

The role of Phytoestrogens in the management of menopausal symptoms

Menopause reflects a change in the woman's physiological hormonal status and is regarded as a pivotal point in a woman's life. The commonest symptoms experienced by women during the menopause are hot flushes and night sweats. Although HRT remains the gold standard for the treatment of menopausal symptoms, certain controversial studies have led to a shift against the regular use of HRT. Many physicians and women have turned to alternative 'natural' products, hoping that these can substitute the need for HRT. The evidence base for the efficacy and safety of phytoestrogens, in particular isoflavones, will be discussed.

Introduction

Menopause reflects a change in the woman's physiological hormonal status, and although not equivalent to an illness, it is regarded as a pivotal point in a woman's life. Its management should not be neglected because while some women may go through it without noticing, it is generally accompanied by a variety of disorders. Top of the list in 40% to 80% of Western women are hot flushes and night sweats which can result in decreased quality of life.¹ Increased public expectations and awareness of health issues have contributed to an increased demand for products related to menopausal symptoms.

The gold standard for the treatment of menopausal symptoms is the conventional HRT that actually corrects the underlying lack of female hormones. Results of major RCTs including the Women Health Initiative², Heart Estrogen/Progestin Replacement Study II³ and the large British observational study the Million Women Study⁴ have demonstrated an increased risk of cardiovascular disease and cancer of the breast with HRT use. Following these controversial studies over 90% of family physicians in Malta have changed their prescribing habits of

HRT.⁵ Due to the fear of these adverse effects and possible long-term risks of HRT, many women are reluctant to use HRT and have turned to alternative 'natural' products hoping that these can substitute the need for HRT.

A number of epidemiological studies suggest that the female populations in Asian nations like Japan, China and South-east Asia, are less burdened by menopausal symptoms than those of Western countries. It has been postulated that these differences may be due to the traditional Asian diet that is rich in Soy, which contains substances that are structurally similar to estrogen and bind to ER and hence have been called phytoestrogens. Since their binding affinity to ER is preferential, i.e. stronger binding affinity to ER β than to ER α , they are better classified as SERMs.

Media coverage has led to an increased consumer awareness of soy, which has resulted in skyrocketing sales of soy products and supplements. Many advertising campaigns have specifically targeted females and

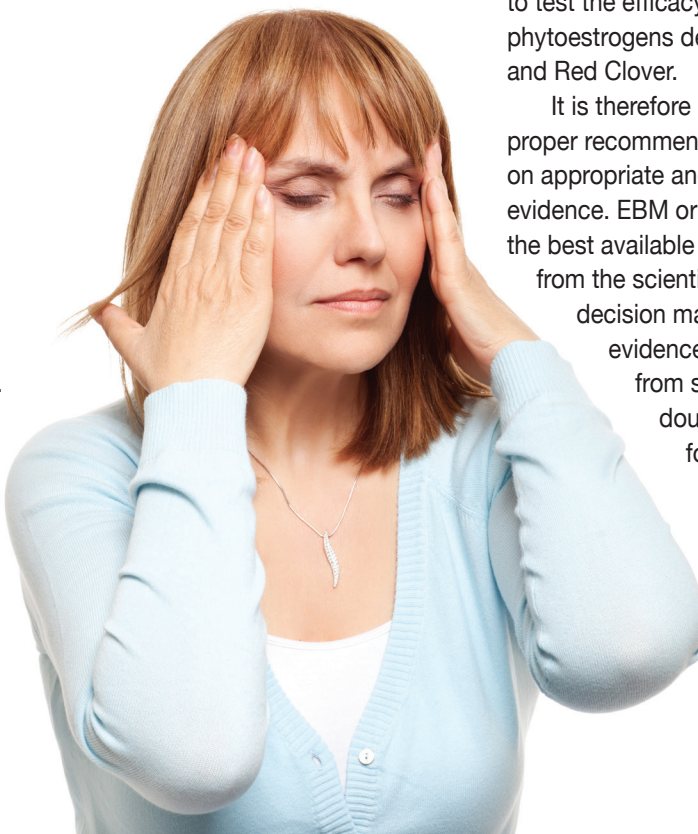
depicted soy and other phytoestrogens as the alternative to conventional HRT for menopausal symptoms with the added benefits of possible protective properties against breast cancer and heart disease. These products are classified under CAM and not as medicinals. Although they are freely available in health shops and pharmacies as over-the-counter products, many women request information and advice from their GP and other health practitioners about the effectiveness, safety and tolerability of these products before purchase.

What is the evidence base to support the effectiveness of phytoestrogen therapy in menopausal women for the control of hot flushes?

CAM products tend to lack a research tradition and infrastructure, since funding is generally limited compared with the amount spent by the pharmaceutical industry on conventional drugs. However over the past 10 years several studies both of experimental animal type and clinical trials have been carried out to test the efficacy and tolerability of phytoestrogens derived from both Soy and Red Clover.

It is therefore important that proper recommendations are based on appropriate and good quality evidence. EBM or EBP aims to apply the best available evidence gained from the scientific method to clinical decision making. The strongest evidence quality is derived from systematic reviews of double/triple blind RCT followed by that of individual properly designed RCTs.

The evidence base from systematic reviews of studies about efficacy of phytoestrogens is sometimes



conflicting. Several reviews have evaluated the clinical evidence relating isoflavone treatment to the relief of menopausal hot flash symptoms. The majority of these reviews included a variety of isoflavone sources, often without differentiating between the identities of individual isoflavones contained in the study product. Hence reports concluding that isoflavone supplements do not significantly reduce hot flash symptoms may be incorrect. The lack of differentiation between individual isoflavones contained in heterogeneous isoflavone mixtures from differing sources can be misleading when designing studies, interpreting results, and conducting reviews.

One critical review conducted by Williamson-Hughes et al.⁶ has demonstrated that a statistically significant reduction of hot flashes is achieved only in those studies which provided more than 15mg genistein (type of isoflavone). Another review by Bolanos et al⁷ analyzed 19 RCTs and demonstrated an overall significant reduction in hot flashes with soy preparations. The systematic review and meta-analysis conducted by Taku et al⁸ also concluded that soy isoflavone supplements, derived by extraction or chemical synthesis, are significantly more effective than

placebo in reducing the frequency and severity of hot flashes.


As described, several double-blinded RCTs with particular standardised formulations of isoflavones have demonstrated positive effects in controlling hot flashes.^{6,7,8,9} The strongest evidence is for formulations containing specifically genistein.^{6,10} It was also suggested that genistein may have a favourable effect on some cardiovascular markers.¹¹ This positive effect of genistein without any adverse effects on the endometrium and vagina after 1 year treatment were also demonstrated by another RCT.¹² The safety concerns of isoflavones were also addressed in another RCT with no effects on the endometrium and the breast, demonstrated by biopsy specimens.¹³

Less evidence exists to address the effects of soy isoflavones on bone metabolism in postmenopausal women and their place in the prevention and treatment of postmenopausal osteoporosis. In vitro and animal studies have shown that they act in multiple ways to exert their bone-supporting effects by acting on both osteoblasts and osteoclasts. Epidemiological studies and clinical trials suggest that soy isoflavones have beneficial effects on bone mineral

density, bone turnover markers, and bone mechanical strength in postmenopausal women.¹⁴

The North America Menopause Society in 2010 published a report stating that Soy-based isoflavones are modestly effective in relieving menopausal symptoms and supplements providing higher proportions of genistein (type of isoflavone) or increased S-equol content (isoflavan, metabolite of the soy isoflavone daidzein) may provide more benefits. However larger studies in younger postmenopausal women, and more research is needed to understand the modes of use of soy isoflavone supplements in women.¹⁵

Conclusion

There is enough evidence to support the use of isoflavones especially genistein, in the treatment of acute menopausal symptoms. Different sources and supplements of phytoestrogens are available on the market however many of them lack standardization of the content of the active ingredient which can seriously affect the bioavailability. Counseling of women regarding which preparations are most suitable and to avoid unrealistic expectations from these preparations is very important. 

Abbreviations

CAM: Complementary and alternative medicine
EBM: Evidence-based medicine
EBP: Evidence-based Practice
ER: Estrogen receptor
HRT: Hormone replacement Therapy
RCT: Randomized controlled trials
SERM: Selective Estrogen receptor modulator

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