calcium alone. All of the women were between 57 and 69 years old and had completed a natural menopause at least one year before starting the study. The IMEFS researchers found that ipriflavone did not increase bone density. The women using calcium alone did just as well as those using the ipriflavone-calcium combination. Dr. Brown's own experience with patients at her clinic indicates that "ipriflavone is generally effective at halting bone loss in postmenopausal women who are undergoing excessive bone loss." As a possible explanation for the IMEFS' negative results, Dr. Brown says that "ipriflavone...may well do very much for those who are not actively losing bone, even though they might have osteoporosis."

The most disturbing aspect of the IMEFS study is that 29 of the 234 women taking the ipriflavone-calcium developed lymphopenia (low numbers of lymphocytes) and were withdrawn from the study. Only 1 woman in the control group developed a comparable condition. According to the report, these women showed no signs of immune suppression. Lymphocyte counts returned to baseline after discontinuing ipriflavone. Dr. Brown reports that delineated lymphocyte decreases appeared in at least two published English-language ipriflavone studies prior to the IMEFS study. IMEFS researchers have no explanation for the lymphocyte decrease or ideas about long-term effects of such a loss. Lymphocyte changes usually occur in the first year of ipriflavone use. To be on the safe side, Dr. Brown recommends checking patients' white blood cell count and lymphocyte count before using ipriflavone and then at six months, a year, and every year thereafter.

In addition to lymphopenia, practitioners need to be aware of other possible safety issues when prescribing ipriflavone. Ipriflavone, like flavonoids in grapefruit juice, can inhibit some liver cytochrome P450 detoxification enzymes that the body uses to breakdown specific drugs and chemicals. Dr. Brown found three reported cases in which blood levels of a medication had become high because of ipriflavone use: two with Coumadin (S-warfarin) and one with theophylline. Italian guidelines recommend that patients using Coumadin and ipriflavone be carefully monitored for clotting parameters. If abnormal values appear, the guidelines advise discontinuing ipriflavone until parameters return to normal. Digestive complaints top the list of ipriflavone's side effects. People with active gastric or duodenal ulcers should not use ipriflavone. Although similar in structure to phytoestrogens like genistein and daidzein, ipriflavone does not appear to have estrogenic activity that affects breast and uterine tissue.

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Nutrition & Bone Health
In their article, "Nutrition in Bone Health Revisited: A Story Beyond Calcium" (American College of Nutrition, 2000), Jasminka Z. Ilich, PhD, RD, and Jane E. Kerstetter, PhD, RD, say that the body needs more than calcium and vitamin D to keep bones healthy. Dietary calcium has been shown to increase or maintain bone mass density in mid-to-late postmenopausal women, particularly if their diet was calcium deficient. Postmenopausal women taking 1000 mg/day of supplemental calcium showed a 30% reduction in fracture risk in at least four studies. The body, however, has limits on the amount of calcium it will use. Ingesting amounts greater than that threshold limit (about 1500 mg/day for adolescents and 1100 mg/day for adults) does not create more bone mass. For people who actually have osteoporosis, the authors believe that calcium supplements should be given with estrogen, bisphosphonates, or calcitonin, which have a stronger effect on bone than calcium alone.

In addition to calcium, at least three other minerals are involved in creating strong bones. Phosphorus (P) is the second most prevalent mineral in the body; 85% is found in bones. Some evidence suggests that too much phosphorus — found in meat, poultry, fish, eggs, dairy products, nuts, legumes, cereals, grains, and soda drinks — encourages bone loss. Nonetheless, some populations (i.e., vegetarians, elderly) may not ingest enough of this necessary mineral. Magnesium (Mg) is another mineral that supports the bones. Without it, impaired parathyroid hormone secretion and hypocalcemia result, along...
with vitamin D abnormalities and neuromuscular hyperexcitability. In animal studies, Mg deficiency causes decreased bone strength and volume, poor bone development, and dysfunctions in bone formation and resorption. Zinc is the fourth mineral known to have a primary role in bone formation. Because zinc is used to metabolize protein, it is necessary for the creation of the collagen that forms a framework for mineralization. Zinc deficiency has been linked to osteoporosis.

Four vitamins are known to take part in bone formation. vitamins D, K, C, and A. Vitamin D3 (calcitriol) stimulates the synthesis of the calcium-binding protein calbindin, necessary for calcium absorption in the intestine. Vitamin D3 also has a role in bone turnover. Rickets in children and osteomalacia (bone softening) in adults result from vitamin D deficiency. Vitamin K takes part in the conversion of glutamate to a GlA protein during which positive Ca ions bond to Gla residues, facilitating calcium's incorporation into the bones' hydroxyapatite crystals. Vitamin C is essential for collagen formation. Severe vitamin C deficiency weakens collagenous structures and results in scurvy. In addition, vitamin C's antioxidant properties apparently reduce the risk of bone fracture in smokers. The presence of nuclear receptors for retinoic acid (vitamin A) on osteoblasts and osteoclasts indicate that vitamin's importance in bone remodeling. In this case, however, too much vitamin C can be as harmful as too little. Excessive vitamin A intake in animals accelerates bone resorption and increases bone fragility and spontaneous fractures.

Protein, like vitamin A, can help or harm bones depending on the amount ingested. While high protein intake is known to increase urine Ca excretion and bone resorption, low protein diets also cause negative effects. Low protein diets inhibit intestinal calcium absorption and cause a rise in serum parathyroid hormone (which regulates calcium and bone remodeling). Because of research in this area, the authors say that "the RDA for protein (0.8 g/kg of body weight) does not support normal Ca homeostasis." They recommend a moderate protein diet of approximately 1.0-1.5 g/kg for optimal bone health.

Bone Mineral Density & Fracture Risk

A commentary in the British Medical Journal that cites a meta-analysis by Deborah Marshall and colleagues highlights some of the problems with using bone mineral density measurements as the sole determinant for antiresorptive therapy. In the meta-analysis (British Medical Journal, 18 May 1996), the researchers analyzed eleven separate studies, published between 1985 and the end of 1994, which looked at bone mineral density measurements and their ability to predict fractures. The researchers also reviewed case control studies of hip fractures published between 1990 and 1994. After comparing the data, the researchers concluded: "Although bone mineral density measurements can predict fracture risk, they cannot identify individuals who will have a fracture, and a screening programme for osteoporosis cannot be recommended."

In his BMJ Commentary, Professor Terence J. Wilkin (Plymouth Postgraduate Medical School, UK) questions the rising use of dual energy X-ray absorptiometry machines in the UK when bone density measurements "cannot identify individuals who will have a fracture." He points out that recommendations for preventive treatment are based on the WHO's definition of osteopenia that arbitrarily defines it as more than 1 standard deviation below the mean for premenopausal white women. Wilkin asserts that bone turnover, not bone density, should be the focus of antiresorptive treatment (hormone replacement and bisphosphonate drugs). He says that the positive effect that these treatments have on preventing fracture cannot be attributed to the small gain in bone density that occurs. Since antiresorptive treatments work equally well in the elderly and the middle-aged, he suggests waiting until fractures are more likely to occur, ages 65-70, instead of starting treatment at menopause. He says that "frequency of impact, which rises exponentially with age, is the main risk factor for fracture."

In response to Wilkin's commentary, C.W. McGregor agrees that focusing on elderly people who show a specific risk is a good idea since antiresorptive treatments are expensive and have side effects. McGregor suggests using a fracture risk score based on factors such as bone mineral density, body sway, and muscle strength. Using these factors, T. Nguyen and colleagues were able to identify 96% and 93% (sensitivities and 88% and 81% of men and women, respectively, who subsequently developed atrumatic fractures" (Nguyen T, et al. Prediction of osteoporotic fractures by postural instability and by density. British Medical Journal 1994 Jan 22). McGregor and colleagues have also researched a risk score approach, published in Osteoporosis International (1998; 8 suppl 3):217-27.

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Osteoporosis Screening Guidelines

In September 2002, a U.S Preventive Services Task Force determined that it had enough clinical data on effective treatments for reducing fracture risk to make its first recommendations concerning osteoporosis screening. An earlier task force, in 1996, found no reason to recommend for or against osteoporosis screening. The 2002 recommendations endorse routine screening for women over 65 years of age and for women, ages 60-64, who have risk factors for osteoporosis. This recommendation received a B rating (recommends) as opposed to an A (strongly recommends). The task force said that the number of fractures prevented by general screening of women under 60 or women without risk factors is too small to justify the expense of testing. Dual-energy X-ray absorptiometry (DEXA) is the most accurate method for measuring bone density, according to the task force. These recommendations, which were published in Annals of Internal Medicine (17 September 2002), plus materials for clinicians are available at the AHRQ (Agency for Healthcare Research and Quality) website: http://www.ahrq.gov/clinic/3rduspt/gideosteoporosis/utPreventiveServicesTaskForceTaskForceUgesRoutineOsteoporosisScreeningforWomen65andOlder.html and at the National Institute of Osteoporosis, May 2004. www.niams.nih.gov