



Bone loss is a major health concern for postmenopausal women

## New clinical research indicates that Douglas Laboratories' Ultra-Ostivone™ formula lowers N-linked telopeptides (NTx), an important marker in measuring bone loss.

The loss of bone density with advancing age is a serious health concern of our population. The results of a recently completed placebo-controlled trial of Ultra-Ostivone™, a dietary supplement containing ipriflavone, demonstrate a dramatic reduction in urinary N-linked telopeptides (NTx), a dynamic indicator of bone breakdown<sup>1</sup>.

This research on Ultra-Ostivone™ is the first to demonstrate an effect of an ipriflavone-containing supplement on NTx levels. Measurement of NTx levels provides the physician with a rapid assessment of treatment efficacy in the fight against bone loss.



## Details of the study

The study involved postmenopausal women not currently receiving hormone replacement therapy. Subjects received either Ultra-Ostivone™ or a placebo for a 3-month period. Women received 2 capsules of Ultra-Ostivone™ daily supplying:

- 600 mg of ipriflavone
- 300 mg of calcium
- 100 I.U. of vitamin D

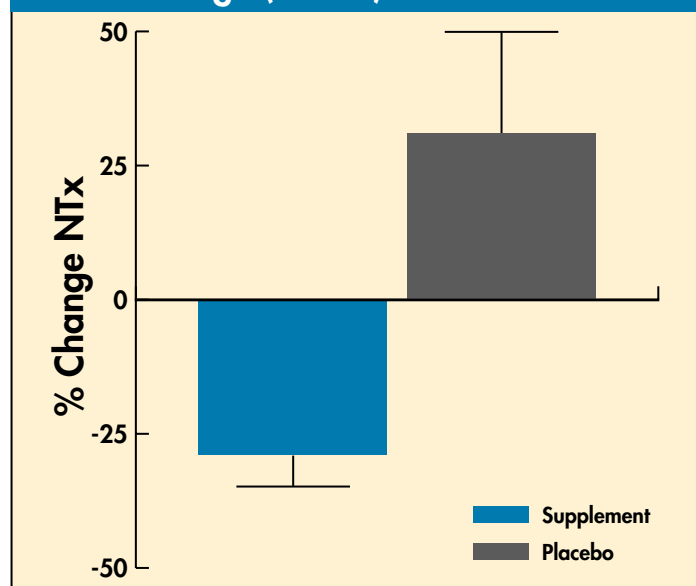
Urinary NTx levels were measured before and after treatment.

## Results

Women receiving Ultra-Ostivone™ experienced a 29% decrease in NTx levels while those receiving the placebo experienced an increase.

The results of this study confirm the findings of other researchers that demonstrate the usefulness of ipriflavone at

**Fig. 1 Effect of an ipriflavone-containing supplement or placebo on percent change ( $\pm$  SEM) in NTx value.**



**A reduction in the NTx level represents a beneficial outcome for postmenopausal women.**

slowing the progression of bone loss in postmenopausal women.

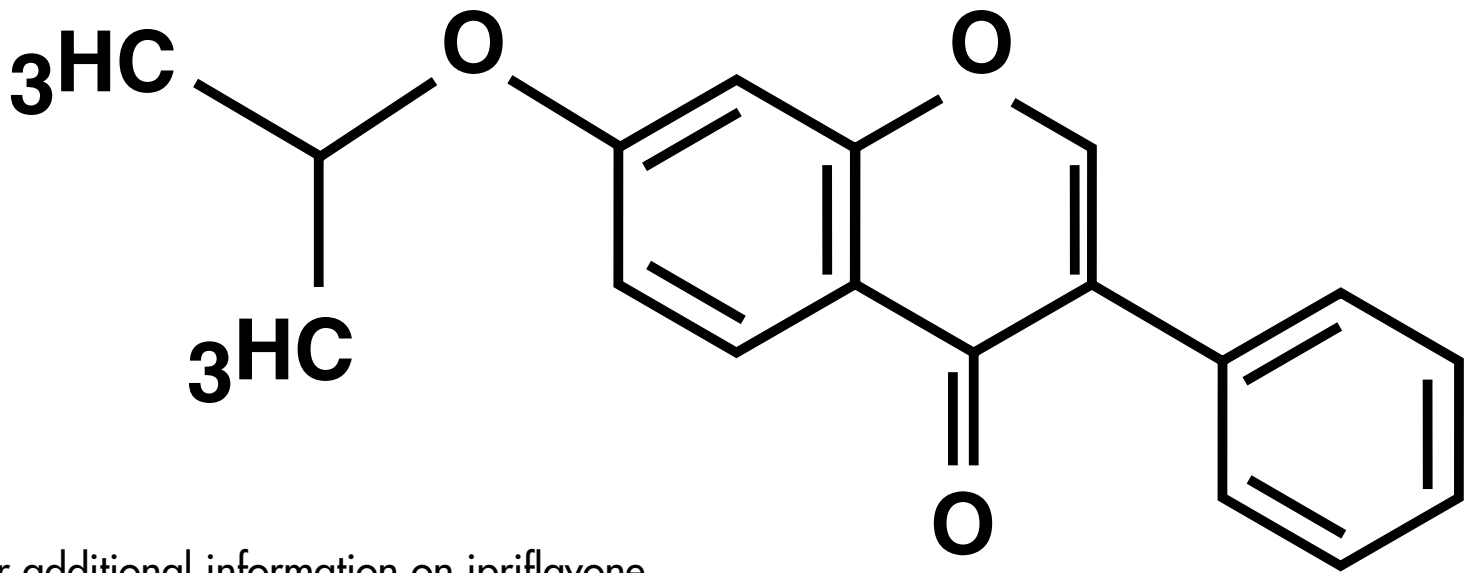
Refer to the chart below for previous research study results on the ability of ipriflavone to prevent the decline in bone loss commonly seen after menopause.

## Previous research on the effect of Ipriflavone in bone loss.

	<u>Treatment</u>	<u>Vertebral Bone Density</u>
<b>Study 1<sup>2</sup></b>	<b>Ipriflavone 600 mg/day</b> <b>Placebo</b>	<b>No change</b> <b>Decrease</b>
<b>Study 2<sup>3</sup></b>	<b>Ipriflavone 600 mg/day</b> <b>Placebo</b>	<b>Increase</b> <b>Decrease</b>
<b>Study 3<sup>4</sup></b>	<b>Ipriflavone 600 mg/day</b> <b>Placebo</b>	<b>No change</b> <b>Decrease</b>

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**Molecular structure  
of Ipriflavone**

For additional information on ipriflavone, N-linked telopeptides and bone loss refer to the accompanying article entitled "Osteoporosis: A review focusing on ipriflavone and other key nutrients." beginning on page 4.

**Combine Ultra-Ostivone™ with our best calcium/magnesium product Cal-6 + Mg.™ for maximum bone defense. Add our Ultra Preventive® III multivitamin formula for the best in overall health maintenance and support.**



For additional information on our complete line of bone health formulations including ipriflavone-containing products as well as calcium/magnesium formulations, such as Calcium Microcrystalline Hydroxyapatite, refer to the latest Douglas Laboratories® product catalog. If you would like a copy of the complete study on Ultra-Ostivone™ or to obtain a copy of our current catalog, call toll-free at 1-800-245-4440 or 1-888-DOUG LAB (368-4522).

# OSTEOPOROSIS: A REVIEW FOCUSING ON IPRIFLAVONE AND OTHER KEY NUTRIENTS

Andrew Halpner, Ph.D.

Osteoporosis is a skeletal condition characterized by a decreased density of normally mineralized bone. This results in an increased risk of fracture, (1) and is a serious health issue facing older adults, especially postmenopausal woman. Approximately 30% of postmenopausal women in the United States have some degree of osteoporosis present in the hip, spine, or forearm and are at risk for a fracture (2). By the age of 65, one third of women will experience a vertebral fracture and by extreme old age, one third of women will experience a hip fracture (3). However, unlike a fracture in a young individual, fractures in the elderly result in significant morbidity and mortality. Despite the fact that current methods of detection and treatment are improving, the diagnosis and initiation of treatment is often not initiated until the disease process has already taken a strong hold.



## Risk Factors

Peak bone mass is reached between the ages of 25 - 30 years, and over a lifetime, a woman will lose about 50% of bone density at the spine and 30% at the hip. This loss can be exacerbated by either a decreased accumulation of bone during puberty, or an increased rate of loss later in life. Osteoporosis occurs more commonly in Caucasians and Asian Americans than in African Americans (4). Certain medications such as steroids and gonadal hormone-releasing hormone agonists such as Lupron contribute to a loss of bone density by decreasing calcium absorption and increasing calcium loss from the body. For example, with only 7.5 mg prednisone/day bone loss has been observed in as little as 3 months (5). Excess thyroid hormone has also been shown to lead to osteoporosis in postmenopausal women not receiving estrogen. Specific risk factors for fracture include; poor balance, medications that cause drowsiness, family history of fracture, and a previous fracture.

## Nutritional Treatment

Although calcium may be the most publicized nutrient effecting bone health, many other nutritional factors have now been

implicated as having a role in maintaining bone structure and health. These factors appear to be essential for or complementary to the proper utilization of calcium, and include ipriflavone, vitamin D<sub>3</sub>, copper, zinc, manganese, silicon, vitamin K, and boron (6). Data are currently accumulating that demonstrate a beneficial effect of supplementation with certain nutrients on bone health.

## Ipriflavone

Flavonoids (also known as bioflavonoids) are ubiquitous in plants that undergo photosynthesis. Scientists first become interested in flavonoids in the early 1930s when it was discovered that many of these compounds exhibited vitamin-like activity. Flavonoids have since been demonstrated to have antioxidant, antimicrobial, antimutagenic and anticarcinogenic activities (7). Recently, focus has centered on the effects that flavonoids may have on bone metabolism. Certain flavonoids, specifically a class of flavonoids called isoflavones, can exert estrogen-like activity. This has caused researchers to investigate their utility in preventing postmenopausal bone loss. While the data regarding the ability of isoflavones to help prevent bone loss are equivocal, ipriflavone (IP), a specific isoflavone derivative has received a significant amount of research with very positive results.

Ipriflavone is a non-hormonal agent currently used in many countries for the treatment of osteoporosis. Numerous well-controlled, clinical trials published in peer-reviewed journals have demonstrated IP's ability to slow the continual decline in bone mineral density commonly observed after menopause (8-14). Kovacs et al. (12) treated postmenopausal women with either IP, 600 mg/day or placebo for 1 year. After 6 months bone mineral density (BMD) of the L2 - L4 vertebral region increased significantly in the IP-treated group and decreased in the placebo group. Gennari et al. (14) also treated postmenopausal women with either 600 mg IP/day or placebo for 2 years. After both 1 and 2 years, vertebral bone density had declined in those receiving the placebo, but did not change in subjects receiving IP. In fact, Melis et al. (15) demonstrated that ipriflavone may be as effective as

estrogen in its ability to prevent bone loss, and the combination of the two treatments may improve the effects of hormone replacement therapy.

The mechanisms by which IP functions are still being elucidated; however, IP has been shown to reduce the rate of bone breakdown by inhibiting osteoclast and stimulating osteoblast activity. The pharmacokinetics of IP have been well studied. Ipriflavone is well absorbed and is metabolized into seven different compounds including daidzein (16). This is of note, as daidzein is a prominent soy isoflavone, and may be responsible for of soy's beneficial effects on bone health. Most interesting is that unlike estrogen, IP has little or no effect on breast or reproductive tissue (17-20), and is without notable side effects. This makes IP a unique and potentially useful compound in the treatment of osteoporosis.

Currently, the measurement of BMD is considered the gold standard in terms of assessing the degree of osteoporosis present. Unfortunately, BMD is a static measurement. Recently, a marker of bone turnover, the N-linked telopeptide assay (NTx) has become available as a clinical tool to dynamically assess the efficacy of anti-resorptive therapy. This assay measures type I collagen degradation products and has been correlated with changes in BMD. A reduction in the NTx value represents a beneficial outcome for the osteoporotic patient. While the effect of calcium and other anti-resorptive therapies have been investigated for their ability to produce changes in this assay (21-22), reports demonstrating the effect of ipriflavone, or ipriflavone-containing products on this marker are lacking. Douglas Laboratories® has recently completed a pilot trial investigating the effect of an ipriflavone-containing dietary supplement on urinary N-linked telopeptide levels in postmenopausal women (23). A total of 8 women, at least 5 years post menopause were recruited to participate in the study. Women were free from any history of bone or kidney disorders and were not receiving hormone replacement therapy. The women received either a supplement containing 300 mg ipriflavone, 150 mg calcium, and 50 IU vitamin D taken twice daily with meals, or an identical looking placebo for 3 months. The participants received NTx measurements before and after the study. After 3 months, there was an average 29% decrease in NTx values for those subjects consuming the supplement, while an increase in NTx values was observed for those taking the placebo.

The effectiveness of IP at slowing changes in postmenopausal bone density has been well established via measurements of changes in bone mineral density (BMD). Although BMD is a useful indicator of fracture risk, BMD provides only a static picture of

bone metabolism. Urinary markers offer the clinician a dynamic and easily measured indication of response to treatment. Our preliminary data provide additional evidence to support the use of IP or IP-containing supplements for the prevention of bone loss in postmenopausal women.

### Calcium and vitamin D<sub>3</sub>

Osteoporotic fractures can be reduced if peak bone mass and age-related bone loss can be minimized. Once women reach menopause, bone loss occurs rapidly (3%/year) over the first 5 years post menopause and then continues at approximately 1%/year during the following years (24). Calcium and vitamin D<sub>3</sub> work in concert, with D<sub>3</sub> mediating the intestinal absorption of calcium as well as having direct effects on calcium metabolism in the kidney and bone. Studies investigating the ability of supplemental calcium and vitamin D<sub>3</sub> to slow bone loss have yielded equivocal results, with some studies demonstrating a positive effect (25-28) and others showing no effect (29-30). These conflicting results may be due to differences in study design, the type of calcium used, the sites of bone loss investigated (spine vs. hip), as well as varying menopausal status and dietary calcium intake in the subjects being investigated. A number of recent studies, however, have reported a positive effect of supplemental calcium alone, or in combination with vitamin D<sub>3</sub> on bone loss. Dawson-Hughes et al. (25) assessed the effect of calcium supplementation on bone density in postmenopausal women. Supplementation with 500 mg/d calcium citrate malate in women with a dietary calcium intake <400 mg/d resulted in significantly less loss of bone density over a two year period compared with placebo. The ability of calcium to diminish the loss of bone was site specific and was less evident in women consuming >400 mg/d from their diet. Dawson-Hughes et al. (31) also reported that supplementation with 400 IU/d vitamin D<sub>3</sub> prevented wintertime bone loss in healthy postmenopausal women. Investigations of the combined supplementation of calcium and vitamin D<sub>3</sub> have also yielded positive results. Aloia et al. (32) found that bone loss was diminished in postmenopausal women receiving 1700 mg/d calcium and 400 IU/d vitamin D<sub>3</sub> over a 3 year period. The positive effect of vitamin D<sub>3</sub> on the efficacy of calcium is not unexpected, as these nutrients function together. Finally, Chapuy et al. (33) recently reported that the combined supplementation of 1200 mg/d calcium and 800 IU/d D<sub>3</sub> in nursing home residents significantly reduced fracture rates during a 3 year trial. None of the trials mentioned above reported any noteworthy side effects as a result of supplementation.

## Vitamin K

Vitamin K has been known for many years to be involved in the synthesis of a number of proteins (vitamin K dependent proteins) by acting as a co-factor for their carboxylation (34). Vitamin K's most well understood function is as a co-factor for proteins involved in blood coagulation; however, vitamin K dependent proteins have also been identified in bone (35). One of these proteins, osteocalcin, is involved in regulating bone mineralization (36), and may require more vitamin K than the proteins involved in blood coagulation in order to function properly (37). This has led to the concept that current intake of vitamin K may be less than adequate and supplemental vitamin K may be beneficial for optimal bone health.

A number of observations have related vitamin K to bone. Postmenopausal bone loss is associated with poor vitamin K intake, and patients with hip fractures have been reported to have very low circulating concentrations of vitamin K (38-39). Additionally, circulating concentrations of undercarboxylated osteocalcin have been reported to be inversely correlated with bone density in the hip (40). It has also been observed that supplementation of postmenopausal women with 1 mg vitamin K for 2 weeks increases serum markers of bone formation and may reduce urinary losses of calcium (41). However, data with respect to the effect of supplemental vitamin K on bone mass or fracture are limited. One Japanese study, (42) has shown a significant reduction in postmenopausal bone loss in women receiving supplemental vitamin K. Similar studies from Western countries assessing the effect of supplemental vitamin K are being awaited.

## Manganese, Copper, Zinc and Vitamin C

The role that manganese, copper, zinc and vitamin C play in the metabolism of bone has been extensively investigated. Nonetheless, compared with calcium and vitamin D<sub>3</sub> their exact biochemistry with respect to bone metabolism is not as well understood. Copper and vitamin C are both required for the proper formation of collagen. Additionally, vitamin C plays a role in the formation of glycosaminoglycans. Manganese is involved in the synthesis of mucopolysaccharides that are essential for the



formation of the bone matrix, and zinc deficiency causes a reduction in collagen synthesis and osteoblasts (cells involved in the formation of new bone) activity. Cross-sectional and animal data report the diets deficient in manganese and copper are associated with a lower bone mineral density. Saltman and Strause (43) supplemented postmenopausal women with either 1) 1000mg/d calcium citrate, 2) trace minerals (5mg/d copper, 2.5 mg/d manganese, and 15 mg/d zinc), 3) a combination of calcium and trace minerals, or 4) a placebo for 2 y. Women receiving the trace minerals plus calcium lost significantly less bone mineral density compared with placebo. Neither the minerals nor the calcium alone showed a significant difference compared with placebo. These data suggest an important interaction between calcium and trace minerals in the prevention of bone loss in postmenopausal women.

## Magnesium

Given that sixty percent of all the magnesium in the body is located in bone, it is reasonable to conclude that magnesium is also closely related to bone structure and function. Magnesium status has been shown to influence various parameters that affect bone metabolism. Magnesium deficiency has been associated with the inhibition of parathyroid hormone release and increased resistance to parathyroid hormone. Additionally, magnesium deficiency is associated with a decreased concentration of serum vitamin D<sub>3</sub> and results in tissue resistance to the action of vitamin D<sub>3</sub>. Prospective studies examining the effect of supplemental magnesium on bone density are very limited. Rude and Olerich supplemented 5 patients with gluten sensitive enteropathy (who often have malabsorption problems) with 504 - 576 mg/d magnesium. Supplementation for 2 years resulted in an increase in bone mineral density and an increase in serum parathyroid hormone. No other data on magnesium supplementation and bone parameters are available.

## Silicon

Silicon is a trace mineral that has been implicated in the formation and maintenance of healthy bone. Its exact function remains unclear; however, animal data have accumulated indicating

its essentiality. Rats and chicks placed on diets containing only 1ppm silicon showed incomplete and deformed skeletal development (44). The defect appears to be in the formation of glycosaminoglycans and collagen, both of which are needed for the formation of the bone matrix (45). Silicon has been found attached to collagen and increases during the early mineralization process of bone (46). It appears that silicon helps to provide a stable organic matrix to allow for the proper formation of bone to occur.

## Boron

Boron is another trace element that is involved in bone metabolism and mineralization, although like silicon, its exact function is unclear. Similar to other trace minerals, boron's action on bone may be mediated through its ability to affect other parameters associated with bone, including calcium, magnesium, parathyroid hormone, calcitonin, osteocalcin (47). The results of supplementing animals and humans with boron have yielded conflicting results based on the amount supplemented and the model studied. Consumption by rats of water containing 300 mg boron/L resulted in a decrease in the calcium content and size of certain bones. Daily consumption of 4 and 8 mg boron/kg body weight in pigs (equivalent to approximately 550 mg/d in humans) resulted in decreased bone mineral content and decreased bone mass. Chapin et al (48) sup-



plemented rats with varying concentrations of boron (1.4 mg - 63 mg/kg body weight) and reported an increase in vertebral strength at all doses of boron supplementation.

Investigations of boron supplementation in humans were started with a report by Nielson (49) who placed postmenopausal women on a low boron diet followed by a diet supplemented with 3 mg/d boron. Supplementation significantly reduced the loss of urinary calcium and magnesium as well as increased serum levels of estrogen (involved in preventing bone demineralization). Peace et al. (50) attempted to repeat these results in a similar study involving postmenopausal women, but was unable to confirm the earlier results. Meacham et al. (51) investigated the effects of boron supplementation (3 mg/d) in premenopausal women over 10 months, and found that boron supplementation increased serum magnesium levels.

Science is continuing to uncover new ways to help slow the continual loss of bone in postmenopausal women. Together with a healthful diet and proper vitamin and mineral supplementation, IP is now recognized to be an effective addition to the arsenal of tools available to the practitioner in the fight against osteoporosis.

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**Written by Andrew Halpner, Ph.D.**

**Dr. Halpner received his Ph.D. in Nutrition from Tufts University School of Nutrition Science and Policy. His extensive research and interests focus around antioxidant nutrients, including their interactions and ability to prevent and treat age-related degenerative diseases. Dr. Halpner is Director of Product Development and Technical Services for Douglas Laboratories®.**