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Managing the menopause: phyto-oestrogens or hormone replacement therapy?

John A Eden

Menopause is a natural event, and understandably many women would like to take a natural therapy rather than a drug for managing their menopause symptoms as well as preventing the long-term sequelae of oestrogen deficiency. In this respect phyto-oestrogens show a lot of promise. However, at this point in time clinical data are inconclusive. There are some data supporting the contention that isoflavones improve hot flushes; however, there are also negative studies. Soy protein has been shown to lower cholesterol, and isoflavones improve arterial compliance. Clinical studies suggest that isoflavones have little impact on menopause-induced bone loss.

Keywords: hot flushes; isoflavones; lipids; menopause; osteoporosis; phyto-oestrogens.

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Introduction

Phyto-oestrogens are a broad group of nonsteroidal phytochemicals that have been shown in cell culture systems to bind to oestrogen receptors (ER). The two main groups that have been studied to date include the lignans, which are cell wall components found particularly in cereals, and isoflavones, which are found almost exclusively in legumes, such as soybeans, chick peas, lentils, and clovers. There have been several excellent reviews in this area (1–3) for the interested reader. With regard to managing menopause, the most extensively investigated group of compounds is the isoflavones. The two main compounds found in beans are the glycosylated compounds genistin and daidzin. After consumption the glucose moieties are cleaved off, principally by gut flora, leaving genistein and daidzein. Clovers typically contain the methylated forms, formononetin and

biochanin A, which are demethylated in the gut and liver to form daidzein and genistein, respectively (1–3). These parent compounds undergo extensive metabolism in the gut and liver; the precise function of these metabolites in humans remains largely unclear. Interestingly, in sheep and cattle grazing on clover, large amounts of the metabolite equol are formed, which produces an anovulatory disorder similar to polycystic ovary syndrome in humans (1). Sheep in particular stop ovulating, have a highly abnormal secretion of luteinizing hormone (LH), develop cystic glandular hyperplasia of the endometrium, and become masculinized (labial fusion). The isoflavones have a phenolic structure which appears to be necessary for binding with ERs. The discovery of the second ER has been important with regard to understanding the function of these compounds. Typically isoflavones, genistein in particular, have low affinity for ER α but generally bind more strongly with ER β (4). As the two ERs have different tissue distributions, it seems likely that the isoflavones will exhibit tissue-specific effects (4).

Human studies with isoflavones have mostly focused on these compounds as a potential treatment for the menopause syndrome. Population studies in Asia have suggested that Asian women consuming their traditional diet, which is high in soya products, such as tofu, appear to have a low rate of menopause symptoms (5). Even if Asian women do have a different menopause experience compared with Western women, it does not necessarily follow that this results from their diet. Cultural differences are also likely to play a role. For example, in some Asian cultures a menopausal woman increases in status, and menopause is thus seen as a positive experience in contrast to the largely negative views about menopause expressed by many Western women.

Finally, it should be noted that foods vary greatly in their phyto-oestrogen content. Most attention has been focused on soya because the soybean contains at least 10 times more isoflavone than other beans. Food processing can also vary the amount and type of isoflavones present in a particular food (1–3).

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The menopause syndrome

In most Western countries, approximately 80% of women suffer from menopause symptoms, and thus a food or supplement based on natural therapy is an attractive concept. In general, randomized controlled trials have shown that soya foods or isoflavone supplements have either no or only a mild effect on menopausal hot flushing. Clinical trials studying menopause symptoms have shown a large placebo effect, typically of the order of 20–40%. Apart from the usual placebo effect, menopause symptoms tend to abate with time. In three 12-week studies ($n = 276$) where soya or isoflavones were shown to be more effective than controls (6–8), the rate of hot flushes was reduced only by 40% (placebo effect 25%), 54% (placebo effect 35%) and 45% (placebo effect 30%). The differences between the groups were statistically significant in the Brzezinski (7) and Albertazzi (8) studies. There have also been a number of negative results including a placebo-controlled cross-over study of a clover extract given to 51 postmenopausal women (9). Some of these studies examined the impact on vaginal dryness and found either no effect or a very mild and probably clinically irrelevant effect.

Many women who have had breast cancer and are suffering from menopause symptoms are increasing their soy intake or taking soy or clover supplements hoping that these will treat their symptoms safely. There is a distinct lack of information in this area, and it is therefore difficult for the clinician to give direct advice to their patients. It can be argued that breast cancer patients in Japan do not change their diet and yet have a prognosis similar to that of Western women with breast cancer; it would seem that the consumption of a soy diet may not be dangerous. However, there is no information available on the use of isoflavone supplements in relation to breast cancer, and it is possible that high doses of isoflavones could have a detrimental effect on patients with breast cancer, particularly those who are ER positive.

In summary, there are some data supporting the efficacy of isoflavones in reducing the incidence and severity of hot flushes, although many studies have failed to find any difference between treatment and controls. It would seem that if these compounds have an effect it appears to be small and probably not clinically relevant for women having severe menopausal symptoms of flushing or vaginal dryness.

Cardiovascular disease

There are numerous clinical trials and animal studies and even a meta-analysis (10) showing a beneficial effect of soya protein on improving plasma cholesterol

Key messages

- Randomized controlled trials have shown that soya foods or isoflavone supplements have either no effect or a mild effect on menopausal hot flushing.
- Soya protein has been shown to have a lipid-lowering effect.
- Isoflavones do not appear to prevent osteoporosis.

levels. A meta-analysis of 38 clinical controlled trials of soya protein showed that an average consumption of 47 g per day of soya protein was associated with a mean 9.3% reduction in total cholesterol, 12.9% reduction in low-density lipoprotein (LDL) cholesterol and 10.5% reduction in triglycerides with no effect on high-density lipoprotein (HDL) cholesterol. Interestingly, a recent trial comparing soya protein with or without isoflavone showed that both products lowered cholesterol, suggesting that the lipid-lowering effect of soya protein may be independent of the isoflavones (11). Also, a placebo-controlled cross-over trial has been performed to examine the impact an isoflavone extract has on arterial compliance (elasticity) (12). This trial used a red clover-derived isoflavone product (40 and 80 mg/day) and found a 23% improvement in arterial compliance in the active group compared with the placebo group. There is also evidence that isoflavones appear to protect LDL cholesterol from oxidation (1–3), and these effects were shown at relatively low levels of isoflavones. Thus the lipid-lowering effect of soya protein would appear to be proven. The impact of isoflavones on arterial compliance and LDL oxidation is also interesting, but clearly further research is needed.

Prevention of osteoporosis

Epidemiological studies have indicated that Asians (living in Asia) have a high rate of vertebral fracture but a lower risk of hip fracture compared with westerners. The lower risk of hip fracture does not appear to relate to consumption of soya foods but rather may relate to anatomical differences in the hip between Asian and Caucasian populations. Randomized trials of soya foods or isoflavone preparations given in an attempt to preserve bone mass have to date been largely disappointing. Several groups have shown in animal studies that isoflavones can

preserve or even increase bone mineral density, but these results have not been duplicated in humans (13, 14). The drug ipriflavone, a synthetic isoflavone, has been shown in randomized controlled trials (in a dose of 400–600 mg per day) to have a bone-sparing effect in postmenopausal women (15). This drug is extensively metabolized to compounds including daidzein. Two small human studies that appeared to support the hypothesis that soya protein helps bone density (in the spine and not the hip) have been criticized for poor study design (16, 17). A 9-month study of postmenopausal women given soya protein found no effect on spine or hip bone mineral density (18). Another study demonstrated that high doses of a red clover extract also failed to influence measures of bone turnover after 12 weeks of treatment (19).

It would appear at present that the data suggesting that isoflavones have a favourable effect on bone health are inconclusive.

Conclusions

At this point in time, the role of isoflavones and the management of the menopause appear uncertain. Most controlled trials examining the impact of isoflavone preparations or foods on menopause flushing have been negative, and the few studies that have shown a positive result have only demonstrated a mild clinical effect which is of dubious clinical relevance to the woman having severe menopausal flushing or vaginal dryness. In contrast, there is strong evidence that soya protein has a lipid-lowering effect, irrespective of whether the effect is caused by isoflavones or some other component. The effect of isoflavones on vascular elasticity and LDL oxidation is interesting and worthy of further research. Finally, the impact of the parent compounds genistein and daidzein on bone loss appears to be minimal. However, it is possible that one of the isoflavone metabolites may prove to be a clinically useful agent in the prevention and treatment of osteoporosis.

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