CLINICAL STUDY

Effects of a six month treatment with selenomethionine in patients with autoimmune thyroiditis

Leonidas H Duntas, Emilia Mantzou and Demetrios A Koutras
Endocrine Unit, Evgenidion Hospital, University of Athens Medical School, 20 Papadiamantopoulou Str, 11528 Athens, Greece

(Correspondence should be addressed to Leonidas H Duntas; Email: ledunt@otenet.gr)

Abstract

Objective: Selenium (Se) in the form of selenocysteine is an essential component of the family of the detoxifying enzymes glutathione peroxidase (Gpx) and of the iodothyronine selenodeiodinases that catalyse the extrathyroidal production of tri-iodothyronine (T3). Thus, Se deficiency may seriously influence the generation of free radicals, the conversion of thyroxine (T4) to T3 and the autoimmune process. Therefore, we performed a randomised, placebo-controlled prospective study to investigate the effects of Se treatment on patients with autoimmune thyroiditis (AIT).

Design and methods: Sixty five patients aged 22 – 61 years (median age 48 years) with AIT were recruited into two groups. Group I (Gr I) (n = 34) was treated with selenomethionine (Seme) 200 μg, plus l-thyroxine (LT4) to maintain TSH levels between 0.3 – 2.0 mU/l, whereas group II (Gr II) (n = 31) received LT4 plus placebo over a period of 6 months. Moreover, the pharmacokinetics of Seme were studied in 10 patients and eight volunteers at baseline and 2 h, 4 h, 6 h and 24 h after oral administration of a 200 μg tablet of Seme. Finally, Se levels were measured at the end of the study in some patients of both groups and their results were correlated with thyroid hormone levels.

Results: In the pharmacokinetics study, basal serum concentration of Se (75 ± 6 μg/l) was within the reference range (70 – 125 μg/l), it promptly increased at 2 h, peaked at 4 h (147 ± 17 μg/l; P < 0.0001) and it was abundant in serum at 24 h. In Gr I, antibodies against thyroid peroxidase (anti-TPO) levels showed an overall decrease of 46% at 3 months (from 1875 ± 1039 U/l to 1013 ± 382 U/l; P < 0.0001) and of 55.5% at 6 months. In Gr II the overall decrease of anti-TPO amounted to 21% at 3 months and to 27% at 6 months (from 1758 ± 917 U/l to 1284 ± 410 U/l; P < 0.005). There were no significant changes of antibodies against thyroglobulin levels between the groups. At the end of this study Se levels were found to be statistically significantly increased in Gr I (n = 9/34) compared with Gr II (n = 11/31) (97 ± 8.4 vs 79 ± 8; P < 0.01) but no correlation with thyroid hormone was found.

Conclusions: Seme is proven to be rapidly absorbed by the gastrointestinal tract. It appears to be useful as adjunctive therapy with LT4 in the treatment of AIT. The exact mechanism(s) is not very well determined, it might enhance the activity of detoxifying enzymes and enforce the defense against oxidative stress.

European Journal of Endocrinology 148 389–393

Introduction

Selenium (Se) in the form of selenocysteine, an analogue of cysteine in which sulphur is replaced by Se, is an essential component of the glutathione peroxidase enzymes (Gpx) and of thioredoxin reductase (TR) which protects tissues from oxidative damage by reduction of hydrogen peroxide (H2O2) (1). Another important class of selenoproteins are the iodothyronine selenodeiodinases, D1 and D2, which are responsible for the production of biologically active tri-iodothyronine (T3) via 5’-deiodination in the various extrathyroidal tissues (2). Se in plasma is incorporated in selenoprotein P, that may serve as a transport protein for Se and facilitate whole body Se distribution (3).

There are scarce data regarding the effects of Se supplementation on thyroid function. In a trial conducted in northern Zaire, a severely Se and iodine deficient area, two months of treatment with 50 μg selenomethionine (Seme) resulted in a spectacular fall in serum thyroxine (T4) that could only be partially recovered after iodine supplementation (4). In animal models, long term Se nutritional deficiency induced only marginal effects on the thyroid T4 and T3 content and on the activity of 5’-D1 in the thyroid gland, revealing a resistance of the gland to Se deficiency (5). In contrast, peripheral 5’-D1 and Gpx activity in the thyroid were markedly decreased (6).

Currently, a study from South Germany, an area with mild iodine and Se deficiency, reported that Se
substitution with sodium selenite led to improvement of inflammatory activity in patients with autoimmune thyroiditis (AIT) (7). However, it is difficult to extrapolate these results to a wider population, as there is a broad variation of Se concentrations in the European population that may reflect dietary habits, bioavailability of Se compounds, racial differences or various analytical methods. South Greece and more precisely the region around Athens (Attiki) is Se and iodine sufficient (8, 9). For the above mentioned reasons, and since there are no data available, we conducted this investigation to assess the effects of long-term treatment with Se combined with i-thyroxine (i-T4) on the autoimmune and thyroid function of patients with AIT.

Subjects and methods

Sixty five patients (mean age 47.8 years, range 22 to 61 years), 56 female and 9 male, with AIT (antibodies against thyroid peroxidase (anti-TPO) >100 U/l) and mild thyroid failure (MTF) characterized by normal free (f)T4 and T3 and increased serum thyroid stimulating hormone (TSH) levels (TSH > 4 mU/l) were randomized into two groups. Group I (Gr I) (n = 34) was treated with i-T4 in a titrated dose to maintain TSH free (f)T4 and T3 and increased serum thyroid stimulating hormone (TSH) levels (TSH > 4 mU/l) were randomized into two groups. Group 1 (Gr I) (n = 34) was treated with i-T4 in a titrated dose to maintain TSH from 0.3 to 2.0 mU/l combined with Se in the form of 200 μg Se (Lamberts, Athens, Greece) administered once daily. Group 2 (Gr II) (n = 31) received i-T4 plus placebo. None of the patients were undergoing treatment with anti-depressive drugs, anti-psychotic drugs, or preparations containing vitamins or trace elements. The investigation was performed over a period of 6 months. Serum concentrations of FT4, T3, TSH, anti-Tg and antibodies against thyroglobulin (anti-Tg) were measured at baseline and after 3 and 6 months of treatment. Moreover, to detect any correlation with thyroid hormone, serum Se levels were measured arbitrarily in 9/34 patients of Gr I and 11/31 of Gr II.

To obtain some kinetic data of Seme, blood samples were collected at 0, 2, 4, 6 and 24 h after the intake of a tablet containing 200 μg Se in 10 patients and 8 volunteers. Informed consent was obtained from all participants in this study.

Measurements

Serum Se levels were determined in duplicate with a graphite furnace atomic absorption spectrometer with the Zeeman background correction (Spectra 300, Varian, Australia) by using a standard addition method. Samples were compared with the standard curve by linear least-squares fit analysis. The detection limit for Se was 7.0 μg/l (0.090 μmol/l). Within run and run-to-run coefficients of variation (CV) for Se were 1.9% and 4.4% respectively.

Serum concentrations of anti-Tg and anti-TPO were measured using IRMA (DiaSorin, Salugia, Italy) with a cut-off value for anti-Tg at 100 U/l, determined as the first standard point, and for anti-TPO at 100 U/l. All values below these cut-off points were graded as negative. The intra-assay CV values were 4.5% for anti-Tg and 4.8% for anti-TPO. The interassay CV values were 4.1% and 9.1% respectively.

Serum T3 levels were determined using Amerlex MT3 RIA Kits (Johnson and Johnson Clinical Diagnostics Ltd, Amersham, UK). The intra-assay CV value was 5%, whereas the interassay CV value was 5.8%. FT4 was measured using a one-site chemiluminescence immunometric method (FT4-Estimate, Nichols, San Juan Capistrano, CA, USA). The normal range for FT4 was 9–25 pmol/l. The mean intra-assay CV was 5.6% and the interassay CV was 8.5%. TSH concentrations were determined with TSH third-generation assay (Nichols). The normal values ranged from 0.3 to 4.0 mU/l. The mean intra-assay CV at 0.01 mU/l was 12% and at 1.29 mU/l was 4.6%. The interassay CV at 0.02 mU/l and at 1.28 mU/l was 15.0% and 5.5%, respectively.

Statistics

All results are presented as mean ± s.d. Comparisons between baseline and post-selenium serum concentrations were performed by the analysis of variance (ANOVA) for repeated measures. Differences between the groups during the treatment period were analyzed by the Mann–Whitney nonparametric test. To study the relationship between TSH, FT4, T3 and Se concentrations, a linear regression was used. A P value of < 0.05 was considered significant.

Results

Serum concentrations of TSH, FT4 and T3 of both groups during the study period are presented in Table 1. There were no statistically significant changes between the two groups at any time during the study.

In the pharmacokinetic study, basal serum concentrations of Se were found to be within the reference range in patients and volunteers (75 ± 6 μg/l vs 77 ± 7 μg/l, non-significant). Se increased 2 h after intake (122 ± 14 μg/l; P < 0.0001 vs baseline), peaked at 4 h in both groups (147 ± 17 μg/l; P < 0.0001 vs baseline) and it was abundant in serum at 24 h (102 ± 10 μg/l) (Fig. 1).

In Gr I anti-TPO levels exhibited an overall decrease of 46.0% at 3 months and of 55.5% at 6 months. In a further analysis, by stratifying the patients according to the percentage decrease of anti-TPO levels, 18/34 (53%) in Gr I exhibited a marked decrease of anti-TPO by 73% at 3 months and by 86% at 6 months, whereas 12/34 (35%) showed a decrease of 22% at
Table 1  TSH, FT₄, T₃ and anti-Tg serum concentrations (mean±s.d.) in patients with autoimmune thyroiditis treated either with selenomethionine plus LT₄ (Gr I) or with LT₄ plus placebo (Gr II) over a period of 6 months.

<table>
<thead>
<tr>
<th>Months</th>
<th>Gr I</th>
<th>Gr II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>TSH mUI/l (nr: 0.3-4 mUI/l)</td>
<td>9.8±3.6</td>
<td>1.4±0.6</td>
</tr>
<tr>
<td>FT₄ pmol/l (nr: 9–25 pmol/l)</td>
<td>12.4±1.1</td>
<td>15.9±1.2</td>
</tr>
<tr>
<td>T₃ nmol/l (nr: 0.9–2.7 nmol)</td>
<td>1.7±0.2</td>
<td>2.1±0.2</td>
</tr>
<tr>
<td>Anti-Tg (&lt;100 U/l)</td>
<td>1724±412</td>
<td>1672±392</td>
</tr>
</tbody>
</table>

Table 2 Overall decrease in percentage of serum anti-TPO concentrations after 6 months of treatment with selenomethionine plus LT₄ (Gr I) or with LT₄ and placebo (Gr II) over a period of 6 months.

<table>
<thead>
<tr>
<th>Months</th>
<th>Gr I</th>
<th>Gr II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Anti-TPO (&lt;100 U/l)</td>
<td>1758±917</td>
<td>1389±520</td>
</tr>
</tbody>
</table>

3 months and 28% at 6 months and 4/34 (12%) did not show any decrease. In absolute numbers anti-TPO levels decreased from 1875±1039 U/l to 1013±382 U/l (P < 0.0001) at 3 months and to 1284±410 U/l (P < 0.001) at 6 months (Table 2). Anti-Tg levels decreased very slightly in both groups without reaching any significant level (Table 1). No side effects have been observed. In Gr I, 25/34 (73.5%) patients reported a satisfactory improvement of mood and sleep and stated less fatigue. In Gr II 15/31 (48.4%) affirmed an amelioration of behavior and tiredness. No correlations could be found between TSH, FT₄, T₃ and serum Se concentrations.

Discussion

In our study Se levels promptly increased in serum after oral administration of Seme indicating a good absorption of the supplement. The data do not allow us to draw any conclusions about bioavailability, as it depends on the conversion of absorbed Se into a biologically active form and tissue retention. Nevertheless, the increase of Se may lead to the presumption that Seme is rapidly transformed to an active form. Although there is some evidence suggesting that Seme is retained more efficiently than inorganic selenate or selenite, the retained fraction may not all be bioavailable (10).

The most important finding of this study was the striking reduction of anti-TPO levels in patients treated with Seme and LT₄ in a borderline Se sufficient region. The mechanism(s) of action of Se on the immune system is not well determined. Several enzymatic systems, such as dismutases and Gpx, have evolved to circumvent the electron spin restriction of O₂ reduction and prevent the accumulation of very reactive free radicals in the various organs such as superoxide.
anion radical ($O_2^-$), hydroxyl radical (OH·) and $H_2O_2$
(11). $H_2O_2$ in the thyroid gland may easily cross the
apical membrane to the luminal site where it reacts
with TPO for the iodination of Tg (12). It is well
known that the iodination of Tg not only requires
$H_2O_2$ and TPO but also iodide in close proximity (13).
Thus, Gpx activity at the apical membrane may
reduce the substrate for Tg iodination decreasing the
hormone metabolism. However, further research is
required to clarify the exact mechanism of action and
demonstrate if modification of Se dietary intake,
especially in areas with selenium deficiency, may also
strengthen immunocompetence.

The levels of thyroid hormone were not affected by
Seme supplementation in patients with autoimmune
thyroiditis decreases thyroid peroxide antibodies concen-
87 1687–1691.

Finally, Seme treatment was very well tolerated. The
striking majority of the patients reported an improve-
ment in mood and well-being. This is supported by
other researchers who showed that healthy men who
consumed dietary Se at high levels (226 mg/day) had
a significant improvement of their moods as compared
with those consuming 32 mg Se per day in their diets (20).
This may be due to changes in dopamine
and/or serotonin metabolism in the CNS (21). Consequently, our study demonstrates that Seme
supplementation combined with $\Delta Tg$ may enhance
immunocompetence without affecting thyroid
hormone metabolism.


