SHORT-TERM EFFECT OF SOY CONSUMPTION ON THYROID HORMONE LEVELS AND CORRELATION WITH PHYTOESTROGEN LEVEL IN HEALTHY SUBJECTS

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Objective. Since soy isoflavones may influence the thyroid hormone feedback system by interference with their biosynthesis, secretion and metabolism, we tested whether their controlled short-term consumption affects thyroid function.

Methods. Eighty six volunteers - university students (32 males and 54 females) were eating unprocessed boiled natural soybeans (2 g/kg body weight/day) for 7 consecutive days. Thyrotropin, free thyroid hormones, antibodies to thyroid peroxidase and to thyroglobulin, and actual levels of unconjugated major soy phytoestrogens, daidzein and genistein, were measured in sera collected before, at the end and one week after finishing soy meal consumption.

Results. Both phytoestrogens increased significantly ($p<0.0001$) at the end of soy-diet and fell down after its termination nearly back to the initial values. No significant changes were found in female group, while in males a significant transitory increase of thyrotropin ($p<0.0001$) was recorded. When actual levels of phytoestrogens were related to thyroid parameters, the only significant correlations were found between basal levels of daidzein and thyrotropin, daidzein and anti-thyroglobulin at the end of soy consumption in males, and between daidzein and free thyroxine at the end of the soy ingestion in females.

Conclusion. Though only modest and transitory effects on thyroid parameters occurred after controlled short-term soy consumption, some actual thyroid hormone parameters do correlate with actual isoflavone levels.

Key words: Soy xenoestrogens – Daidzein – Genistein – Thyrotropin – Thyroid hormones – Autoantibodies

Various, mostly beneficial effects on human health are ascribed to soy phytoestrogens of isoflavone series, as documented by large population screening and controlled dietary intervention studies. Many excellent reviews concern their putative protective effects from cancer risk (ADLERCREUTZ 2002; MISHRA et al. 2003), mitigation of bone loss (SETCHELL and LYDEKING-OLSEN 2003), beneficial role in obesity and diabetes (BHATHENA and VELASQUEZ 2002), and even cardiovascular diseases (ADLERCREUTZ et al. 2004; TEEDE et al. 2001; CLARKSON 2002), not always with definite results (CASSIDY 2003). Their mild estrogenic potency render them alternatives to classical estrogens in estrogen replacement therapy WUTTKE et al. 2002; KURZER 2003).

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On the other hand, their consumption may bring about, besides undoubted benefits also some risks (CASSIDY 2003). One of the questions addressed was their effect on hormonal balance. Among hormones, of especial interest are parameters of thyroid function. As early as in late fifties and sixties goitrogenic effect in children fed with soy formula was reported, which could be reversed by iodine supplementation; for review of the literature see (CHEN and ROGAN 2004). Other studies revealed that isoflavones, above all genistein, may affect thyroid hormone biosynthesis as inhibitors of thyroid peroxidase (DIVI and DOERGE 1996; DIVI et al. 1997; CHANG and DOERGE 2000; DOERGE and CHANG 2002). Genistein is also well-known inhibitor of tyrosine proteinkinase (RAVINDRANATH et al. 2004), thus capable to influence various signaling pathways. At least animal studies demonstrated that even thyroid hormone deiodination in thyroid gland by type I 5´-deiodinase may be affected by isoflavones, especially by genistein, through its inhibitory effect on tyrosine phosphorylation (MORI et al. 1996; WHITE et al. 2004). Taken together, soy isoflavonoids may affect the thyroid hormone feedback system by interference with their biosynthesis, secretion, and metabolism (HAMANN et al. 2006).

The concern that soy isoflavonoids may adversely affect thyroid function led to a series of human intervention studies in some subsets of population. 14 Trials undertaken until 2005 were reviewed by MESSINA and REDMOND (2006), with general conclusion that with one exception (ISHIZUKI et al. 1991), only modest if any hormonal effects occurred following soy-rich diet. It is to be noted that effects on thyroid parameters was not the primary health outcome of these investigations (MESSINA and REDMOND 2006). In addition to reviewed trials, one more cross-over study appeared in healthy young men on three diet regimes with respect to soy isoflavone content (DILLINGHAM et al. 2007).

Here we report the effect of controlled short-term soy consumption on thyroid laboratory parameters including the most common thyroid autoantibodies, in relation to actual concentration of major circulating soy phytoestrogens in a group of young people without overt thyroid, autoimmune or allergic disorders.

Some data and materials collected during this study were used also for investigation of the effects of short-time soybean consumption on the levels of sex hormones with respect to their plausible effects on spatial cognition abilities. The results revealed that soy intake improved spatial cognition in premenopausal women, and were published elsewhere (CELEC et al. 2005).

Subjects and Methods

Subjects. The studied group consisted of 86 university students, 54 females and 32 males aged 18 to 25 years (mean age 20.7±0.9 years). All of them were without overt thyroid diseases, their basal TSH levels were within the physiological range reported by the author's laboratory (0.27-4.20 mIU/l). None of them mentioned allergic disorders at least three month before the study. There were nine females with basal positive level of thyroperoxidase antibodies (TPOab, >25 IU/l) or thyroglobulin antibodies (TGab, >125 IU/l). They were not excluded deliberately from the study in order that the group reflected as much as possible the European population, where up to 10 % of subjects display positive titres of anti-thyroid antibodies (VANDERPUMP et al. 1995). After basal investigation including anthropometrical evaluation, determination of serum sex steroid hormone and lipid levels, the subjects were asked to eat 2 g of unprocessed boiled natural soybeans (Alfa Bio Slovakia) for every kilogram of body weight (approximately 140 g per day for males and 120 g per day for females) for the period of 7 consecutive days. Unprocessed soybeans contain 1.2 – 4.2 mg of isoflavones per 1 g of dry weight (KURZER and XU 1997; RITCHIE et al. 2006). The amount of soybeans consumed was chosen so as to approximate or exceed the top amount of isoflavones in the Asian diet (20-150 mg of isoflavones per day). All the subjects were omnivores, for whom soy food did not belong to an every-day diet. They filled a form in which they were instructed not to ingest any additional soy containing or soy-derived products or food supplements and vitamins, to reduce physical and irregular sport activities and to abstain from sex to reduce its influence on hormonal levels. Eventual bias resulting from synchronization of phases of the menstrual cycle in female participants was checked using the chi-square test and could be, thus, excluded.

Morning peripheral blood was collected on the day of introductory investigation (= before), on the 8th day (the next morning after last soybean consumption = at the end), and 7 days after termination of soy food consumption (after). All the subjects were asked to keep the dietary record and note physical and sexual activities in case they were not avoided during the study. The study protocol was approved by the Ethical Board of the School of Medicine, Comenius University, Bratislava, Slovak Republic. All the subjects signed a written informed consent.

Analytical methods. Serum thyroid stimulating hormone (TSH), free triiodothyronine (fT_4) and free trioiodothyronine (fT_3) were measured by ECLIA from Roche Diagnostics GmBH, Mannheim, Germany, using commercial Elecsys System 2010. Autoantibodies to thyroperoxidase (TPOab) and thyroglobulin (TGab) were assessed by enzyme-linked immunosorbent assay (ELISA) (Milenia Biotec, Bad Nauheim, FRG). Serum daidzein and genistein were measured by original in house radioimmunoassays (Lapcík et al. 1997, 1998). The respective intra-assay variability was 3.0, 2.0, 2.0, 5.4, 5.6, 7.9 and 7.1 %, and inter-assay variability was 7.2, 4.8, 3.4, 8.4, 8.6, 9.5 and 9.6 for TSH, fT_4, fT_3, TPOab, TGab, daidzein and genistein, respectively.

Statistical analyses. The dynamics of observed parameters was evaluated using repeated measures ANOVA with Bonferroni's corrected post hoc t-test for multiple comparisons of dependent variables. Pearson correlation coefficient and test were used for the evaluation of dependence of quantitative variables. P-values less than 0.05 were considered significant. If significant Pearson correlations were found, the results were further checked by Spearman rank correlations. Data are presented as mean + SEM. All statistic analyses were performed using the software package GraphPad Prism 4.0 and SPSS 11.5.

Results

Actual levels of daidzein and genistein before, at the end and after soy consumption are presented on Fig.1.

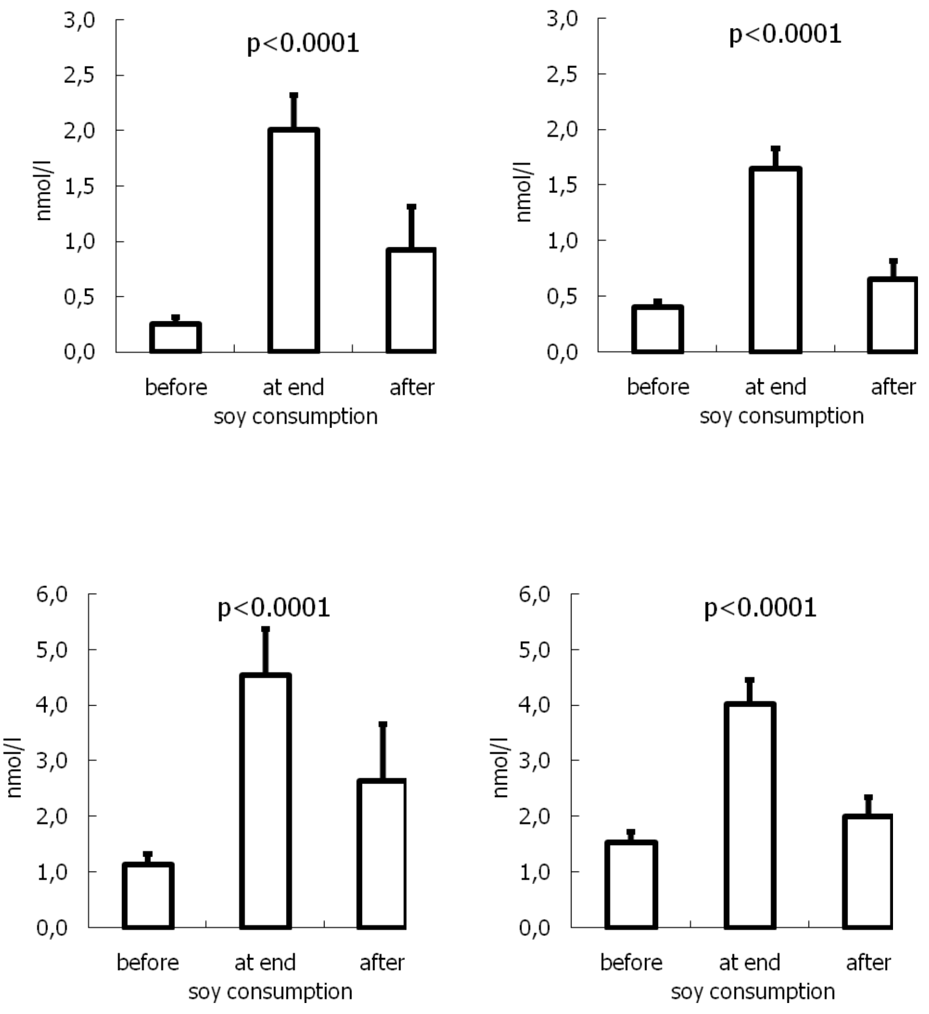

Fig. 1 The effect of 7 days-lasting soy food consumption on serum levels of daidzein (upper panel) and genistein (lower panel) in young men (left part) and women (right part)

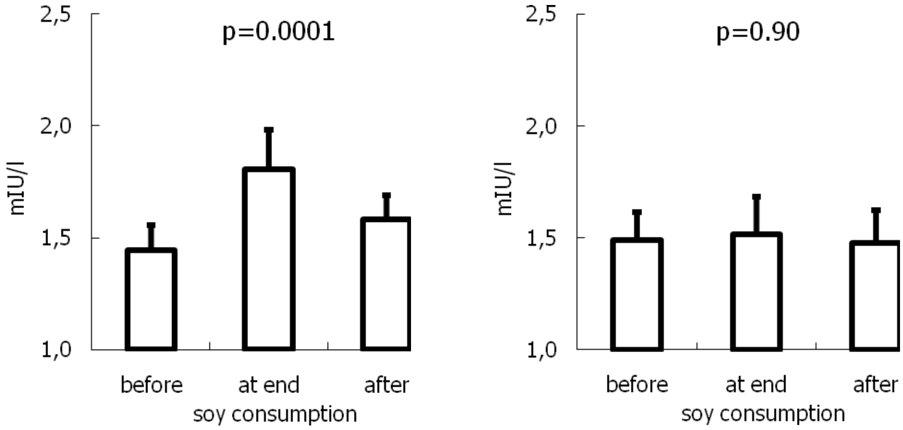

Fig. 2 The effect of 7 days-lasting soy food consumption on serum levels of TSH in young men (left) and women (right)

Table 1
Pearson´s correlation matrix for soy phytoestrogens and selected parameters of thyroid function. Basal values, before soy consumption.

Above the diagonal (upper right part): females, below the diagonal (lower left part): males. Each cell from above represents the correlation coefficient (r), significance (p value) and number of correlated pairs (*n; in italics*). Significant correlations are in bold.

Dai	**0.637** **0.001**** *54*	0.148 0.285 *54*	0.215 0.118 *54*	-0.158 0.254 *54*	-0.156 0.261 *54*	-0.132 0.340 *54*
0.601 **0.001**** *31*	**Gen**	0.117 0.401 *54*	0.222 0.107 *54*	-0.029 0.834 *54*	-0.123 0.376 *54*	-0.109 0.432 *54*
0.599 **0.001**** *31*	0.254 0.169 *31*	**TSH**	0.155 0.263 *54*	-0.106 0.444 *54*	0.087 0.530 *54*	**0.209** **0.034*** **54**
0.076 0.686 *31*	0.258 0.161 *31*	0.082 0.654 *32*	**fT3**	**0.449** **0.001**** *54*	-0.019 0.889 *54*	-0.001 0.992 *54*
-0.131 0.484 *31*	-0.025 0.892 *31*	-0.126 0.493 *32*	-0.092 0.618 *32*	**fT4**	0.027 0.847 *54*	-0.028 0.840 *54*
-0.040 0.832 *31*	-0.103 0.580 *31*	0.181 0.321 *32*	0.060 0.743 *32*	0.019 0.919 *32*	**TPOab**	**0.554** **0.001**** *54*
-0.111 0.552 *31*	-0.097 0.603 *31*	-0.240 0.187 *32*	-0.088 0.631 *32*	-0.085 0.643 *31*	**0.373** **0.035*** *32*	**TGab**

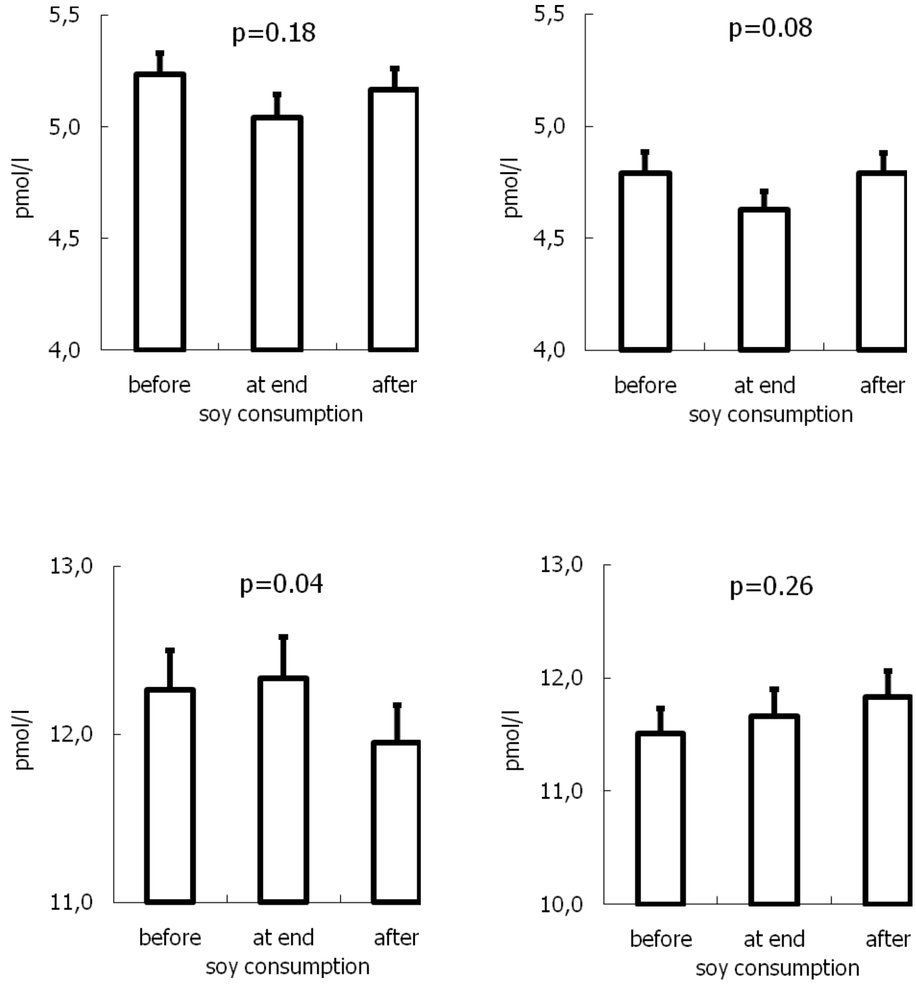

Fig 3 The effect of 7 days-lasting soy food consumption on serum levels of free triidothyronine (upper panel) and thyroxine (lower panel) in young men (left part) and women (right part)

Both phytoestrogens increased significantly (p<0.0001) during soy-diet consumption period and fell down 7 days after its termination nearly to the initial values. Corresponding levels of TSH and thyroid hormones in females and in males are given on Figures 2 and 3, respectively. No significant changes were found in the female group, while in males a significant increase of TSH was recorded (p<0.0001) at the end of soy consumption, which was accompanied by insignificant decrease of fT_3 and increase of fT_4, followed by the drop of the latter after stopping the soy intake (p<0.05). No differences were found at any stage of experiment between phytoestrogen levels in the subgroups of subjects with- or without positive titres of anti-thyroid autoantibodies. The levels of anti-thyroid autoantibodies did not change significantly during the experiment.

Actual levels of laboratory parameters of thyroid function and major phytoestrogens in each stage of experiment (before, at the end and one week after the soy consumption) were further mutually correlated. The Pearson´s correlation matrices with depicted significant correlations are presented in Tables 1-3. The values above the diagonal represent the female group, those below the diagonal males. Each cell from above shows the correlation coefficient (*r*), the significance (*p*) and the number of correlated pairs (*n*). Significant correlations were recorded between both phytoestrogens in both sexes in all stages of the experiment. Significant positive correlations between both free thyroid hormones in all stages were found only in the female group. In females significant correlations over all stages were also found between both anti-thyroid autoantibodies,

Table 2
Pearson´s correlation matrix for soy phytoestrogens and selected parameters of thyroid function. Values at the end of soy consumption.

Above the diagonal (upper right part): females, below the diagonal (lower left part): males. Each cell from above represents the correlation coefficient (r), significance (p value) and number of correlated pairs (*n; in italics*). Significant correlations are in bold.

Dai	**0.617** **0.001**** ***53***	0.029 0.836 *53*	0.153 0.275 *53*	**0.287** **0.037*** ***53***	-0.032 0.819 *53*	-0.130 0.355 *53*
0.640 **0.001**** ***53***	**Gen**	-0.063 0.654 *53*	0.032 0.822 *53*	0.160 0.252 *53*	-0.134 0.340 *53*	-0.187 0.180 *53*
-0.012 0.947 *32*	-0.083 0.650 *32*	**TSH**	0.013 0.925 *53*	-0.096 0.496 *53*	0.053 0.704 *53*	**0.313** **0.023*** ***53***
0.047 0.800 *32*	0.109 0.552 *32*	0.131 0.475 *32*	**fT3**	**0.498** **0.001**** ***53***	-0.099 0.480 *53*	-0.179 0.199 *53*
-0.108 0.556 *32*	-0.095 0.606 *32*	0.181 0.321 *32*	0.292 0.105 *32*	**fT4**	-0.026 0.855 *53*	-0.216 0.121 *53*
0.007 0.969 *32*	-0.051 0.780 *32*	0.056 0.763 *32*	-0.091 0.620 *32*	-0.035 0.851 *32*	**TPOab**	**0.559** **0.001**** ***53***
0.433 **0.013*** ***32***	0.143 0.435 *32*	-0.213 0.241 *32*	-0.140 0.443 *32*	0.010 0.958 *32*	0.348 0.051 *32*	**TGab**

while in males the only positive correlation between anti-thyroid autoantibodies was recorded before the experiment. Positive correlations were also found between TGab and TSH before and during treatment in females, and between TPOab and TSH after termination of the experiment in males.

As phytoestrogens concern, following significant Pearson correlations were revealed: in males between basal levels of daidzein and TSH (Table 1), and daidzein and TGab during soy consumption (Table 2), but these results were not confirmed by Spearman rank correlations. In females the only significant Pearson correlations were found between daidzein and fT_4, at the end of the experiment (Table 2).

Discussion

Out of 14 recently reviewed trials (Messina and Redmond 2006), 8 dealt with women only (1 premenopausal, 7 postmenopausal), 4 with men only and 2 with both women and men. In general, with exception of the Japanese trial (Ishizuki et al. 1991), these studies provided only little evidence that soy isoflavones possess antithyroid effects. These results were confirmed by the most recent comprehensive intervention study with 35 young men well-characterized as to their body parameters and principal nutrient composition (energy, protein, carbohydrate, fat, dietary fiber, calcium) (Dillingham et al. 2007). The authors measured also urinary excretion of major isoflavones, daidzein and genistein, which both increased markedly following high isoflavone diet. They took into the account the fact that the subjects differ in excretion of the main isoflavone metabolite equol, in dependence on composition of their intestinal flora (Rowland et al. 2000).

In our study with young men and women consuming the soy diet for one week we measured, in addition to major thyroid hormones, also the main thyroid autoantibodies with respect to their plausible goitrogenic (Doerge and Sheehan 2002) and autoimmunity-stimu-

Table 3
Pearson correlation matrix for soy phytoestrogens and selected parameters of thyroid function. Values after soy consumption.
Above the diagonal (upper right part): females, below the diagonal (lower left part): males. Each cell from above represents the correlation coefficient (r), significance (p value) and number of correlated pairs (*n; in italics*). Significant correlations are in bold.

Dai	**0.924** **0.001**** ***52***	0.021 0.882 *52*	-0.068 0.630 *52*	0.121 0.394 *52*	-0.121 0.391 *52*	-0.100 0.482 *52*
0.806 **0.001**** ***30***	**Gen**	0.085 0.547 *52*	-0.060 0.675 *52*	0.149 0.290 *52*	-0.130 0.358 *52*	-0.110 0.438 *52*
0.175 0.356 *30*	-0.042 0.824 *30*	**TSH**	0.129 0.362 *52*	-0.179 0.203 *52*	-0.022 0.875 *52*	0.237 0.091 *52*
0.018 0.924 *30*	-0.036 0.850 *30*	0.016 0.931 *30*	**fT3**	**0.588** **0.001**** ***52***	0.019 0.893 *52*	-0.072 0.613 *52*
0.018 0.924 *30*	-0.063 0.742 *30*	0.108 0.569 *30*	0.214 0.256 *30*	**fT4**	-0.107 0.450 *52*	-0.178 0.207 *52*
-0.045 0.812 *30*	-0.057 0.765 *30*	**0.362** **0.049*** ***30***	-0.285 0.128 *30*	0.035 0.854 *30*	**TPOab**	**0.727** **0.001**** ***52***
-0.075 0.693 *30*	-0.062 0.745 *30*	0.112 0.556 *30*	-0.285 0.127 *30*	-0.220 0.242 *30*	0.270 0.138 *30*	**TGab**

lating effects (Fort et al. 1990). For the first time, the data were put in relation to actual circulating unconjugated isoflavonoid levels, taking advantage of the recent in house immunoassays, enabling us to measure subnanomolar concentrations of free isoflavones in sera (Lapčík et al. 1997, 1998). Though circulating isoflavones are almost completely present in glucuronidated form, only free aglycones are thought to be biologically active (Rowland et al. 2003).

Two statistical approaches were applied: 1. The changes from the basal values of the studied parameters were compared in order to evaluate significance of the effect of soy-consumption, 2. The data in each group and stage of the experiment (i.e. before, at the end and a week after termination of the soy consumption) were mutually correlated, with a particular respect to relation between isoflavone levels on one side, and thyroid parameters on another.

As expected, the levels of both phytoestrogens at the end of soy consumption increased significantly, but one week after the termination of soy consumption they returned to basal levels. The consumption of phytoestrogen containing diet resulted in only transitory increase of TSH, similarly as reported by Persky et al. (2002), but without significant changes of both free thyroid hormones; moreover, these changes were recorded only in the male group. This finding is, however in agreement with animal experiments, which demonstrated that the loss of TPO activity need not be accompanied with hypothyroid state with decrease of T_3/T_4 ratio and increased TSH (Doerge and Chang 2002; Doerge and Sheehan 2002). The authors suggested that an excess of the enzyme in the apical membrane provides a sufficient reserve even in presence of the inhibitor. Additional risk factors, especially iodine deficiency are necessary before soy consumption can induce anti-thyroid effects (Doerge and Chang 2002; Doerge and Sheehan 2002). Temporary increase of TSH during soy consumption, which however remained within normal range was observed also by Japanese authors (Ishizuki et al. 1991), but this study was criticized for incomplete data on the consumed product (Messina and Redmond 2006). In our study short term soy consumption did not influence circulating anti-thyroid autoantibodies, positive titres of which are commonly found in a part of healthy population (Vanderpump et al. 1995).

The correlation analysis confirmed the expected relations between both isoflavonoids as well as among thyroid parameters. Of interest is the finding of a positive significant correlation of daidzein with TSH in the male group before soy food consumption. In our another recent non-intervention study with a group of 268 school children on a common diet we have also found a positive significant correlation of daidzein levels (but not genistein) with TSH (Milerova et al. 2006). It may be speculated that actual TSH serum levels reflected long-term dietary habits rather than the last food consumption, as may probably be the reason for correlation of free thyroxine with thyroid autoantibodies in the female group.

In conclusion our data confirm that soy phytoestrogens possess only modest and transitory effect on thyroid hormone values, but, on the other hand, revealed that some thyroid hormone parameters do correlate with actual isoflavone levels.

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