Icariin Flavonoid in Horny Goat Weed Boosts Bone Density in Postmenopausal Women

James Meschino, DC, MS, ND

The incidence of osteoporosis in North America is estimated to affect one in four women and one in four men over the age of 50, with complications from osteoporotic fractures accounting for more deaths each year than the combined mortality from breast and ovarian cancer in the Canadian female population (Canadian Osteoporosis Society). Many patients are seeking natural answers to the prevention and management of osteoporosis (and ostopenia) and many research investigations have been undertaken in recent years.

In addition to exercise, the best results have been occurred from the use of supplements using various forms of calcium (e.g. carbonate, citrate, citrate-malate) and vitamin D, as well as supplementation with ipriflavone. Most recently we have seen that the unique flavonoid (icariin) from the Horny Goat Weed plant has shown a proven ability to increase bone density at the hip and lumbar spine in postmenopausal women. Health practitioners should be aware that Horny Goat Weed (with standardized icariin content) will likely soon replace ipriflavone in most bone support supplements, due to new legislation which is making ipriflavone available only by prescription in many countries.

Calcium and Vitamin D

Many studies over the years have shown that calcium supplementation and/or vitamin D supplementation could slow down the loss of bone after age 50 and decrease osteoporotic fractures, but the search remained to identify ideal amounts of calcium and vitamin D that could increase bone density (if it were even possible) in this population. A recent study shed light on this matter by demonstrating that supplementation with calcium carbonate (1550 mg per day) **and** vitamin D (1400 IU per day) increased bone density in postmenopausal women and older men (over 50), who had previously sustained bone fractures. This was the first study to demonstrate that the combination of calcium with vitamin D (in the absence of exercise) could increase bone density in individuals who were at high risk for osteoporosis fractures. Note that those who exercised showed the greatest increase in bone density. Thus, it appears prudent for individuals 50 and over (and possibly starting at a younger age) to supplement with calcium and vitamin D at doses within the above noted range (and to exercise), as a natural means to prevent and reverse bone loss. (1)

Ipriflavone

Prior to this study, the only other natural agent shown to improve bone density was a supplement known as ipriflavone. Ipriflavone is a semi-synthetic agent produced chemically from either genistein or diadzein (the common flavonoids found in soy beans). There is little naturally-occurring ipriflavone in plants and food. It is primarily a man-made flavonoid (semi-synthetic agent), which has been shown to improve bone density in postmenopausal women. There is considerable evidence to show that it inhibits osteoclasts and also appears to stimulate osteoblasts to build more bone. The liver metabolizes ipriflavone into 7-hydroxy-ipriflavone and 7-(1-carboxy-ethoxy)-isoflavone. Ipriflavone and its derivatives are then bound to albumin and distributed to tissues throughout the body.

The down side to ipriflavone is that it can produce lymphocytopeina (which is reversible prior to discontinuation) and it acts in a similar manner as the flavonoid in grapefruit juice (naringin), inhibiting certain detoxification enzymes in the liver and thus, changing drug metabolism (potentiating their effects) of:

- Theophylline
- Zafirlukast (Accolate)
- Caffeine
- Celecoxib (Celebrex)
- Cyclobenzaprine (Flexeril)
- Nonsteroidal anti-inflammatory medications and pain relievers
- Tacrine (Cognex)
- Tamoxifen (Nolvadex)
- Tolbutamide
- Warfarin (Coumadin)

Ipriflavone may also potentiate the effects of:

- Bisphosphonates for the treatment of osteoporosis
- Calcitonin
- Estrogen
- Selective estrogen receptor modulators (SERMs)

Ipriflavone is a classified as a drug in Japan, Argentina, Italy and many parts of Europe, where it is available by prescription only, and used for the prevention and treatment of osteoporosis and osteopenia. Recently, the Canadian government has also changed the status of ipriflavone from a supplement to a drug. This means that ipriflavone must be removed from all supplements sold in Canada. The US government is closely monitoring the results of ipriflavone research studies and may classify ipriflavone as a drug in the near future, in which case it will not be available without a prescription from a medical doctor, and will be no longer be available in dietary supplements sold in the US. (2-17)

Icariin Flavonoid Proven To Increase Bone Density

Icariin is a flavonoid glycoside compound derived from several species of plants in the Epimedium family, which are commonly known as Horny Goat Weed or Yin Yang Huo. (18)
A number of experimental and human studies have shown that icariin can inhibit osteocalastic activity of bone as well as stimulate osteoblast activity, which has been linked to a possible therapeutic role in the treatment of osteoporosis (19-24).
A recent study (2007) showed that icariin could increase bone density in postmenopausal women. Researchers in China recruited 85 healthy late postmenopausal women, and randomly assigned them to receive either a daily dose of Epimedium (60 mg icariin, 15 mg daidzein, and 3 mg genistein) or placebo. All the women received a daily calcium supplement (300 mg).
After two years of supplementation, bone mineral density at the hip (femoral neck) and lower spine (lumbar) increased by 1.6 and 1.3 per cent, respectively, in the epimedium (icariin) group, and decreased by 1.8 and 2.4 per cent, respectively, in the placebo group.

The researchers stated, "The difference in lumbar spine between the two groups was significant at both 12 and 24 months, whereas the difference in the femoral neck was marginal at 12 months and significant at 24 months."

As well, the women supplemented with epimedium (icariin) showed a 39% decrease in levels of deoxypyrdinoline (a urinary marker of bone resorption) after two years, whereas urinary levels of deoxypyrdinoline was unchanged in women in the placebo group,

In addition, no increase in endometrial (lining of the uterus) thickness was observed in either group, nor were there any other changes consistent with risk of endometrial cancer (by comparison, there are concerns that ipriflavone may increase risk of uterine cancer by acting as a selective-estrogen-receptor-modulator on uterine tissue in a similar manner as estrogen). This was the first human study to show that supplementation with epimedium can increase bone

density in the hip and lumbar spine in postmenopausal women. It is important for health practitioners to note that the dosage of icariin was 60 mg per day – this appears to be the critical daily dosage at which increase in bone density is likely to occur.

Summary

At present the pharmaceutical approach to the prevention and treatment of osteoporosis remains problematic. Many women report untoward side effects from the use of biphosphonate drugs and compliance is often very poor. The same is true for other osteoporosis treatment drugs, with respect to adverse side effects, complications, contra-indications and drug-drug interactions.

Complementary health care practitioners are in a position to counsel patients on preserving and improving their bone density, and the critical importance of doing so, with respect morbidity mortality and quality of life issues. In addition to regular weight bearing exercise (which should be individually tailored to the person's circumstances), supplementation with calcium and vitamin D, as well ipriflavone and icariin flavonoid, are the only evidence-based natural agents shown to **increase** bone density in postmenopausal women and other high risk individuals.

Of course, bones also require other nutrients such as zinc, copper, magnesium, vitamin K, silica, manganese, B-vitamins, vitamin C, and possibly boron, at optimal levels. Vitamin C, zinc, copper, manganese and B-vitamins can easily be provided by a high potency multiple vitamin and mineral supplement, and adequate vitamin K is provided by gut bacteria and green leafy vegetables.

In addition to taking a high potency multiple vitamin and mineral each day the newest generation of bone support supplements (that are in line with the latest science) provide additional amounts of calcium, vitamin D, magnesium, boron, silica and icariin (which is quickly replacing ipriflavone in many bone support supplements) at levels that enable individuals to achieve intake levels consistent with the those reported in this research review.

For more information on this or other related topics, please visit:
http://www.meschinohealth.com

References:

1. Hitz MF, Jenson JB, Eskildsen PC. Bone mineral density and bone markers in patients with recent low-energy fracture: effect of 1-year treatment with calcium and vitamin D. Am J Clin Nutr, 86:251-9. 2007
2. Agnusdei D, Bufalino L. Efficacy of ipriflavone in established osteoporosis and long-term safety. *Calcif Tissue Int* 1999:61:S23–7
3. Head KA. Ipriflavone: an important bone-building isoflavone. *Altern Med Rev* 1999;4:10–22
4. Avioli LV. The future of ipriflavone in the management of osteoporotic syndromes. *Calcif Tissue Int* 1997;61 Suppl 1:S33–5 [review].
5. 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;7:119–25.
6. Nozaki M, Hashimoto K, Inoue Y, et al. Treatment of bone loss in oophorectomized women with a combination of ipriflavone and conjugated equine estrogen. *Int J Gynaecol Obstet* 1998;62:69–75.
7. 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:S19–22.
8. Gennari C, Agnusdei D, Crepaldi G, et al. Effect of ipriflavone—a synthetic derivative of natural isoflavones—on bone mass loss in the early years after menopause. *Menopause* 1998;5:9–15.
9. Agnusdei D, Buffalino L. Efficacy of ipriflavone in established osteoporosis and long-term safety. *Calcif Tissue Int* 1997;61 Suppl 1:S23–7.

10. Passeri M, Biondi M, Costi D, et al. Effects of 2-year therapy with ipriflavone in elderly women with established osteoporosis. *Ital J Mineral Electrolyte Metabol* 1995;9:137–44.
11. Kovacs AB. Efficacy of ipriflavone in the prevention and treatment of postmenopausal osteoporosis. *Agents Actions* 1994;41(1–2):86–7.
12. Alexandersen P, Toussaint A, Christiansen C, et al. Ipriflavone in the treatment of postmenopausal osteoporosis: a randomized controlled trial. *JAMA* 2001;285:1482–8.
13. Acerbi D, Poli G, Ventura P. Comparative bioavailability of two oral formulations of ipriflavone in healthy volunteers at steady-state. Evaluation of two different dosage schemes. *Eur J Drug Metabol Pharmacokinet* 1998,23:172–7.
14. Alexandersen P, Toussaint A, Christiansen C, et al. Ipriflavone in the treatment of postmenopausal osteoporosis. *JAMA* 2001;285:1482–8.
15. Agnusdei D, Bufalino L. Efficacy of ipriflavone in established osteoporosis and long-term safety. *Calcif Tissue Int* 1997;61:23–27.
16. Agnusdei D, Bufalino L. Efficacy of ipriflavone in established osteoporosis and long-term safety. *Calcif Tissue Int* 199:61:S23–7
17. Rondelli I, Acerbi D, Ventura P. Steady-state pharmacokinetics of ipriflavone and its metabolites in patients with renal failure. *Int J Clin Pharm Res* 1991;11:183–92.
18. Liu JJ, Li SP, Wang YT (January 2006). "Optimization for quantitative determination of four flavonoids in Epimedium by capillary zone electrophoresis coupled with diode array detection using central composite design". *J Chromatogr A* . 2005. 1103 (2): 344–9.
19. Yin XX, Chen ZQ, Liu ZJ, Ma QJ, Dang GT (February 2007). "Icariine stimulates proliferation and differentiation of human osteoblasts by increasing production of bone morphogenetic protein 2". *Chin. Med. J.* 120 (3): 204–10.
20. Zhang G, Qin L, Shi Y (July 2007). "Epimedium-derived phytoestrogen flavonoids exert beneficial effect on preventing bone loss in late postmenopausal women: a 24-month randomized, double-blind and placebo-controlled trial". *J. Bone Miner. Res.* 22 (7): 1072–9.
21. Chen KM, Ge BF, Liu XY, *et al.* (May 2007). "Icariin inhibits the osteoclast formation induced by RANKL and macrophage-colony stimulating factor in mouse bone marrow culture". *Pharmazie* 62 (5): 388–91.
22. Huang J, Yuan L, Wang X, Zhang TL, Wang K (August 2007). "Icaritin and its glycosides enhance osteoblastic, but suppress osteoclastic, differentiation and activity in vitro". *Life Sci.* 81 (10): 832–40.
23. Zhang DW, Cheng Y, Wang NL, Zhang JC, Yang MS, Yao XS (January 2008). "Effects of total flavonoids and flavonol glycosides from Epimedium koreanum Nakai on the proliferation and differentiation of primary osteoblasts". *Phytomedicine* 15 (1-2): 55–61.
24. Qin L, Han T, Zhang Q, *et al.* (July 2008). "Antiosteoporotic chemical constituents from Er-Xian Decoction, a traditional Chinese herbal formula". *J Ethnopharmacol* 118 (2): 271–9.
25. G. Zhang, L. Qin, Y. Shi. (July 2007) Epimedium-Derived Phytoestrogen Flavonoids Exert Beneficial Effect on Preventing Bone Loss in Late Postmenopausal Women: A 24-Month Randomized, Double-Blind and Placebo-Controlled Trial. *Journal of Bone and Mineral Research* 22:1072-1079