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In a nutshell

There is evidence on a number of fronts that soy isoflavones exert a positive effect on bone density and dynamics which, although modest, would be potentially therapeutically useful.

The balance of evidence does not yet, however, make clear the important details of which patients, what formulation, at what dose and for how long.

Soy, isoflavones and bone health

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NUTRITION RESEARCH REVIEW

Studies 1/2: Meta-analysis on soy isoflavone trials

Two new meta-analyses from China have looked at the effect of soy isoflavone on bones.

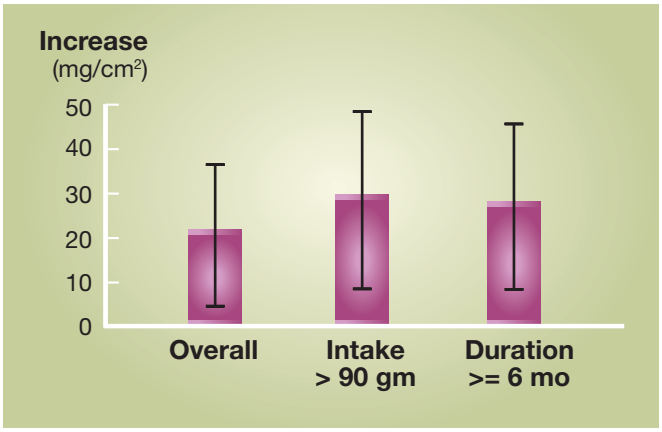
Method: Both meta-analyses focused on RCTs in which the active treatment was supplementation with soy isoflavones. In the first, the outcome measure was bone density, in the second bone resorption and formation.

Results: In the first meta-analysis, collated data from 10 RCTs involving 608 menopausal women showed a significant benefit on spine bone mineral density (BMD) for active vs placebo intervention, particularly when soy isoflavone was given in higher doses and for longer periods - see Graph.

In the second meta-analysis, combining data from 9 RCTs on 432 subjects showed that soy isoflavones significantly increased bone formation (increase in bone -specific alkaline phosphatase - BAP) and decreased bone resorption (lower urinary deoxypyridinoline excretion).

Ref.: Ma DF. et al. Soy isoflavone intake increases bone mineral density in the spine of menopausal women: Meta-analysis of randomized controlled trials. Clin Nutr. 2008 Feb;27(1):57-64
and
Ma DF. et al. Soy isoflavone intake inhibits bone resorption and stimulates bone formation in menopausal women: meta-analysis of randomized controlled trials. Eur J Clin Nutr. 2008 Feb;62(2):155-161.

Graph: Increase in spine BMD: meta-analysis
(Study 1) soy isoflavone vs placebo (with 95% CI)



Study 3: Genistein as treatment

A new Italian trial tested the usefulness of the phytoestrogen genistein in treating osteopenic women.

Method: RCT on 289 post-menopausal women with low BMD (femoral neck < 79.5 mg/cm^2) given calcium and vitamin D plus either placebo or genistein (54 gm/day) for 2 years.

Results: Compared with placebo, genistein subjects had an increase in BMD of both lumbar spine (100 mg/cm^2, 95% CI: 80-120, p<0.001) and femoral neck (62 mg/cm^2, 49-73, p<0.001). The genistein patients also had significant decreases in urinary excretion of pyridinoline and deoxypyridinoline, increased BAP and insulin-like growth factor I, but no differences in endometrial thickness. At the same time, significantly more genistein than placebo patients reported GIT side-effects (19% vs. 8%; p=0.002).

Ref.: Marini H. et al. Effects of the phytoestrogen genistein on bone metabolism in osteopenic postmenopausal women: a randomized trial. Ann Intern Med. 2007 Jun 19;146(12):839-47.

Study 4: Soy protein with exercise

A recent American trial looked at the effects and any interaction of taking soy protein and doing moderate exercise on bone health in post-menopausal women.

Method: RCT on 61 post-menopausal women (of whom 43 completed the trial) given either milk protein or soy protein isolate powder (both including calcium and vitamin D), with or without a supervised moderate exercise program (3 x/wk) for 9 months.

Results: Compared with milk powder placebo, women on soy powder had significant reductions in bone turnover (serum C-terminal cross-linked telopeptides and bone-specific alkaline phosphatase), but not in bone mineral density. There were no beneficial or additive effects from the exercise.

Ref.: Evans EM. et al. Effects of soy protein isolate and moderate exercise on bone turnover and bone mineral density in postmenopausal women. Menopause. 2007 May-Jun;14(3 Pt 1):481-8.

COMMENTARY

Soy foods are a long established part of the healthy diet of many cultures. They are one of the richest dietary sources of the phenolic compounds known as isoflavones.

Individual isoflavones include: genistein, daidzein and glycitein. Being sufficiently similar in molecular structure to the oestrogen oestradiol so as to affect oestrogen receptors, they can have either oestrogen inhibitory or stimulatory effects, depending on circumstances [1-3].

There is more data on soy foods (tofu, soy milk etc.) than `pure' isoflavones in terms of bone health

It is therefore natural to wonder whether they may have some potential to combat the bone loss associated with the fall of oestrogen at menopause. They are already popular in lay use for this purpose, motivating both consumption of soy foods and in supplements [4].

Several lines of evidence have suggested that this is a possibility worth pursuing. Epidemiological evidence links higher soy and isoflavone intake with higher bone mineral density and lower incidence of osteopaenia, osteoporosis and osteoporotic fracture [5-8]. Animal studies have found that isoflavones such as genistein can help prevent bone loss through both inhibiting bone resorption and stimulating bone formation [9, 10], (although not all such studies have reported this [11, 12]). Apart from its impact on bone turnover, an observed anti-inflammatory action could also benefit bones [13].

The question then is whether this works in human clinical trials. That was addressed by the two new meta-analyses, both of which found some overall evidence of a benefit in either bone density or bone formation dynamics.

Our own informal review of a wider range of 23 RCTs on this question showed that 12 of them (52%) reported positive clinical outcomes in relation to bone density or osteopaenia, whilst 9 trials (39%) failed to do so and 2 trials (9%) had mixed or only very minor effects. An additional 8 trials had positive outcomes on markers of bone formation or resorption only.

This kind of mixed `report card' is consistent with other reviews of the topic [14-16]. For example, a very thorough review prepared for an American government agency in 2005 concluded that "it is difficult to draw an overall conclusion about the effects of soy on bone outcomes" [14], whilst a review published in 2006 found the data "somewhat less convincing *[than for other benefits]*, although promising, for increasing bone mass density" [15].

This suggests that either the research itself has limitations, and/or that the clinical benefit to be had is unreliable or not without its limitations [3]. This in turn could potentially relate to the type of isoflavone used (including any advantages or disadvantages of using isolated isoflavone vs soy as a food), dosage, life cycle stage, genetic predisposition or the baseline clinical condition of the subject (e.g. osteopenic or not).

On the question of soy vs `purified' isoflavones, the overall progress of research has frankly been too *ad hoc* to provide us with any clear answer. The bulk of the epidemiological evidence and many of the clinical trials have been based on soy foods or isoflavones consumed as soy. It is only more recently that we are building up a body of trial data using isolated, specific isoflavones - particularly genistein - as was the case with new Study 3. At least one recent carefully controlled trial has attempted to demonstrate differential effects on bone of soy with and without isoflavones, but could not find any [17].

Dietary calcium density and absorption may also be a factor in the impact of isoflavones on bone, and has been found in both animal and human studies to exert a synergistic effect [17-19], as does exercise [20, 21].

In regard to life cycle, there seems to be some contradiction between human epidemiological evidence which suggests isoflavones may be more effective post-menopausally (particularly younger post-menopausal), and animal studies in which the main effect was seen in young, growing subjects [3, 16].

There is some evidence of a genetic factor in play, for example, greater responsiveness in those with certain genotypes affecting bone metabolism or the equol-producing phenotype [22-24].

There is definitely consistent evidence of a dose-response effect, as reported in the new meta-analysis Study 1, and in other trials [25]. However, we cannot yet say what is a sufficient dose for an individual patient.

This issue is compounded by the possibility of adverse reactions, as well as effects that may be physiological but perhaps simply not welcome, for example on menstrual function. This would not be unexpected since isoflavones act, at least in part, through interaction with oestrogen receptors that are widely spread through the body. So, for example, in aiming to prevent osteoporosis, isoflavones may also affect breast or endometrial tissue [26, 27].

Soy foods have been eaten as part of balanced diets by Asian cultures for many centuries. But proper toxicological studies will be needed as isolated isoflavones become more widely used in therapeutics (e.g. bonistein [28]). Reported adverse events in clinical studies have generally been greater in the soy arm, but of minor nature (e.g. gastrointestinal and menstrual) [14], with many reviews characterising soy isoflavones as having a “lack of safety concerns” in the short term [15]. But the main safety issues would be more likely to be long term, such as worry about possible negative impact in specific kinds of hormone-sensitive cancer [29]. Although evidence in this area so far appears reassuring, it is the lack of long term trial data, including on higher doses and isolated isoflavones, which suggest the need for some caution.

In summary, there is evidence on a number of fronts that soy isoflavones exert a positive effect on bone density and dynamics which, although modest, would be potentially therapeutically useful [16]. The balance of evidence does not yet, however, make clear the important details of which patients, what formulation, at what dose and for how long. For this information we will have to `stay tuned’.

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