Introduction

Menopause is clinically characterized by an increasingly loss of estradiol, an endogenous form of estrogen and the cessation of menstruation in the human female (1). This estrogen deficiency is known to have several accompanying symptoms and health complications including hot flashes, mood changes, vaginal dryness, accelerated bone loss, and cardiovascular diseases such as atherosclerosis (2). Traditionally, hormone replacement therapy has been used to treat climacteric associated symptoms; however, not all women are eligible or chose to receive this treatment and seek out alternative therapies. The search for such a treatment was accelerated when studies demonstrated that conventional estrogen replacement treatments can cause unwanted side effects including vaginal bleeding, bloating, depression, cholelethiasis, breast tenderness, and increased the risk for endometrial cancer (2). Although compliance of hormone replacement therapy ranges from 10-50%, many women stop treatment after several months for fear of long term complications and the fore mentioned side effects (3).

Consequently, there is a significant interest among patients for alternative remedies to HRT that have fewer unwanted side effects yet still provide health advantages. According to an investigation performed by the North American Menopausal Society in 1997, menopausal women account for one of the largest factions of alternative medicine users, documenting that 80% of women aged 45-60 reported the utilization of non-prescriptive medications for the relief of menopausal symptoms (4). Such treatments include herbal remedies, dietary manipulation, meditation, traditional Chinese medicine, vitamin and mineral supplements, homeopathy, acupuncture, and chiropractic practices. Most notably in the search for more effective alternative care was epidemiological data that pointed to the use of herbs and dietary supplements containing phytoestrogens as the most promising cure for menopausal symptoms. More specifically, it was found fewer than 25% of Japanese and 18% of Chinese climacteric women (5, 6) suffer from hot flashes as compared to 85% of North American (7) women and 70% of European women (8). This finding lead to the hypothesis that the higher average daily intake of phytoestrogens found in customary Asian diets was responsible for the observed inverse relationship between soy product consumption and hot flashes. Thus, a substantial number of studies have been initiated to determine whether a causal relationship exists between phytoestrogen intake and various aspects of postmenopausal women's health. Such research and up-to-date clinical information is crucial for both the general public that chose to use such

alternatives as a physician-independent source of treatment and also for physicians in order to provide appropriate advisement on an individual patient basis.

Phytoestrogens: What are they and how do they work?

Largely derived from soy products, phytoestrogens are naturally occurring compounds produced by plants that are similarly both structurally and functionally to 17β-estradiol and can generate estrogenic effects (1). There are three main classes of phytoestrogens, which include isoflavones, lignans, and cumestans. Isoflavones are the most extensively investigated as a result of their proven potency as compared to other phytoestrogens (9). The two major types of isoflavones are genistein and daidzein, which are abundant in soybeans, soy products, chickpeas, and red clover (10). The two main types of lignans include enterdiol and enterolactone, and examples of food containing these compounds are rye grains, linseeds, carrots, spinach, broccoli, and cauliflower (10). Coumestrol is the predominant substance in the cumestran group, which includes mug beans and soy and alfa-alfa sprouts (10).

Most phytoestrogens are introduced into the body in their inactive forms. The active conformations are produced through enzymatic deconjugation in the gastrointestinal tract (11). In their active forms, phytoestrogens have a cyclic heterophenolic structure that appears to be a prerequisite for selective binding to estrogen receptors. Moreover, recent studies have demonstrated that there exist two types of estrogen receptors, the classical ER-α receptor found primarily in the breast and uterus and the newly discovered ER-β receptor found in bone and the cardiovascular system (12). In addition, isoflavones appear to have a higher binding affinity to ER-β receptors, indicating the potential for tissue specific effects. Phytoestrogens only demonstrate modest agonist activity, however, at approximately one third of the potency of estradiol at the ER-β receptor and with 0.1 % potency at the ER-α receptor, thereby eliciting a weaker cellular response (13). The degree of effect will also depend on the concentration of the phytoestrogen and the specific target organ involved. Thus, the concept behind an increased consumption of phytoestrogens in postmenopausal women is that these substances can marginally compensate for the reduction in hormonal estrogen.

Phytoestrogens and Hot Flashes

The most common manifestation of menopause is the hot flash. Over 75% of North American postmenopausal women suffer from significant episodes of hot flashes, enough to

warrant physician visits (14). A hot flash is a symptom that is characterized as a transient sensation of warmth or burning with visible flushing over the face, neck, and upper thorax and back, followed by profuse perspiration in the same areas. Episodes can also cause chills, severe headaches, and anxiety. These events can last from several seconds to many minutes and can have variable frequency throughout the day. Although the molecular mechanism causing hot flashes is not completely understood, it is believed that central temperature regulation center in the hypothalamus is affected by decreasing levels of estrogen. This could potentially cause a loss of autonomic control of the peripheral vasculature leading to inappropriate and sudden vasomotor effects (15).

A series of experiments by independent research groups were performed to determine the effect of phytoestrogens on the incidence and severity of hot flashes on perimenopausal and postmenopausal women. In a double blinded placebo-controlled study of 104 women, Albertazzi et al. showed that sixty grams of isolated soy protein powder containing 40 grams of protein and 76 mg of active form isoflavones was effective in reducing the number of hot flashes by 45% as compared to 30% in the placebo group. During this study it was also observed that slight decreases in the amount of isolated soy protein given resulted in a decrease in effectiveness, thereby suggesting that 76 mg of isoflavones given daily is the minimal amount of phytoestrogens needed to elicit the documented decreases in hot flash frequency (16).

Similar results were found in experiments by Brzezinski et al. which conducted a randomized phytoestrogen-rich dietary study of 145 women that included a daily consumption of 80 g/day tofu (75mg/g daidzein, 200 mg/g genistein), 400 ml of soy drink (7 mg/g daidzein, 20 mg/g genistein), one teaspoon of miso (40 mg/g daidzein, 35 mg/g genistein), and two teaspoons of linseeds (4 mg/g lignans). This dietary manipulation was effective in reducing the number of hot flashes by 50% over the course of the twelve week study and also improved vaginal dryness. The results of this research are difficult to interpret since this study was not blind or placebo controlled, a potential drawback in designing a dietary study involving conventional foods (17).

Another investigation lead by Washburn et al. observed a decrease in the severity of hot flashes but not a decrease in number of hot flashes in a randomized double blinded study that involved giving 51 women 20 grams of isolated soy protein containing 34 mg of phytoestrogens daily (18). Two studies performed in by Scambia et al. and Upmalis et al. each administering 50 mg of isoflavones daily over the course of 6 and 12 weeks recorded a decrease in the number of

hot flashes by 45% and 28% respectively (19, 20). It is interesting to note in the trials conducted by Scambia et al., six weeks into the experiment, both the soy-treated group and the placebo group received estrogen replacement therapy. When compared to the pretreatment data on week 6 of the study, a significant reduction in the mean number of hot flashes per week was observed in the group that received the soy extract, whereas a more notable relief in symptoms was reported in both soy and placebo groups during the estrogen replacement therapy phase of the trial.

Kostsopoulos et al. and Germain et al. performed similar double blinded studies in 2000 and 2001, administering 118 mg and 80 mg of phytoestrogens daily respectively, and found no climacteric symptom relief (21, 22). Nonetheless, it is believed that both study designs lacked significant sample size and duration, and also that the women involved in the trials experienced only mild hot flashes, potentially underestimating the effect of the treatment.

Further studies involving red clover derived isoflavone tablets have shown conflicting results. Investigations lead by Baber et al. and Knight et al. administered doses of 40 and 160 mg tablets, respectively, that failed to reduce the incidence of hot flashes over a three month period (23, 24). On the other hand, another randomized, double-blinded study of red-clover derived tablets (Promensil, 40 mg) produced a 75% decrease in the number of hot flashes and night sweats over the period of 16 weeks in 30 women (25). There is no current explanation for the difference in the results except for biological variability and experimental duration.

A review of these investigations suggest that in order to increase the strength of future studies, a standardized protocol should be established so that results can be appropriately compared in order to extract valuable data and modify trials if required. As recommended by the FDA for medical trials for hormone replacement therapy, three important conditions apply: 1) duration of three months, 2) placebo arm, and 3) enrollment of patients with moderate to severe hot flash symptoms (10). These conditions should be unanimously applied in all future phytoestrogen studies. Additional ways to increase the sensitivity of these studies include increasing the sample size, increasing the duration of the studies, and requiring follow-up appointments with women to report a potential difference in symptomatology after completing the study.

<u>How do American and Asian diets compare?</u>

The use of phytoestrogen derivatives to treat menopausal symptoms drew interest after epidemiological studies suggested that increased phytoestrogen intake as found in Asian diets may improve climacteric symptoms, and could potentially be protective against breast, endometrial and bowel cancers, in addition to a reduction in the risk of cardiovascular disease and osteoporosis (28). It is estimated that a traditional Japanese diet contains an intake of approximately 50-200 mg of phytoestrogens per day, with a mean of about 40 mg from tofu and miso (14, 26). By comparison, the SWAN study performed in part by UCLA to analyze variations in nutrient intakes by ethnicity found that approximately 40% of the African American, Caucasian, and Hispanic women in America recorded no daidzein or genistein intakes. Additionally, it was found that even if women in the above mentioned ethnic categories documented isoflavone intake, such levels were so low to be considered of biological significance (Mean values of daidzein; genistein: African Americans (.13 mg; 0.27 mg), Caucasian (0.44 mg; 0.83 mg), Hispanic (0.17 mg; 0.31 mg) (27). Moreover, it was noted that both Chinese and Japanese women (Mean values of daidzein; genistein : Chinese (3.3 mg; 6.4 mg), Japanese (7.8 mg; 11.2 mg) consumed uniformly higher amounts of isoflavones daily that other ethnic groups and also noted less complaints in menopausal symptoms such as vaginal dryness and urine leakage (27).

Safety Issues and Relative Effectiveness

Unfortunately, the regulation of alternative therapies for menopausal symptoms has not maintained pace with the tremendous growth and demand of the industry. In 1994, the Dietary Supplemental Health and Education Act (DSHEA) was passed which declared that dietary supplements such as herbs and vitamins would not be considered food products and thus would not be required to pass strict clinical standard before being released to the public (29). Further investigations into the content of such dietary supplements have shown larger discrepancies in labeled active ingredients in many over the counter products. For example, a study performed by the California branch of the FDA showed that 32% of patent Asian medicines contain undocumented pharmaceutical and heavy metals (30). Additionally, independent quality checks performed in the United Kingdom on commercially available phytoestrogen products have shown that the content in prepared tablets varies drastically in phytoestrogen content, and in some instances is totally absent (31). Since no notable dose-ranging studies of phytoestrogens

have been performed, high doses of these substances could have unwanted side effects. Moreover, it is believed that the effectiveness of phytoestrogens varies widely among individuals depending on an individual's metabolism, even when a controlled amount is administered. Considering that the gastrointestinal flora predominately determines dietary phytoestrogenic metabolism and activation, conditions such as bowel diseases, antibiotic use, ethnicity, and gender may affect bioavailability and excretion of phytoestrogens (14). Many investigators believe that presently the use of phytoestrogen tablets such be discouraged until safety and efficacy standards are established.

Conclusions

There is a great interest among postmenopausal women in alternative therapies for treating climacteric associated symptoms, namely the use of phytoestrogens. Despite the recommendation of the use of phytoestrogens in lay literature, there have not been substantial clinical results confirming their effectiveness or appropriate dosage amounts. Although some investigations have demonstrated that the use of certain isoflavones has decreased the frequency and severity of hot flashes, they have not absolutely proven their superiority to placebo and additional interventional trials must be performed to reach more definitive conclusions. However, patients still showing interest in using phytoestrogens should be advised to incorporate more isoflavones through dietary manipulation rather than in capsule form. Since tablets containing phytoestrogens are not regulated by the FDA and can vary in content, foods such as chickpeas, tofu, soybeans, and soy powder are more reliable sources of intake and also many have other beneficial health effects. Nonetheless, it does appear that phytoestrogens are emerging as a promising class of compounds to treat the menopausal syndrome.

Reference:

1. Ewies AA. Phytoestrogens in the Management of Menopause: Up-To-Date. *CME Review Article in the Obstetrical and Gynecological Survey.* 2002;57(5):306-313.
2. Warren MP, Shortle B, Dominguez J. Use of alternative therapies in menopause. *Best Practice & Research Clinical Obstetrics and Gynecology*. 2002;16(3):411-448.

3. Kessel B. Alternatives to estrogen for menopausal women. *Proc Soc Exp Biol Med.* 1998;217:38-44.
4. Kaufert P, Boggs, P, Ettinger B, Woods NF, Utian WH. Women and Menopause: beliefs, attitudes, and behaviors. *The North American Menopause Society 1997 Survey*. 1997;5(4):1161-1172.
5. Boulet M, Oddens B, Lehert P, Vemer H, Visser A. Climeratic and menopause in seven south-east Asian countries. *Maturitas*. 1994;19:157-176.
6. Lock M. Encounters with aging: mythologies of menopause in Japan and North America. Berkeley, CA. University of California Press, 1993.
7. Notelovitz M. Estrogen replacement therapy indications, contrindications and agent selection. *Am J Obstet Gynecol*. 1989;167:8-17.
8. Rekers H. Mastering the menopause. In: Burger H, Boulet M, eds. *A Portrait of the Menopause*. Park Bridge, NJ: The Pathenon Publishing Group; 1991:23-43.
9. Jones KP. Menopause and cognitive function: estrogens and alternative therapies. *Clin Obstet Gynecol*. 1998;217:38-44.
10. Albertazzi P, Purdie D. The nature and utility of the phytoestrogens: a review of the evidence. *Maturitas.* 2002;42:173-185.
11. Setchell KDR, Aldercreutz H. Mammalian ligans and phytoestrogens; recent studies on their formation, metabolism, and biological role in health and disease. In: Rowland I, editor. *Role of the gut flora in toxicity and cancer*. London: Academic Press, 1988. p. 315-345.
12. Couse JF, Lindsey J, Grandien K. Tissue distribution and quantitiative analysis of estrogen receptor alpha and estrogen receptor beta messenger ribonucleic acid in the wild-type and ERalpha-knockout mouse. *Endocrinology*. 1997;138:4613-4621.
13. Kuiper G, Lemmen J, Carlsson B, Corton JC, Safe SH, van der Saag RT. Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor beta. *Endocrinology*. 1998; 139(10):4252-4263.
14. Elkind-Hirsch, K. Effect of dietary phytoestrogens on hot flashes: can soy-based proteins substitute for traditional estrogen replacement therapy? *Menopause*. 2001;8(3):154-156.

15. Varner RE, Younger JB. Menopause. In: Seltzer VL, Pearse WH (eds) *Women's Primary Health Care: Office Practice and Procedures*, pp 249-266. New York: McGraw-Hill, 1995.
16. Albertazzi P, Pansini F, Bonaccorsi G, Zanotti L, Forini E, De Aloysio D. The effects of soy supplementation on hot flashes. *Obstet Gynecol*. 1998;91:6-11.
17. Brzezinski A, Adlercreutz H, Shaoul R, Rosler A, Shmueli A, Tanos V, Schenker GJ. Short-term effects of phytoestrogen-rich diet on postmenopausal women. *Menopause*. 1997;4(89):124-129.
18. Washburn S, Burke GL, Morgan T, Antony M. Effect of soy protein supplementation on serum lipoproteins, blood pressure, and menopausal symptoms in perimenopausal women. *Menopause*. 1999;6(7):7-13.
19. Scambia G, Mango D, Signorile PG. Clinical effects of a standardized soy extract in postmenopausal women: a pilot study. *Menopause*2000;2:150 -151.
20. Upmalis DH, Lobo R, Bradley L, Warren M, Cone FC, Lamia CA. Vasomotor symptom relief by soy isoflavone extract tablets in postmenopausal women; a multicenter, double-blinded, randomized, placebo-controlled study. *Menopause*2000;18:1068 -74.
21. Kostsopoulos D, Dalais FS, Liang YL, McGrath PB, Teede HJ. The effects of soy protein containing phytoestrogens on menopausal symptoms on postmenopausal women. *Climeratic.* 2000;316:161-7.
22. Germain AS, Peterson CT, Robinson JG, Aleker L. Isoflavone-rich or isoflavone-poor soy protein does not reduce menopausal symptoms during 24 weeks of treatment. *Menopause*. 2001;8:17-26.
23. Baber RJ, Templeman C, Morton T, Kelly GE, West L. Randomized placebo-controlled trial of isoflavone supplement and menopausal symptoms in women. *Climeratic*. 1999;2:85-92.
24. Knight DC, Howes JB, Eden JA. The effects of Promensil^{TM} an isoflavone extract on menopausal symptoms. *Climeratic*. 1999;2:79-84.
25. Jeri AR, de Romana C. The effect of isoflavone phytoestrogens in relieving hot flashes in Peruvian postmenopausal women. 9th International Menopause Society World Congress on Menopause; 1999; Yokohama, Japan.

26. Kang, HJ, Ansbacher R, Hammound MM. Use of alternative and complementary medicine in menopause. *International Journal of Gynecology and Obstetrics*. 2002;79:195-207.
27. Huang, MH, Schocken M, Block G, Sowers MF, Gold E, Sternfield B, Seeman T, Greendale G. Variations in nutrient intakes by ethnicity: results from the Study of Women's Health Across the Nation (SWAN). *Menopause*2002; 9:309 -19.
28. Rees M, Purdie D. Non-hormone replacement therapy options and alternative therapies. *Management of the Menopause: The Handbook of the British Menopause Society, 2nd Edition.* Marlow: BMS Publications Ltd, 1999, pg 42-49.
29. Dietary Supplementary Health and Education Act. 1994. p. S784.
30. Ko RJ. Adulterants in Asian patent medicines. [Lett.]. *N Eng J Med*. 1998;339:847.
31. Setchell KDR, Brown NM, Desai P. Bioavailability of pure isoflavones in healthy humans and analysis of commercial soy isoflavones supplements. *J of Nutrition*. 2001;131:3625-755.