the actions attributed to DHEA.<sup>69</sup>

No trial of isoflavones in men with osteoporosis has yet appeared in the literature, but there is every reason to believe that they will be at least as effective as in women. Given differences in the ways that bone loss occurs in men and women, it is possible that the osteoblast-stimulating effect of isoflavones will result in even more gain in bone density in men.

Ipriflavone, a synthetic isoflavone, has attracted much attention and research, especially in Europe, where it is now used as a drug in treating osteoporosis.<sup>75</sup> It has been shown to effectively inhibit bone resorption and enhance bone formation in both women and men.<sup>76</sup> A double-blind, placebo-controlled study of ipriflavone in 255 postmenopausal women found that forearm bone mineral density remained constant for two years in the treatment group while diminishing significantly in the placebo group. Markers of bone turnover were higher in the

placebo group than in the treated group.<sup>77</sup>

The same investigators discovered virtually identical results in a larger trial of 453 postmenopausal women. In the ipriflavone-treated group, bone sparing of between 1.6% and 3.5% occurred, and bone turnover was reduced.<sup>78</sup> Similar results have been reported in many other studies.<sup>79-82</sup> Ipriflavone's safety has also been well established, with primary side effects being mild gastrointestinal upset; these effects seemed to occur with equal frequency in both ipriflavone and placebo groups in all the trials.<sup>83</sup>

Like natural isoflavones, ipriflavone enhances estrogen's effect on bone without acting as a female sex hormone,<sup>76</sup> so that it may have many fewer of the undesirable feminizing effects of estrogen and related drugs. These weak estrogenic effects of isoflavones and ipriflavone are thought to account not only for their demonstrated ability to enhance bone mineral density and prevent osteoporosis, but also to explain the encouraging data on their effect in reducing prostate cancer risk. These data come from both rodent studies and limited human experience.<sup>84</sup> Rodent models so far provide the only direct interventional data about the roles of these substances in males.



The data from animal models of ipriflavone in males is very encouraging. Two studies of ipriflavone's effects on male rats found that the bones of animals in the treated group had an average 23% greater capacity to withstand stress, and required almost 50% more energy to cause a fracture, compared to animals in the untreated groups.<sup>85</sup> The proportions of calcium, phosphorus, and magnesium in the bones did not differ between the groups, suggesting that there were no abnormalities in the overall mineral composition or crystalline structure of the hydroxyapatite in the stronger bones.<sup>86</sup>

## Summary

For men, maintaining good bone health starts with regular doctor visits to screen for bone mineral density and prostate cancer. Other essentials are regular, weight-bearing exercise, healthy, moderate-protein diets, and supplements including vitamin D, calcium, magnesium, and isoflavones to help prevent bone mineral losses. Men at risk for hormone-dependent cancers should always discuss supplementation plans with their physicians to ensure that the supplements and medications are working together for best effect.

---

## References

---

1. Gennari L, Merlotti D, Martini G, et al. Longitudinal association between sex hormone levels, bone loss, and bone turnover in elderly men. *J Clin Endocrinol Metab.* 2003 Nov;88(11):5327-33.
2. Kamel HK. Male osteoporosis: new trends in diagnosis and therapy. *Drugs Aging.* 2005;22(9):741-8.
3. Levy P, Levy E, Audran M, et al. The cost of osteoporosis in men: the French situation. *Bone.* 2002 Apr;30(4):631-6.
4. Duan Y, Seeman E. Bone fragility in Asian and Caucasian men. *Ann Acad Med Singapore.* 2002 Jan;31(1):54-66.
5. Seeman E. Unresolved issues in osteoporosis in men. *Rev Endocr Metab Disord.* 2001

Jan;2(1):45-64.

6. Moyad MA. Complementary therapies for reducing the risk of osteoporosis in patients receiving luteinizing hormone-releasing hormone treatment/orchiectomy for prostate cancer: a review and assessment of the need for more research. *Urology*. 2002 Apr;59(4 Suppl 1):34-40.
7. Higano CS. Management of bone loss in men with prostate cancer. *J Urol*. 2003 Dec;170(6 Pt 2):S59-S63.
8. Khosla S, Melton LJ, III, Riggs BL. Osteoporosis: gender differences and similarities. *Lupus*. 1999;8(5):393-6.
9. Jalava T, Sarna S, Pylkkanen L, et al. Association between vertebral fracture and increased mortality in osteoporotic patients. *J Bone Miner Res*. 2003 Jul;18(7):1254-60.
10. Haentjens P, Johnell O, Kanis JA, et al. Evidence from data searches and life-table analyses for gender-related differences in absolute risk of hip fracture after Colles' or spine fracture: Colles' fracture as an early and sensitive marker of skeletal fragility in white men. *J Bone Miner Res*. 2004 Dec;19(12):1933-44.
11. Siqueira FV, Facchini LA, Hallal PC. The burden of fractures in Brazil: a population-based study. *Bone*. 2005 Aug;37(2):261-6.
12. Seeman E. The structural basis of bone fragility in men. *Bone*. 1999 Jul;25(1):143-7.
13. Hijazi RA, Cunningham GR. Andropause: is androgen replacement therapy indicated for the aging male? *Annu Rev Med*. 2005;56:117-37.
14. Skouby SO, Al-Azzawi F, Barlow D, et al. Climacteric medicine: European Menopause and Andropause Society (EMAS) 2004/2005 position statements on peri- and postmenopausal hormone replacement therapy. *Maturitas*. 2005 May 16;51(1):8-14.
15. Cherrier MM, Asthana S, Plymate S, et al. Testosterone supplementation improves spatial and verbal memory in healthy older men. *Neurology*. 2001 Jul 10;57(1):80-8.
16. Genazzani AR, Inglese S, Lombardi I, et al. Long-term low-dose dehydroepiandrosterone replacement therapy in aging males with partial androgen deficiency. *Aging Male*. 2004 Jun;7(2):133-43.
17. Orwoll E, Ettinger M, Weiss S, et al. Alendronate for the treatment of osteoporosis in men. *N Engl J Med*. 2000 Aug 31;343(9):604-10.
18. Morales A. Andropause (or symptomatic late-onset hypogonadism): facts, fiction and controversies. *Aging Male*. 2004 Dec;7(4):297-303.
19. Dovio A, Perazzolo L, Osella G, et al. Immediate fall of bone formation and transient increase of bone resorption in the course of high-dose, short-term glucocorticoid therapy in young patients with multiple sclerosis. *J Clin Endocrinol Metab*. 2004 Oct;89(10):4923-8.
20. Kannisto S, Laatikainen A, Taivainen A, et al. Serum dehydroepiandrosterone sulfate concentration as an indicator of adrenocortical suppression during inhaled steroid therapy in adult asthmatic patients. *Eur J Endocrinol*. 2004 May;150(5):687-90.
21. Conde FA, Aronson WJ. Risk factors for male osteoporosis. *Urol Oncol*. 2003 Sep;21(5):380-3.

22. Hussain SA, Weston R, Stephenson RN, George E, Parr NJ. Immediate dual energy X-ray absorptiometry reveals a high incidence of osteoporosis in patients with advanced prostate cancer before hormonal manipulation. *BJU Int.* 2003 Nov;92(7):690-4.
23. Rashid MH, Chaudhary UB. Intermittent androgen deprivation therapy for prostate cancer. *Oncologist.* 2004;9(3):295-301.
24. Dawson-Hughes B. Racial/ethnic considerations in making recommendations for vitamin D for adult and elderly men and women. *Am J Clin Nutr.* 2004 Dec;80(6 Suppl):1763S-6S.
25. Monier-Faugere MC, Mawad H, Qi Q, Friedler RM, Malluche HH. High prevalence of low bone turnover and occurrence of osteomalacia after kidney transplantation. *J Am Soc Nephrol.* 2000 Jun;11(6):1093-9.
26. Dodidou P, Bruckner T, Hosch S, et al. Better late than never? Experience with intravenous pamidronate treatment in patients with low bone mass or fractures following cardiac or liver transplantation. *Osteoporos Int.* 2003 Jan;14(1):82-9.
27. Kapoor D, Jones TH. Smoking and hormones in health and endocrine disorders. *Eur J Endocrinol.* 2005 Apr;152(4):491-9.
28. Wawrzynska L, Tomkowski WZ, Przedlacki J, Hajduk B, Torbicki A. Changes in bone density during long-term administration of low-molecular-weight heparins or acenocoumarol for secondary prophylaxis of venous thromboembolism. *Pathophysiol Haemost Thromb.* 2003 Mar;33(2):64-7.
29. Wong SY, Lau EM, Lau WW, Lynn HS. Is dietary counselling effective in increasing dietary calcium, protein and energy intake in patients with osteoporotic fractures? A randomized controlled clinical trial. *J Hum Nutr Diet.* 2004 Aug;17(4):359-64.
30. Kerstetter JE, O'Brien KO, Insogna KL. Dietary protein, calcium metabolism, and skeletal homeostasis revisited. *Am J Clin Nutr.* 2003 Sep;78(3 Suppl):584S-92S.
31. Haderslev KV, Tjellesen L, Sorensen HA, Staun M. Effect of cyclical intravenous clodronate therapy on bone mineral density and markers of bone turnover in patients receiving home parenteral nutrition. *Am J Clin Nutr.* 2002 Aug;76(2):482-8.
32. Robbins J, Hirsch C, Whitmer R, Cauley J, Harris T. The association of bone mineral density and depression in an older population. *J Am Geriatr Soc.* 2001 Jun;49(6):732-6.
33. Geusens PP. Review of guidelines for testing and treatment of osteoporosis. *Curr Osteoporos Rep.* 2003 Sep;1(2):59-65.
34. Heidenreich A. Bisphosphonates in the management of metastatic prostate cancer. *Oncology.* 2003;65 Suppl 15-11.
35. Graham DY, Malaty HM. Alendronate gastric ulcers. *Aliment Pharmacol Ther.* 1999 Apr;13(4):515-9.
36. Marshall JK, Rainsford KD, James C, Hunt RH. A randomized controlled trial to assess alendronate-associated injury of the upper gastrointestinal tract. *Aliment Pharmacol Ther.* 2000 Nov;14(11):1451-7.
37. Francis RM. Non-response to osteoporosis treatment. *J Br Menopause Soc.* 2004 Jun;10(2):76-80.

38. Papaioannou A, Giangregorio L, Kvern B, et al. The osteoporosis care gap in Canada. *BMC Musculoskelet Disord*. 2004 Apr 6;5:11.
39. Peacock M, Liu G, Carey M, et al. Effect of calcium or 25OH vitamin D3 dietary supplementation on bone loss at the hip in men and women over the age of 60. *J Clin Endocrinol Metab*. 2000 Sep;85(9):3011-9.
40. Siffledeen JS, Fedorak RN, Siminoski K, et al. Randomized trial of etidronate plus calcium and vitamin D for treatment of low bone mineral density in Crohn's disease. *Clin Gastroenterol Hepatol*. 2005 Feb;3(2):122-32.
41. Cortet B, Vasseur J, Grardel B, et al. Management of male osteoporosis. *Joint Bone Spine*. 2001 May;68(3):252-6.
42. Kubodera N, Tsuji N, Uchiyama Y, Endo K. A new active vitamin D analog, ED-71, causes increase in bone mass with preferential effects on bone in osteoporotic patients. *J Cell Biochem*. 2003 Feb 1;88(2):286-9.
43. Moyad MA. Promoting general health during androgen deprivation therapy (ADT): a rapid 10-step review for your patients. *Urol Oncol*. 2005 Jan;23(1):56-64.
44. Resch H, Gollob E, Kudlacek S, Pietschmann P. Osteoporosis in the man. *Wien Med Wochenschr*. 2001;151(18-20):457-63.
45. Elliott ME, Farrah RM, Binkley NC, Carnes ML, Gudmundsson A. Management of glucocorticoid-induced osteoporosis in male veterans. *Ann Pharmacother*. 2000 Dec;34(12):1380-4.
46. Devogelaer JP, Goemaere S, Boonen S, et al. Evidence-based guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis: a consensus document of the Belgian Bone Club. *Osteoporos Int*. 2005 Oct 11.
47. Boonen S, Rizzoli R, Meunier PJ, et al. The need for clinical guidance in the use of calcium and vitamin D in the management of osteoporosis: a consensus report. *Osteoporos Int*. 2004 Jul;15(7):511-9.
48. Reginster JY, Zegels B, Lejeune E, et al. Influence of daily regimen calcium and vitamin D supplementation on parathyroid hormone secretion. *Calcif Tissue Int*. 2002 Feb;70(2):78-82.
49. Ringe JD, Dorst A, Kipshoven C, Rovati LC, Setnikar I. Avoidance of vertebral fractures in men with idiopathic osteoporosis by a three year therapy with calcium and low-dose intermittent monofluorophosphate. *Osteoporos Int*. 1998;8(1):47-52.
50. Erlacher L, Kettenbach J, Kiener H, et al. Salmon calcitonin and calcium in the treatment of male osteoporosis: the effect on bone mineral density. *Wien Klin Wochenschr*. 1997 Apr 25;109(8):270-4.
51. von Bothmer MI, Fridlund B. Gender differences in health habits and in motivation for a healthy lifestyle among Swedish university students. *Nurs Health Sci*. 2005 Jun;7(2):107-18.
52. Patel A, Coates PS, Nelson JB, et al. Does bone mineral density and knowledge influence health-related behaviors of elderly men at risk for osteoporosis? *J Clin Densitom*. 2003;6(4):323-30.
53. Bisse E, Epting T, Beil A, et al. Reference values for serum silicon in adults. *Anal Biochem*.

2005 Feb 1;337(1):130-5.

54. Hayter J. Trace elements: implications for nursing. *J Adv Nurs*. 1980 Jan;5(1):91-101.

55. Perez-Granados AM, Vaquero MP. Silicon, aluminium, arsenic and lithium: essentiality and human health implications. *J Nutr Health Aging*. 2002;6(2):154-62.

56. Jugdaohsingh R, Tucker KL, Qiao N, et al. Dietary silicon intake is positively associated with bone mineral density in men and premenopausal women of the Framingham Offspring cohort. *J Bone Miner Res*. 2004 Feb;19(2):297-307.

57. Chapuy MC, Meunier PJ. Prevention and treatment of osteoporosis. *Aging (Milano)*. 1995 Aug;7(4):164-73.

58. Tucker KL. Dietary intake and bone status with aging. *Curr Pharm Des*. 2003;9(32):2687-704.

59. Hott M, de PC, Modrowski D, Marie PJ. Short-term effects of organic silicon on trabecular bone in mature ovariectomized rats. *Calcif Tissue Int*. 1993 Sep;53(3):174-9.

60. Rico H, Gallego-Lago JL, Hernandez ER, et al. Effect of silicon supplement on osteopenia induced by ovariectomy in rats. *Calcif Tissue Int*. 2000 Jan;66(1):53-5.

61. Lang KJ, Nielsen BD, Waite KL, Hill GM, Orth MW. Supplemental silicon increases plasma and milk silicon concentrations in horses. *J Anim Sci*. 2001 Oct;79(10):2627-33.

62. Eisinger J, Clairet D. Effects of silicon, fluoride, etidronate and magnesium on bone mineral density: a retrospective study. *Magnes Res*. 1993 Sep;6(3):247-9.

63. Jugdaohsingh R, Anderson SH, Tucker KL, et al. Dietary silicon intake and absorption. *Am J Clin Nutr*. 2002 May;75(5):887-93.

64. Spector TD, Callome MR, Anderson S, et al. Effect on bone turnover and BMD of low-dose oral silicon as an adjunct to calcium/vitamin D3 in a randomized, placebo-controlled trial. 2005 Sep; Washington, DC, USA: American Society for Bone and Mineral Research; 2005.

65. Dimai HP, Porta S, Wirnsberger G, et al. Daily oral magnesium supplementation suppresses bone turnover in young adult males. *J Clin Endocrinol Metab*. 1998 Aug;83(8):2742-8.

66. Available at: [www.pdrhealth.com](http://www.pdrhealth.com). Accessed October 27, 2005.

67. Plaza SM, Lamson DW. Vitamin K2 in bone metabolism and osteoporosis. *Altern Med Rev*. 2005 Mar;10(1):24-35.

68. Villareal DT. Effects of dehydroepiandrosterone on bone mineral density: what implications for therapy? *Treat Endocrinol*. 2002;1(6):349-57.

69. Yanase T, Suzuki S, Goto K, Nawata H, Takayanagi R. DHEA and bone metabolism. *Clin Calcium*. 2003 Nov;13(11):1419-24.

70. Khalil DA, Lucas EA, Juma S, Smith BJ, Payton ME, Arjmandi BH. Soy protein supplementation increases serum insulin-like growth factor-I in young and old men but does not affect markers of bone metabolism. *J Nutr*. 2002 Sep;132(9):2605-8.

71. Humfrey CD. Phytoestrogens and human health effects: weighing up the current evidence.

Nat Toxins. 1998;6(2):51-9.

72. Glazier MG, Bowman MA. A review of the evidence for the use of phytoestrogens as a replacement for traditional estrogen replacement therapy. *Arch Intern Med.* 2001 May 14;161(9):1161-72.

73. Harkness LS, Fiedler K, Sehgal AR, Oravec D, Lerner E. Decreased bone resorption with soy isoflavone supplementation in postmenopausal women. *J Womens Health (Larchmt.).* 2004 Nov;13(9):1000-7.

74. Chen X, Anderson JJ. Isoflavones and bone: animal and human evidence of efficacy. *J Musculoskelet Neuronal Interact.* 2002 Jun;2(4):352-9.

75. Messina M, Messina V. Soyfoods, soybean isoflavones, and bone health: a brief overview. *J Ren Nutr.* 2000 Apr;10(2):63-8.

76. Head KA. Ipriflavone: an important bone-building isoflavone. *Altern Med Rev.* 1999 Feb;4(1):10-22.

77. Adami S, Bufalino L, Cervetti R, et al. Ipriflavone prevents radial bone loss in postmenopausal women with low bone mass over 2 years. *Osteoporos Int.* 1997;7(2):119-25.

78. Gennari C, Adami S, Agnusdei D, et al. Effect of chronic treatment with ipriflavone in postmenopausal women with low bone mass. *Calcif Tissue Int.* 1997;61 Suppl 1S19-S22.

79. Agnusdei D, Crepaldi G, Isaia G et al. A double blind, placebo-controlled trial of ipriflavone for prevention of postmenopausal spinal bone loss. *Calcif Tissue Int.* 1997 Aug;61(2):142-7.

80. Valente M, Bufalino L, Castiglione GN, et al. Effects of 1-year treatment with ipriflavone on bone in postmenopausal women with low bone mass. *Calcif Tissue Int.* 1994 May;54(5):377-80.

81. Kovacs AB. Efficacy of ipriflavone in the prevention and treatment of postmenopausal osteoporosis. *Agents Actions.* 1994 Mar;41(1-2):86-7.

82. Passeri M, Biondi M, Costi D, et al. Effect of ipriflavone on bone mass in elderly osteoporotic women. *Bone Miner.* 1992 Oct;19 Suppl 1S57-S62.

83. Agnusdei D, Bufalino L. Efficacy of ipriflavone in established osteoporosis and long-term safety. *Calcif Tissue Int.* 1997;61 Suppl 1S23-7.

84. Messina MJ. Legumes and soybeans: overview of their nutritional profiles and health effects. *Am J Clin Nutr.* 1999 Sep;70(3 Suppl):439S-50S.

85. Civitelli R, bbasi-Jarhomi SH, Halstead LR, Dimarogonas A. Ipriflavone improves bone density and biomechanical properties of adult male rat bones. *Calcif Tissue Int.* 1995 Mar;56(3):215-9.

86. Ghezzi C, Civitelli R, Cadel S, et al. Ipriflavone does not alter bone apatite crystal structure in adult male rats. *Calcif Tissue Int.* 1996 Dec;59(6):496-9.

87. Smith MR, McGovern FJ, Fallon MA, Schoenfeld D, Kantoff PW, Finkelstein JS. Low bone mineral density in hormone-naive men with prostate carcinoma. *Cancer.* 2001 Jun 15;91(12):2238-45.

88. Strum SB, Scholz MC. Quantitative computerized tomography in prostate cancer. *J Urol.*

2003 (submitted).

89. Bolotin HH. Inaccuracies inherent in dual-energy X-ray absorptiometry in vivo bone mineral densitometry may flaw osteopenic/osteoporotic interpretations and mislead assessment of antiresorptive therapy effectiveness. *Bone*. 2001 May;28(5): 548–55.

90. Frahm C, Link J, Hakelberg K, et al. Densitometry in suspected preclinical osteoporosis: quantitative computerized tomography versus dual energy roentgen absorptiometry. *Bildgebung*. 1994 Dec;61(4):256–62.

91. von Stremple A, Prokopp M, Flindt C. A comparison of two noninvasive measurement methods for determining central osteoporosis taking into consideration the ash content. *Aktuelle Radiol*. 1993 Jan;3(1): 31–6.

92. Meirelles ES, Borelli A, Camargo OP. Influence of disease activity and chronicity on ankylosing spondylitis bone mass loss. *Clin Rheumatol*. 1999;18(5):364–8.