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# Selenium supplementation could restore euthyroidism in subclinical hypothyroid patients with autoimmune thyroiditis

## Wpływ suplementacji selenu na przywrócenie eutyreozy u chorych na subkliniczną niedoczynność tarczycy w wyniku autoimmunologicznego zapalenia tarczycy

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**Abstract**

**Intriduction:** The thyroid is an organ with one of the highest selenium concentrations, containing many selenoproteins implicated in thyroid hormone metabolism. Treatment with levothyroxine has been recommended for all subclinical hypothyroid patients with TSH levels > 10 mU/L, whereas for those with TSH < 10 mU/L treatment remains controversial.

**Aim:** A randomised controlled prospective study was performed to investigate the effects of Se treatment on patients with autoimmune thyroiditis and mild sub-clinical hypothyroidism (TSH < 10 mU/L).

**Material and methods**: A total of 196 patients with autoimmune thyroiditis were recruited in the study. Patients were assigned to receive (case) or not receive (control) an oral selenomethionine treatment. Cases received 83 mcg selenomethionine/day orally for four months. All the patient's charts were submitted to thyroid hormonal profile (TSH, fT4) and TPOAb evaluation upon enrolment and at the end of the study.

**Results:** In total 192 patients completed the study. Cases and controls were superimposable for age, gender, thyroid hormonal profile, and TPOAb levels.

At the end of the study, 33/192 (17.2%) participants restored euthyroidism (Responders). Responders were significantly more frequent among Cases than Controls (30/96 [31.3%] *vs.* 3/96 [3.1%], p < 0.0001).

**Conclusion:** Selenium supplementation could restore euthyroidism in one third of subclinical hypothyroidism patients with autoimmune thyroiditis. **(Endokrynol Pol 2016; 67 (6): 567–571)**

**Key words:** *selenium, Hashimoto's thyroiditis, hypothyroidism, selenoproteins*

**Streszczenie**

**Wstęp:** Tarczyca jest narządem, w którym występuję jedno z najwyższych stężeń selenu, zawierającym wiele selenoprotein biorących udział w metabolizmie hormonów tarczycy. Leczenie lewotyroksyną jest zalecane u wszystkich chorych z subkliniczną niedoczynnością tarczycy, u których stężenia TSH wynoszą > 10 mj./l, natomiast u osób ze stężeniem TSH < 10 mj./l takie leczenie pozostaje kontrowersyjne.

**Cel:** Randomizowane prospektywne badanie z grupą kontrolną przeprowadzono w celu oceny wpływu leczenia selenem u chorych z autoimmunologicznym zapaleniem tarczycy i łagodną subkliniczną niedoczynnością tarczycy (TSH < 10 mj./l).

**Materiał i metody**: Do badania włączono 196 chorych z autoimmunologicznym zapaleniem wątroby. Chorych podzielono na dwie grupy: badaną i kontrolną, którym doustnie podawano preparat selenometioniny. Osobom z grupy badanej podawano doustnie 83 mcg selenometioniny/dobę przez 4 miesiące. U wszystkich chorych oznaczono stężenia hormonów tarczycy (TSH, fT4) przeciwciał przeciw TPO na początku i na końcu badania.

**Wyniki:** Badanie ukończyło 192 chorych. Grupa badana i grupa kontrolna były porównywalne pod względem wieku, płci oraz stężeń hormonów tarczycy i przeciwciał przeciw TPO. W momencie zakończenia badania przywrócenie eutyreozy stwierdzono u 33/192 (17,2%) uczestników (odpowiedź na leczenie). Odpowiedź na leczenie występowała istotnie częściej w grupie badanej niż w grupie kontrolnej (30/96 [31,3%] *vs.* 3/96 [3,1%]; p < 0,0001).

**Wnioski:** Suplementacja selenem spowodowała przywrócenie eutyreozy u jednej trzeciej chorych z subkliniczną niedoczynnością tarczycy w wyniku autoimmunologicznego zapalenia tarczycy. **(Endokrynol Pol 2016; 67 (6): 567–571)**

**Słowa kluczowe:** *selen; choroba Hashimoto; niedoczynność tarczycy; selenoproteiny*

## Intrduction

Selenium (Se) is an essential trace mineral, which was discovered in 1817 by the Swedish chemist Berzelius. Later on in the 1980s the fundamental role of sodium selenite supplementation in preventing or reversing the clinical signs of severe selenium deficiency was discovered [1].

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The thyroid gland is an organ with one of the highest selenium concentrations, containing many selenoproteins implicated in thyroid hormone metabolism, and also as antioxidants. The main selenoproteins in the thyroid gland are glutathione peroxidase (GPXs), thioredoxin reductases (TRs), and the three deiodinase isoforms (D1, D2, and D3). The main function of GPXs and TRs is to protect from damage caused by oxygen free radicals and they have an essential role in the antioxidant process. Another major function is regulation of certain transcription factors (NF-K b, Ref-1, P53) and in gene expression. Finally, D1 and D2 are responsible for the local activation of thyroid hormones [2].

The link between severe Se deficiency and thyroid dysfunction was established in the 1990s when children with iodine and selenium deficiencies were supplemented with selenium alone, which led to thyroid destruction and myxoedematous cretinism, suggesting that selenium should not be supplemented prior to correction of the iodine deficit [3].

Since then, many studies have shown that selenium supplementation may be useful for autoimmune thyroid disorders [4–6].

Hashimoto's thyroiditis (HT) is the most common cause of acquired hypothyroidism and is characterised by the presence of anti-thyroid peroxidase autoantibodies, which are closely associated with overt thyroid dysfunction and correlated with progressive thyroidal damage and lymphocytic inflammation [7].

Subclinical hypothyroidism (SCH) is biochemically defined as an elevated serum concentration of thyroid-stimulating hormone (TSH) with normal concentration of free thyroxine (FT4) levels occurring simultaneously, and it is mainly due to HT. Two categories in relation to the elevation of TSH serum level were considered: mildly increased TSH levels (4.0–10.0 mU/L) and more severely increased TSH levels (> 10 mU/L) (14). Treatment with levothyroxine was recommended for all SCH patients with TSH levels > 10 mU/L, whereas for those with TSH levels below 10 mU/L the treatment remained controversial [8].

The aim of this study was to evaluate the thyroid hormone profile and levels of antiperoxidase antibodies (TPOAb) in patients affected by HT and mild subclinical hypothyroid (TSH < 10 mU/L) after selenium supplementation.

## Material and methods

Patients were eligible if they were 18–65 years old, had mild subclinical hypothyroidism due to Hashimoto's thyroiditis, and had had no previous treatment. In this study pregnant women, those who wanted to become pregnant, and patients that had had to start levothyroxine treatment in accordance with recent guidelines [8] were excluded. All participants were otherwise healthy.

Patients were recruited from October 2013 to November 2014 at our Endocrine Unit. The diagnosis of Hashimoto's thyroiditis was assessed by the presence of detectable TPOAb serum levels and by the typical ultrasound features [9,10]. Thyroid sonography was performed with a real-time instrument (Vision 900; Hitachi Medical System, Tokyo, Japan) equipped with a linear probe with a central frequency of 6–13 MHz, by the same skilled sonographer (CC). Patients were assigned to either receive an oral selenomethionine treatment (supplemented patients) or not receive anything (control patients). Regimen sequence order was randomised according to a permuted blocks allocation scheme (1:1 ratio, with random block size of 2, 4, 6).

Cases received 83 mcg selenomethionine/day orally in a soft gel capsule (Syrel®, IBSA Italia) for four months with water after a meal. No further treatment was given to them.

All the patient's charts were submitted to thyroid hormonal profile (TSH, fT4) and TPOAb evaluations upon enrolment and at the end of the study.

Serum concentrations of free T4 (fT4; normal range: 8.0–19.0 pg/mL) and TSH (third generation TSH assay; normal range: 0.4–4.5 mIU/L) were measured using immuno-chemiluminescent assays by an automated analyser (Immulite 2000, DPC Cirrus, Los Angeles, CA, USA) using commercial kits (Diagnostic Products Corporation, Los Angeles, CA, USA).

The serum concentrations of TPOAb (normal range: < 60 U/mL) were measured using immuno-chemiluminescent assays using commercial kits (Brahms, Hennigsdorf, Germany).

The study protocol was approved by the Ethics Committee of our institution (Medical School, University of Brescia). Written informed consent was obtained from all participants.

### *Statistical analysis*

Data are presented as mean ± standard deviation. A Mann-Whitney U test was performed to evaluate TSH and FT4 distribution. Comparisons between continuous variables were performed using paired samples t-test or related samples by the Wilcoxon signed rank test, as appropriate. Comparisons between groups and difference between proportions were calculated using the ANOVA test for quantitative variables, as appropriate.

A p-value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS software version 17 (SPSS, Inc., Chicago, IL, USA).

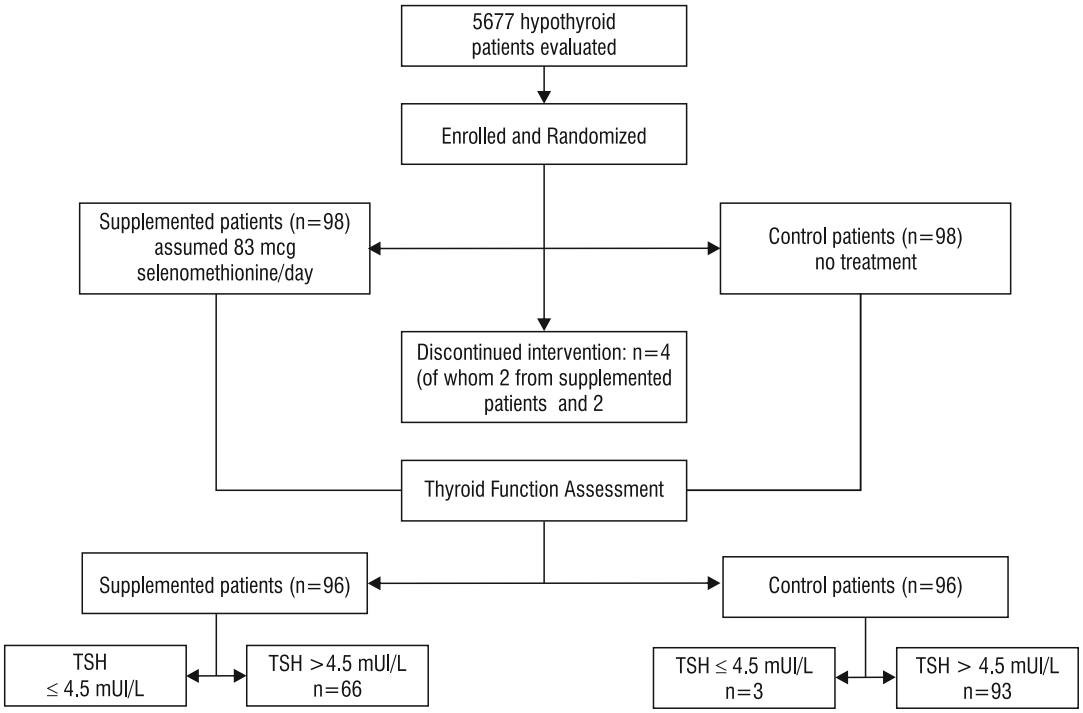


**Figure 1.** *Flow chart of the study*
**Rycina 1.** *Schemat badania*

## Results

From October 2013 to November 2014 we evaluated 5677 subjects (4310 females, 1367 males, mean age 48.2 ± 11.9 years) referred to our department for thyroid disease. One hundred and ninety-six patients (166 females, 30 males, mean age 32.4 ± 7.1 years) affected by Hashimoto's thyroiditis were eligible and were enrolled in this study.

Four of 196 patients withdrew from the study for unspecified personal reasons, so that 192 patients (163/29 female/male, mean age 32.2 ± 7.0 years) completed the study. The study design is shown in Figure 1.

Supplemented and control patients were superimposable for age, gender, thyroid hormonal profile, and TPOAb at recruitment (Table I).

At the end of the study 33/192 (17.2%) participants restored euthyroidism (Responders). Responders were significantly more frequent among supplemented than control patients (30/96 [31.3%] *vs.* 3/96 [3.1%], $p < 0.0001$) (Table II).

In detail, at baseline TSH, fT4, and TPOAb serum levels were superimposable between Responders and Non Responders among supplemented patients (TSH: 5.88 ± 1.25 *vs.* 6.11 ± 1.51, mU/L, p = 0.471, fT4: 10.4 ± ± 1.3 *vs.* 10.2 ± 1.5, pg/mL, p = 0.530, TPOAb: 453 ± 110 *vs.* 444 ± 102, U/mL, p = 0.697) and control patients (TSH: 5.92 ± 1.15 *vs.* 6.39 ± 1.48, mU/L, p = 0.588, fT4: 10.4 ± 1.2 *vs.* 10.3 ± 1.4, pg/mL, p = 0.903, TPOAb: 467 ± 120 *vs.* 520 ± 130, U/mL, p = 0.488).

**Table I**. *Clinical and biochemical data of the subjects enrolled in the study*

**Tabela I.** *Dane kliniczne i biochemiczne chorych włączonych do badania*

| | Supplemented patients (96) | Control patients (96) | p value |
|---|---|---|---|
| Gender (M/F) | 36/60 | 33/63 | – |
| Age (years) | 32.2 ± 7.0 | 33.1 ± 6.4 | 0.925 |
| BMI [kg/m²] | 24.3 ± 1.3 | 24.7 ± 1.1 | 0.079 |
| TSH [mU/L] | 6.11 ± 1.51 | 6.31 ± 1.22 | 0.314 |
| fT4 [pg/mL] | 10.6 ± 1.6 | 10.4 ± 1.3 | 0.343 |
| AbAntiTPO [U/mL] | 447 ± 108 | 480 ± 140 | 0.069 |

Thyroid peroxidase antibodies significantly decreased only among supplemented patients both in Responders and in Non Responders.

## Discussion

The result of this study shows that selenium supplementation could restore euthyroidism in one third of patients with subclinical hypothyroidism due to HT.

Recent guidelines and consensus clearly indicate that all hypothyroid patients can be treated, whereas treatment for those with sub-clinical hypothyroidism

**Table II.** *Thyroid hormonal profile at recruitment and after selenium supplementation*
**Tabela II.** *Stężenia hormonów tarczycy w czasie rekrutacji do badania i po suplementacji selenu*

| | Supplemented patients | | | Control patients | | |
|---|---|---|---|---|---|---|
| | Responders (30) | | | Responders (3) | | |
| | Baseline | After 4 months | p value | Baseline | After 4 months | p value |
| TSH [mU/L] | 5.88 ± 1.25 | 3.21 ± 0.61 | < .0001 | 5.92 ± 1.15 | 3.47 ± 0.91 | 0.044 |
| fT4 [pg/mL] | 10.4 ± 1.3 | 10.7 ± 1.4 | .393 | 10.4 ± 1.2 | 10.6 ± 1.4 | 0.860 |
| TPOAb [U/ml] | 453 ± 110 | 422 ± 88 | < .0001 | 467 ± 120 | 401 ± 110 | 0.521 |
| | Non Responders (66) | | | Non Responders (93) | | |
| TSH [mU/L] | 6.11 ± 1.51 | 5.97 ± 0.94 | .524 | 6.39 ± 1.48 | 6.10 ± 0.99 | 0.122 |
| fT4 [pg/mL] | 10.2 ± 1.5 | 10.5 ± 1.5 | .253 | 10.3 ± 1.4 | 10.4 ± 1.5 | 0.643 |
| TPOAb [U/mL] | 444 ± 102 | 399 ± 78 | < .001 | 520 ± 130 | 498 ± 140 | 0.273 |



and TSH below 10 mU/L remains controversial [8]. For these patients, recommendations appear to be a type of "wait and see" situation.

Spontaneous recovery has been recorded in patients affected by HT with subclinical hypothyroidism, although the frequency of this phenomenon is unclear [11, 12]. Diezz et al. showed that during a five-year follow-up period, TSH levels became normal in the absence of treatment in 62% of patients. However, normalisation of serum TSH concentrations is more likely to occur in patients with negative antithyroid antibodies, TSH serum levels of < 10 mU/I, and within the first two years of diagnosis [13]. On the other hand, a substantial proportion of patients with subclinical hypothyroidism develop overt hypothyroidism. In prospective studies with nearly 10 to 20 years of follow-up, the cumulative incidence of overt hypothyroidism ranges from 33 to 55 per cent [11, 14].

Genetic predisposition or certain environmental factors including selenium deficits appear to be implicated in the pathogenesis of the disease [15].

The thyroid is in fact the organ with the highest selenium concentration per gram among all tissues [16].

It has been reported that Se deficiency has been associated with many conditions, such as increased thyrocyte damage, infections and the incidence of cancer [1].

Se deficiency can also cause decline in GPXs, deiodinases activity, and the concentrations of hydrogen peroxide (H2O2) and impair the synthesis of thyroid hormone [17]. All these factors may be an indication that Se deficiency could cause a condition to induce or to increase the damage to thyroid cells and tissue.

In previous years selenium supplementation with the purpose of improving autoimmune processes has been explored with discordant results. In a study published in 2005 Moncayo et al. reported a few cases of patients with autoimmune hypothyroidism that exhibited a marked recovery of thyroid function after Se treatment [18].

Very recently, Nordio and Pajalich confirmed potential beneficial effects of Se supplementation in a small number of patients with subclinical hypothyroidism affected by Hashimoto thyroiditis.

In this study a major effect on TSH levels was recorded between two groups of patients who were treated with both selenium and myo-inositol compared to those who were treated with selenium alone [19]. Considering these data, the study showed that 31% of patients treated with Se supplementation had restored TSH levels after four months of treatment.

The potential benefits of selenium supplementation have also been explored in pregnant woman. Negro et al. have in fact shown that selenium supplementation during pregnancy and the postpartum period reduces TPOAb concentrations, the incidence of postpartum thyroid dysfunction, and permanent hypothyroidism [2]. Moreover, Polanska et al. have recently shown a positive effect of prenatal selenium status on child psychomotor abilities within the first years of life [20].

Several prospective studies have been done in countries where selenium supply is lower and have shown a significant decrease in TPOAb titres after four months of Se supplementation [5,21]. In contrast, a very recent study performed in Italy among patients with normal selenium concentration values has shown that selenium supplementation had no positive effect on thyroid echogenicity or TPOAb levels [22].

Conversely to the study by Pilli et al., but in agreement with those by Gärtner R et al. and Mazokopakis E et al. [5, 21], we showed a significant decrease in TPOAb titres in subjects subjected to Se supplementation, although thyroid peroxidase antibodies significantly decreased both in Responders ($p < 0.0001$) and in Non Responders ($p < 0.001$). To compare thyroid echogenicity

at baseline and after four months of selenomethionine treatment we used the method validated by Nacamulli et al. [23] Interestingly, ultrasound features improved in both groups (data not shown). Considering this data, we could hypothesise that a decrease in the antibody titre does not improve the TSH values.

A possible explanation among our data and those obtained by Pilli et al. could be due to the different selenium concentrations of the population studied; although these studies were performed in Italy, data about selenium concentrations in different regions was lacking, and unfortunately we do not have this data. It is possible that patients enrolled in our study could have had low levels of selenium concentration conversely to those reported by Pilli et al. [21] Further studies and research is needed on this topic.

A major factor that has not been directly addressed by this study is whether the recovery of thyroid function after treatment with selenium will be maintained over time.

Indeed, we have double-checked the TSH values of the all the 33 Responders after five months of selenium withdrawal and the results showed that 30 subjects of supplemented patients were in euthyroidism, whereas 2/3 of the control patients became hypothyroid again; interestingly, no patients received any further selenium supplementation (data not shown).

In conclusion, the present study suggests that selenium supplementation could restore euthyroidism in one third of subclinical hypothyroid patients with autoimmune thyroiditis.

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