The primary outcome was progression to overt hypothyroidism (serum TSH >10 mU/L and free T\textsubscript{4} <9 pmol/L), with secondary outcome measures of blood pressure, insulin resistance, lipids, and highly sensitive C-reactive protein (hsCRP).

RESULTS

The mean age of the study group was 57.2 yr; there were 8 male and 52 female subjects with clinical hypothyroidism, of whom 38 (63.3%) were thyroid peroxidase–positive (TPO+).

Six patients (10%) had clinical hypothyroidism after high-dose phytoestrogen and none had it after low-dose phytoestrogen. Of the 6 subjects in whom clinical hypothyroidism developed, 3 had high-dose phytoestrogen supplementation before the low-dose phytoestrogen, and 3 had high-dose phytoestrogen supplementation after low-dose phytoestrogen supplementation. Only 1 patient in whom clinical hypothyroidism developed was TPO+ (no cause was provided for the other 5 patients). TPO antibody titers did not change before or after either supplementation regimen.

For the six patients in whom hypothyroidism developed, TSH values increased by 57% (8.0±0.8 [SD] vs. 13.1±0.7 mU/L, P<0.05) and free T\textsubscript{4} decreased by 25% (12.0±0.4 vs. 8.8±0.1 pmol/L, P<0.05). When the six patients in whom overt hypothyroidism developed were compared with the rest of the patients, there were no significant differences in post–high-dose phytoestrogen supplementation daidzein levels (26.3±1 vs. 25±0.9 ng/ml, P = 0.5) or genistein levels (46.1±0.9 vs. 48.6±1.2 ng/ml, P = 0.1). The urine iodine levels were adequate in all patients, including those in whom clinical hypothyroidism developed and the remainder of the patients (272.5±10.2 vs. 234.0±6.2 µg/d; P = 0.2).
Of the secondary outcomes, there was a significant reduction in both systolic and diastolic blood pressure and significant improvement in insulin resistance and hsCRP levels after the 16-mg phytoestrogen supplementation, but not after the 2 mg phytoestrogen supplementation. There were no significant changes in lipid profiles.

CONCLUSIONS

Six female patients (10%) in the study progressed into overt hypothyroidism after dietary supplementation with 16 mg of soy phytoestrogen. However, dietary supplementation with 16 mg of soy phytoestrogens significantly reduces the insulin resistance, hsCRP, and both systolic and diastolic blood pressure in these patients, whereas systolic pressure also decreased with 2 mg of phytoestrogens. There is a threefold increased risk (relative risk, 3.6; 95% confidence interval, 1.9 to 6.2) of overt hypothyroidism developing in subjects with subclinical hypothyroidism after a few weeks of dietary supplementation with 16 mg of soy phytoestrogens in a vegetarian diet. Conversely, supplementation with 16 mg of soy phytoestrogen significantly reduces insulin resistance, hsCRP, and blood pressure, improving cardiovascular risk profiles in these patients.

COMMENTARY

This is the first human study showing a statistically significant effect of a few weeks of dietary intake of high concentrations of isoflavones on thyroid function tests in an untreated group of subjects with subclinical hypothyroidism. Unfortunately, the authors did not speculate on the mechanisms by which clinical hypothyroidism developed. Isoflavones bind to both estrogen receptors (ERs) but preferentially bind to ERβ; however, the estrogenic effects of isoflavones are not observed in vivo (1). The effect on serum levels of thyroid-binding globulin (not measured in the present study) is very mild, as demonstrated by Duncan et al. in both premenopausal and postmenopausal women (2). In animal studies, isoflavones may inhibit TPO activity, with no effects on serum thyroid hormone levels (3). Goiter in laboratory animals appeared to be due to iodine deficiency, since correction of iodine deficiency prevented goiter formation (4). The effects of soy protein and soybean isoflavones (phytoestrogens) on thyroid function in healthy adults and patients with hypothyroidism were reviewed by Messina and Redmond in 2006 (5), and a systematic review and meta-analysis on the effects of soy products and isoflavones on circulating hormone concentrations in premenopausal and postmenopausal women (6) were just published. Included in the reviews are nine trials, eight in premenopausal women and one in postmenopausal women. In all the studies but one, subjects were fed isolated soy protein containing varying amounts of isoflavones and for different lengths of time up to 12 months. In most of the trials, thyroid function was not the primary health outcome under investigation. In one Japanese study (7), several groups of patients (both premenopausal and postmenopausal women and men) were fed with 30 g of roasted soy beans for 1 to 3 months. Serum TSH levels increased, although the values remained within the normal range. Messina and Redmond concluded in their review “it is reasonable to ask whether there is a reason for concern that a direct effect of isoflavones on the thyroid might predispose susceptible individuals to developing hypothyroidism. There are no clinical data in support of this contention, but among soy food consumers it is especially prudent to make sure that iodine intake is sufficient.” The work of Sathyapalan et al. appears to confirm their prediction; it may be concluded that only very high doses of soy phytoestrogen supplementation may induce clinical hypothyroidism in a minority of patients with subclinical hypothyroidism. The improvement in cardiovascular risk factors despite worsening of thyroid function is of interest.

The other issue to keep in mind is the effect of soy consumption in the absorption of desiccated thyroid...
or levothyroxine, which affects patients on thyroid hormone replacement therapy, requiring an increase in the dosage of hormone or a decrease in cases in which soy protein is discontinued from the diet. Finally, the effect of estrogen replacement on thyroid function in women on thyroid therapy is well known (8) and carefully analyzed in an editorial by the late Robert Utiger (9).

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References


