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Soy isoflavones as a first-line approach to the treatment of menopausal vasomotor complaints

Abstract: *The association between an increased uptake of isoflavones and a reduced frequency of menopausal hot flushes was first described in 1992, based on a lower incidence of hot flushes in countries with a high consumption of soy (Adlercreutz et al. 1992). Since then, numerous clinical trials with various sources of isoflavones including soy and red clover have been presented, with practically all of the studies with adequate design delivering an outcome in favour of isoflavone supplementation (Kurzer 2008). An in-depth risk assessment (EFSA 2015) concludes that the amply available human data does not indicate any suspected harmful effects from a potential interaction of isoflavones with hormone-sensitive tissues in the mammary gland, the uterus and the thyroid gland. Safety was ascertained with long term intake of up to 150mg isoflavones per day ingested for the duration of at least three years. Moreover, high isoflavone intake was found to have preventive effects with respect to breast cancer (Boucher et al. 2013, Iwasaki et al. 2008, Verheus et al. 2007, Wu et al. 2008). Clinical findings indicate potential benefits of isoflavone exposure even during breast cancer treatment with tamoxifen or anastrozole.*

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Regulatory opinions

The European Food Safety Authority recently concluded a lengthy debate on the clinical importance of hypothetical risks of isoflavones on the health of menopausal women (EFSA 2015). The assessment concluded on the absence of adverse effects on breast, uterus and thyroidal gland with the intake of 35–150mg of isoflavones daily through food or supplements. The extensive review did especially not confirm the hypothesis of breast or endometrial cancer promoting effects of the "phyto-estrogens" after up to 30 months of supplementation with 150mg isoflavones per day – which is not really surprising, as isoflavones are not "phyto-estrogens", but rather "phyto-SERMs", selective estrogen receptor modulators. They activate the estrogen receptor beta and therefore protect against overshooting estrogen receptor alpha-modulated effects on cell proliferation. With this unambiguous statement of the EFSA, the issue of efficacy of isoflavone-containing preparations against menopausal disorders should now return to the focus of attention.

In its 2011 report, the North American Menopause Society (NAMS) had confirmed an efficacy of isoflavones against hot flushes, as demonstrated in predominantly Caucasian women in early menopause who had at least four hot flushes daily (NAMS 2011). This finding corroborated the earlier 2004 recommendation of first considering lifestyle changes, either alone or in combination with a non-prescription remedy such as isoflavones, for the treatment of women with mild vasomotor symptoms (NAMS 2004). Likewise, the International and Austrian Menopause Society (Clementi et al. 2005) had issued a position paper, in which the available evidence for the efficacy of isoflavones against mild to moderate menopausal hot flushes is rated as evidence grade I. Isoflavones are recommended as first-line treatment option alternative to hormone replacement therapy.

Efficacy against menopausal hot flushes

The efficacy of soy isoflavones has been demonstrated in clinical trials, and confirmed in meta-analyses and reviews (Chen et al. 2014; Hooper et al. 2009; Howes et al. 2006; Lethaby et al. 2013; Li et al.2015; Messina and

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Hughes 2003; Messina 2014; Thomas et al. 2014; Williamson-Hughes et al. 2006). The effect is obviously independent of the dietary source of isoflavones: positive results have been obtained with soy food (Albertazzi et al. 1998), soy or red clover extracts (Cheng et al. 2007; Drapier-Fauré et al. 2002; Imhof et al. 2008; Lipovac et al. 2012; Mainini et al. 2013; Petri Nahas et al. 2004; Scambia et al. 2000; Ye et al. 2012) and with isolated isoflavones (Crisafulli et al. 2004; D'Anna et al. 2007; D'Anna et al. 2009; Evans et al. 2011; Han et al. 2002; Nahas et al. 2007).

Hooper's meta-analysis revealed an average improvement of menopausal symptoms of approximately 20% above the effect of placebo. One of the currently largest meta-analyses on soy, performed by Taku et al. (2012), included 19 trials with data on hot flush severity and/or frequency. It concluded that ingestion of soy isoflavones for 6 weeks to 12 months significantly reduced the frequency of hot flushes by more than 20% compared with placebo (95% CI, –28.38 to –12.86; $p<0.00001$). Soy isoflavones also significantly reduced hot flush severity by more than 26% compared with placebo (95% CI: –42.23 to –10.15, $p=0.001$). The analysis found that the decrease in hot flush frequency in longer duration trials (more than 12 weeks) was approximately threefold greater than the decrease in shorter duration trials. Isoflavone supplements providing more than 18.8mg of genistein (the median for all studies) were more than twice as potent at reducing hot flush frequency than lower genistein supplements. Almost all studies in the meta-analysis showed a consistent reduction in hot flush frequency and severity.

Li et al. (2015) found very similar results by analysing 16 studies on soy isoflavone effects on menopausal hot flushes. The maximal percentage change of hot flushes reduction by soy isoflavones was 25.2% after elimination of the placebo effect, accounting for 57% of the maximum effects of estradiol (Emax-estradiol = 44.9%). However, a time interval of 13.4 weeks was needed for soy isoflavones to achieve half of its maximal effects (estradiol required 3.09 weeks). Soy isoflavones show less expressed and slower effects in attenuating menopausal hot flushes, compared with estradiol. Studies that assess the effect of isoflavones on menopausal hot flushes should have a duration of at least 12 weeks, possibly more, so that they can achieve their maximal effects.

Effect on bone

In the Singapore Chinese Health Study, a gender-specific association between soy and the risk of hip fracture has been found for women (Koh et al. 2009). Most clinical trials performed with soy isoflavones have observed a reduction of the loss of bone mineral density (BMD) in postmenopausal women. Several studies have shown a positive effect up to 6 and 12 months, using as study variables BMD and biochemical markers of bone remodeling, and showing a beneficial effect on postmenopausal bone loss. There is an increase of bone mass or a decrease of its loss, assessed by BMD and remodeling markers, with a however inconsistent decrease in bone resorption markers and an increase or absence of effects in bone formation markers (Atkinson et al. 2004, Chen et al. 2003, Morabito et al. 2002, Marini et al. 2007).

Genistein showed a positive effect on bone mass in postmenopausal osteopenic women during 24 months (Marini et al. 2007). Genistein (54 mg/day) and HT (1 mg of estradiol associated with 0.5 mg of norethindrone) resulted both in increased BMD at the femoral neck and the lumbar spine (Marini et al. 2007). The only epidemiological cohort study consecrated to the association between dietary soy intake and the risk of bone fractures has shown an inverse relationship between soy food consumption and the rate of bone fractures (Zhang et al. 2005).

Therefore, soy isoflavones may suppress bone resorption and minimize bone loss under some conditions. Two systematic reviews and meta-analysis of randomized controlled trials by ingestion of soy isoflavones in menopausal women revealed a significant improvement in lumbar spine BMD, significant decrease in urine deoxypyridinoline as a bone resorption marker, improvement in bone strength and decrease in the risk of fracture, but did not affect the serum alkaline phosphatase and osteocalcin as bone formation markers (Wei et al. 2012). However, efficacy studies of soy isoflavones on bone density and RCTs on fracture reduction performed for a minimum of 24 months are still needed.

Positive effects in long-term use

The study of Zamora-Ros et al. (2013) with 334,850 European women in the age of 35 to 70 years did not indicate an increased cancer risk through soy isoflavones. A meta-analysis by Chen et al. (2014) evaluating 35 studies even showed that isoflavone significantly reduce the pre- and postmenopausal risk of breast cancer occurrence.

A Canadian paper by Boucher et al. (2013) found that the intake of high dose isoflavone supplements is associated with reduced breast cancer risk.

The protective effect of isoflavones was also described in a study of Verheus et al. (2007) documenting the data of 383 Dutch women, and in a publication of Iwasaki et al. (2008) including more than 24,000 Japanese women in the age of 40 to 60 years. Especially noteworthy is the inverse association between genistein intake and breast cancer risk: Wu et al. (2008) calculated a 16% reduction of the relative breast cancer risk for each 10mg of genistein intake.

In a recent randomised controlled trial by Alekel et al. (2015) 224 women received 80 or 120mg of isoflavones for three years. This exposure did not lead to changes in endometrial thickness or thyroid hormones.

Use in women with a history of breast cancer

Recently, a double-blind, randomized 12-month soy intervention study in previously treated breast cancer patients and high risk women did not reveal an adverse effect on breast fibroglandular tissue density by MRI, or on mammographic breast density (Wu et al. 2015).

There are no indications for a contraindication of isoflavone-containing preparations in women with a history of breast cancer or even under treatment with tamoxifen or anastrozole. A Relatively recent research indicates that the exposure to isoflavones is associated with life-prolonging effects in breast cancer patients (Marini et al. 2008; Shu et al. 2009). Shu et al. (2009) found that soy food intake, measured by soy protein and/or soy isoflavone intake, was inversely correlated with mortality and cancer recurrence. The hazard ratio associated with the highest quartile of soy protein intake was 0.67 (95% CI 0.52–0.84) for recurrence compared with the lowest quartile. The multivariate adjusted mortality rates were 13.1 and 9.2%, and the five-year-recurrence rates were 13.0 and 8.9%, respectively, for women in the lowest and highest quartiles of soy protein intake. Higher isoflavone exposure of breast cancer patients clearly improves the prognosis. The improved prognosis was evident among women with ER(-) and with ER(+) breast

cancer, and was also found in users and non-users of tamoxifen. Soy protein and isoflavones both correlated with the time of disease-free survival. Best effects were noted with approximately 11g of soy protein daily, or with 30–70mg of isoflavones. There was no difference with respect to pre- or postmenopausal women.

There was likewise no impairment of cancer therapy in large case control studies (Boyapati et al. 2005; Fink et al. 2007). In one cohort study in 1,954 breast cancer patients there was not only a reduced rate of cancer recurrence, but also no undesired interaction with tamoxifen (Guha et al. 2009). The study explicitly mentioned positive effects against estrogen-receptor-positive breast cancer, and thus against a form of cancer which reacts very sensitively to estrogens by growth stimulation.

Wu et al. (2007) conducted a cross-sectional study in Asian Americans with breast cancer who were tamoxifen users (n=380) to investigate the association between soy intake and circulating levels of tamoxifen and its metabolites (N-desmethyl tamoxifen [N-DMT], 4-hydroxytamoxifen [4-OHT], and 4-hydroxy-N-desmethyl-tamoxifen [endoxifen]). Serum levels of tamoxifen or its metabolites were found unrelated to self-reported intake of soy or serum levels of isoflavones.

Synergistic effects were concluded from a study by Kang et al. (2010), where the impact of soy isoflavones on breast cancer treatment by anastrozole was examined: Isoflavone exposure had no impact on breast cancer mortality and significantly reduced breast cancer recurrence during the 5.1 year follow-up period.

These findings uniformly indicate potential benefits of isoflavone exposure for breast cancer patients with and without treatment with tamoxifen or anastrozole. Even though additional studies would be welcome, current clinical data do not longer justify advising against isoflavone exposure in breast cancer patients.

Conclusions on isoflavones and menopausal hot flushes:

- **The efficacy of isoflavones against menopausal hot flushes has been confirmed in independent meta-analyses, and has the evidence grade Ia.**
- **The effect against hot flush frequency and severity is approximately 25% superior over placebo, and reaches 57% of the effect of estrogen replacement.**
- **Reaching the maximum effect takes more time than under treatment with estrogen. This is an important message to give to the patients. On the risk side fewer adverse effects and a high patient compliance can be expected.**
- **Additional beneficial effects may be expected for the bones.**
- **High exposure to isoflavones is associated with reduced breast cancer risk.**
- **Long-term studies in breast cancer patients indicate advantages for soy exposure, expressed as an improved cancer recurrence rate and a lack of undesired treatment interactions with tamoxifen and anastrozole. Isoflavone exposure in breast cancer patients should no longer be discouraged.**
- **Long term safety in hormone-sensitive tissues such as breast, endometrium and thyroid gland is undisputed and officially confirmed by the European Food Safety Authority (EFSA) with exposures as high as 150mg isoflavones daily and a duration of intake of up to three years.**

Summarizing, isoflavones can be recommended as first-line treatment of natural menopausal hot flushes.

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