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Soybean isoflavone exposure does not have feminizing effects on men: a critical examination of the clinical evidence

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Objective: To critically evaluate the clinical evidence, and when not available, the animal data, most relevant to concerns that isoflavone exposure in the form of supplements or soy foods has feminizing effects on men.
Design: Medline literature review and cross-reference of published data.
Result(s): In contrast to the results of some rodent studies, findings from a recently published metaanalysis and subsequently published studies show that neither isoflavone supplements nor isoflavone-rich soy affect total or free testosterone (T) levels. Similarly, there is essentially no evidence from the nine identified clinical studies that isoflavone exposure affects circulating estrogen levels in men. Clinical evidence also indicates that isoflavones have no effect on sperm or semen parameters, although only three intervention studies were identified and none were longer than 3 months in duration. Finally, findings from animal studies suggesting that isoflavones increase the risk of erectile dysfunction are not applicable to men, because of differences in isoflavone metabolism between rodents and humans and the excessively high amount of isoflavones to which the animals were exposed.
Conclusion(s): The intervention data indicate that isoflavones do not exert feminizing effects on men at intake levels equal to and even considerably higher than are typical for Asian males. (Fertil Steril® 2010;93:2095–104. ©2010 by American Society for Reproductive Medicine.)

Key Words: Isoflavones, testosterone, estrogen, men, feminization, gynecomastia, erectile dysfunction, clinical

For several decades, soy-based foods have been recognized as plant sources of high-quality protein (1), but in recent years, these foods have received considerable attention for their possible role in providing health benefits independent of their nutritional content (2, 3). In large part, this is because they are essentially unique dietary sources of isoflavones, a group of diphenolic chemicals classified as phytoestrogens (4). However, isoflavones are also the reason that soy foods have become controversial, because there are concerns that the estrogen-like properties of these soybean constituents might lead to adverse effects in some individuals. Most notable in this regard is the concern that isoflavones pose a risk to patients with breast cancer and women at high risk of developing it, although the relevant clinical and newly published epidemiologic data are reassuring (5, 6), in contrast to the animal data upon which concerns are based (7).

More recently, questions have been raised regarding possible adverse effects of soy consumption in men, including feminization (8) and infertility (9–11). Sensationalized media stories on these topics (12, 13) may have led some men to avoid soy foods, which may be particularly unfortunate because speculative but intriguing evidence suggests that soy foods reduce risk of developing prostate cancer (14) and perhaps even inhibit prostate cancer metastasis (15, 16). Peripherally related to feminization concerns is the hypothesis that xenoestrogen exposure is responsible for an assortment of male ailments, including testicular germ cell cancer, cryptorchidism, and some cases of hypospadias and low sperm counts—collectively referred to as testicular dysgenesis syndrome (TDS)—although TDS is thought to result primarily from exposure to xenoestrogens in utero or during the neonatal period rather than adulthood (9, 17, 18).

Despite the large populations in soy food–consuming countries (19), suggesting that soy foods might impair fertility in Western men is not as nonsensical as might first appear. Estrogen is involved in sperm production (20, 21), and isoflavones (especially genistein) affect sperm in vitro (22–26) and reproductive health in animals (27–31). In addition, it is yet to be definitively established whether Asians and non-Asians respond similarly to isoflavones. In theory, the long history of exposure, traditional lifestyle factors (including but not limited to dietary habits), and possible genetic differences could limit the ability to extrapolate findings from Asians to non-Asians. In fact, preliminary evidence indicates there may be some differences in isoflavone metabolism between these two groups (32, 33). Another obvious difference is that Asian men are exposed to isoflavones from an early age via the consumption of

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traditional soy foods, whereas exposure in non-Asian men usually begins later in life, although there is no evidence indicating that this differing exposure pattern would affect the possible effects of isoflavones on fertility-related parameters.

Of potential relevance to the fertility issue is the recently expressed concern that environmental hormones, including dietary phytoestrogens (9), but especially pesticides (34), act through multiple mechanisms to adversely affect reproduction. To this point, in a small Indian study, infertile men ($n = 21$) with low sperm count (<20 million/ml) and no obvious etiology for their condition were found to have higher seminal plasma levels of polychlorinated biphenyls and phthalate esters than fertile controls ($n = 32$). Furthermore, xenoestrogen concentrations were inversely related to total motile sperm counts in the former group of men (35).

Interestingly, the possibility that isoflavones impair fertility has been a subject of discussion for more than 60 years (36). The potential biologic effects of isoflavones first came to the attention of the scientific community in the 1940s, because of breeding problems in female sheep in Western Australia that grazed on a type of clover rich in isoflavones (36–38). Three decades later, Setchell et al. (39) established that the isoflavone-rich soy, which was part of the standard diet of captive cheetahs in North American zoos, was a factor in the decline of their fertility.

However, the fertility problems in these species occurred in females and not males, and problems likely occurred in the cheetah because felines are barely able to glucuronidate phenolic compounds (40-43). Because glucuronidation is a primary step in the bodily elimination of isoflavones, circulating levels in the cheetah are much higher than they would be in species that readily possess this ability, such as humans (44, 45). It is widely recognized that there is much species variation in the metabolism of and biological response to isoflavones (38, 43). In the case of sheep, serum levels of the isoflavone equol (a bacterially-derived metabolite of the soybean isoflavone daidzein) far exceeded anything approaching human levels simply because daily isoflavone intake was estimated to be as much as several grams, which dwarfs the average Japanese intake of approximately 40 mg/d (46).

The aim of this review is to evaluate evidence most relevant to the possible feminizing effects of soy food and isoflavone exposure in men with a specific focus on the clinical data. Before doing so, brief background information on isoflavones is provided.

BACKGROUND ON ISOFLAVONES

Isoflavones have been the subject of intense investigation, as evidenced by the more than 10,000 peer-reviewed journal articles published during the past 20 years since the U.S. National Cancer Institute first announced a research program aimed at establishing the possible chemopreventive properties of these diphenolic molecules (47). Isoflavones have a limited distribution in nature, and among commonly consumed foods they are found in physiologically relevant amounts only in soybeans and foods derived from this legume (4), although a variety of plants such as red clover (48) are also rich sources. One serving of a traditional soy food contains approximately 25 mg of isoflavones (approximately 3.5 mg per gram of protein; isoflavone amounts in this text refer to the aglycone weight) (46).

In total, there are 12 different soybean isoflavone isomers. These are the three aglycones genistein (4',5,7-trihydroxyisoflavone), daidzein (4',7-dihydroxyisoflavone), and glycitein (7,4'-dihydroxy-6-methoxyisoflavone); their respective β-glycosides genistin, daidzin, and glycitin; and the three β-glucosides esterified with either malonic or acetic acid. In nonfermented soyfoods, nearly all of the isoflavones are present as glycosides; however, more of the isoflavones are present as aglycones in fermented soy foods because of microbial hydrolysis (49). Typically, there is somewhat more genistein/genistin than daidzein/daidzin in soybeans and soy foods, whereas glycitein/glycitin comprises only 5%–10% of the total isoflavone content.

To absorb isoflavones present in the intestine as glycosides, the sugar molecule must first be hydrolyzed, which occurs in a relatively efficient manner (45, 50). Once absorbed, isoflavones circulate primarily as the glucuronide and to a lesser extent sulfate conjugate. Generally, only 1%–2% is in the unconjugated and biologically active form (44, 51). In response to an isoflavone intake of between 50 and 100 mg/d, peak serum levels can reach the low micromolar range, although there are huge interindividual differences in isoflavone metabolism such that levels of the parent isoflavones and their metabolites vary markedly among subjects in clinical studies (52).

Isoflavones have a chemical structure similar to the hormone estrogen, bind to and transactivate estrogen receptors (ER) (53–55), and exert estrogen-like effects under certain experimental conditions in vitro and in vivo (56). Isoflavones have been classified by some as selective estrogen receptor modulators (mixed estrogen agonists/antagonists) (57–59), in part because of their preferential binding to and transactivation of ER-β compared with ER-α (54, 60). Therefore, isoflavones have been discussed as possible natural alternatives to conventional hormone therapy, and most of the clinical research involving isoflavones has focused on understanding their effects in postmenopausal women (61, 62).

Aside from ER binding, isoflavones also exert nongenomic actions that modulate a diverse array of intracellular signaling cascades (63, 64), including affecting the activity of enzymes involved in hormone synthesis and metabolism (65–67), although the concentrations required to exert these effects often exceed circulating levels of isoflavones attained in vivo. There is a need to better establish tissue isoflavone concentration, because relatively limited work in this area has been conducted, although there is some suggestion that isoflavones may be concentrated in tissues relative to serum and plasma (68–70). Given the potential hormone-dependent and independent effects of isoflavones, the interest in establishing their effects on hormone status and balance in both men and women is understandable.

GYNECOMASTIA, ESTROGEN, AND TESTOSTERONE

Findings from case reports are not a basis for forming conclusions, but they can be grounds for hypothesis generation. In 2008, Martinez and Lewis (8) published a case report of a 60-year old man with gynecomastia and dramatically elevated estrogen levels thought to have resulted from the consumption of isoflavone-containing soymilk. Gynecomastia is not merely excessive breast adipose tissue, rather it is a benign enlargement of the male breast attributable to proliferation of the ductular elements (71). This condition is actually common, occurring in 50%–70% of boys during puberty (72) and 30%–70% of men (73-76).

The subject described in the case report (8) was said to have consumed 3 quarts of soymilk daily, an amount (assuming it is made using the whole soybean) that would be expected to provide approximately 300 mg of isoflavones (the authors suggested 361 mg) (46). In comparison, typical intake among older men in Japan (46) and Shanghai (77) is approximately 40 mg/d. Clearly, excessive intake of even very nutritious foods can produce untoward effects. In fact,