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Original article

The effect of vitamin D and selenomethionine on thyroid antibody titers, hypothalamic-pituitary-thyroid axis activity and thyroid function tests in men with Hashimoto's thyroiditis: A pilot study

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ABSTRACT

Background: Both selenium and vitamin D were found to reduce thyroid antibody titers in women with Hashimoto's thyroiditis.

Methods: The study enrolled 37 young drug-naïve euthyroid men with autoimmune thyroiditis, who were treated for 6 months with either exogenous vitamin D (group A, n = 20) or selenomethionine (group B, n = 17). Serum titers of thyroid peroxidase and thyroglobulin antibodies, serum levels of thyrotropin and free thyroid hormones, serum levels of 25-hydroxyvitamin D, as well Jostel's thyrotropin, the SPINA-GT and the SPINA-GD indices were determined at the beginning and at the end of the study.

Results: At baseline, there were no differences between the study groups. Both vitamin D and selenomethionine reduced antibody titers and increased the SPINA-GT index. Only selenomethionine affected the SPINA-GD index, while only vitamin D increased 25-hydroxyvitamin D levels. Neither selenomethionine nor vitamin D significantly affected thyrotropin and free thyroid hormone levels. The effect of vitamin D on antibody titers correlated with baseline and treatment-induced changes in serum levels of 25-hydroxivitamin D.

Conclusions: Both vitamin D and selenomethionine have a beneficial effect on thyroid autoimmunity in drug-naïve men with Hashimoto's thyroiditis.

Introduction

Hashimoto's thyroiditis is an autoimmune disorder destroying thyroid follicular cells by cell and antibody-mediated immune processes [1,2]. Despite strong female predominance, increasingly more and more men are being diagnosed with this disorder, which is by far the most common cause of thyroid hypofunction in developed countries [3].

Both vitamin D (cholecalciferol) and selenium seem to play a role in the development and progression of Hashimoto's thyroiditis. The prevalence of vitamin D deficiency was significantly higher in patients with Hashimoto's thyroiditis compared with healthy individuals and patients with other endocrine disorders [4,5]. Each 5 ng/mL increase in serum 25-hydroxyvitamin D levels was found to decrease the risk of Hashimoto's thyroiditis by 19% [6]. Severity of vitamin D deficiency correlated with titers of thyroid antibodies, thyroid volume and duration of Hashimoto's thyroiditis [7]. The negative association between 25-hydroxyvitamin D levels and TPOAb in patients with autoimmune thyroiditis persisted after adjusting for age, sex, and body mass index [6,8]. Serum levels of 25-hydroxyvitamin D correlated also with the results of thyroid function tests [4,5]. Some genetic studies demonstrated an association between autoimmune thyroiditis and polymorphisms of the vitamin D receptor, mediating most of the known biological effects of cholecalciferol [9,10]. Exogenous vitamin D preparations reduced thyroid antibody titers in women with hypovitaminosis D and women with normal cholecalciferol status [11,12].

Selenium is a micronutrient playing an essential role in the metabolism of thyroid hormones and contributing to the antioxidant defense in the thyroid [13]. Because selenium concentration was not measured before, during and after treatment, the association of selenium status with thyroid autoimmunity is weakly understood. However, three recent meta-analyses have shown that selenium supplementation reduces titers of thyroid antibodies [14–16]. The effect of selenium was more pronounced

Abbreviations: CI, confidence interval; IU, international unit; SD, standard deviation; SPINA, structure parameter inference approach; TgAb, thyroglobulin antibodies; TPOAb, thyroid peroxidase antibodies.

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for TPOAb than TgAb, observed mainly in patients receiving levothyroxine treatment, as well as stronger for 200 μg of selenomethionine than for sodium selenite and other selenium preparations [14–16]. Moreover, selenium was found to improve thyroid echogenicity, which is reduced in patients with autoimmune thyroiditis [17]. The beneficial effect on thyroid autoimmunity is, at least in part, associated with anti-inflammatory and immune-suppressive effect of selenium [18].

Recently, we have found that the effect of metformin on hypothalamic-pituitary-thyroid axis activity and thyroid secretory function differs between men and women with subclinical hypothyroidism [19] and hyperprolactinemia [20]. Because studies investigating associations between vitamin D or selenium and thyroid autoimmunity included either only women or mainly women, similar data are not available for males. Moreover, to the best of our knowledge, the impact of both agents on thyroid antibody titers has not been compared head-to-head. Therefore, the aim of the present study was to investigate the effect of selenomethionine and vitamin D on thyroid autoimmunity, hypothalamic-pituitary-thyroid axis activity and thyroid function tests in drug-naïve euthyroid men with Hashimoto's thyroiditis.

Materials and methods

Patients

The participants (n = 37) were selected among young men (aged 20–50 years) with recently diagnosed and untreated Hashimoto's thyroiditis. To be included, they had to meet the following criteria: (a) positive TPOAb (>100 U/mL); (b) the reduced echogenicity of the thyroid parenchyma on thyroid ultrasonography; (c) serum levels of thyrotropin in the range between 0.4 and 4.0 mU/L; and (d) serum levels of free thyroxine and free triiodothyronine within the reference range.

The subjects were excluded if they met at least one of the following criteria: positive antibodies against thyrotropin receptor, other autoimmune or endocrine disorders, chronic inflammatory processes, myocardial infarction or stroke within 3 months preceding the study, impaired renal or hepatic function and non-compliance with the study protocol. Moreover, no patient had been ever treated with glucocorticoids, other immune-suppressive agents or drugs affecting hypothalamic-pituitary-thyroid axis activity. We also excluded patients treated with other drugs within 12 weeks preceding the study.

The study protocol was approved by the local review board. Before enrollment, all participants were informed about the benefits and harms of vitamin D and selenomethionine therapy and gave written, informed consent to participate in the study.

Study design

On the basis of patient preference, the participants were allocated to one of two groups. Throughout the study, lasting 6 months, the participants once daily in the morning received either vitamin D (4000 IU daily) (n = 20) or selenomethionine (200 μg daily) (n = 17) and no changes in dosage were allowed. Treatment compliance, measured by pill counting, was considered satisfactory if the number of tablets returned ranged from 0% to 10%.

Laboratory assays

Blood samples for laboratory assays were obtained at approximately 8:00 a.m. following at least a 12-h overnight fasting at the beginning and at the end of the study. Serum levels of thyrotropin, free thyroxine and free triiodothyronine and titers of TPOAb and TgAb were assayed by direct chemiluminescence using acridinium ester technology (ADVIA Centaur XP Immunoassay System, Siemens Healthcare Diagnostics, Munich, Germany). Serum 25-hydroxyvitamin D levels were detected by competitive immunoassay using Roche Diagnostic commercial kits and a multichannel automatic analyzer (Roche Cobas e 411, Mannheim, Germany). All measurements were performed by persons blinded to individuals' identity and clinical details. Jostel's thyrotropin index, the structure parameter inference approach (SPINA)-GT index as we as the SPINA-GD indices were calculated by the investigators using SPINA-Thyr 4.0.1 for Windows software in accordance with the formulas described previously [21–23].

Statistical analysis

Quantitative data without a normal distribution (thyrotropin, free thyroid hormones, antibody titers and all indices) were natural log-transformed to yield normal distributions prior to statistical analysis. Between-group comparisons were performed by the *t* test for independent samples. Student's paired *t* tests were applied to compare differences between the means of variables within the same treatment arm. The clinical importance of the result was assessed based on the 95% confidence interval. A *t* statistic and two sample means were used to generate an interval estimate of the difference between two population means. The χ^2 test was employed to compare the proportional data. Correlations between the study parameters were calculated using Pearson's r-tests. Differences were described as statistically significant if 95% confidence intervals did not include the null value and/or two-tailed *p* values were below 0.05.

Results

At study entry, there were no significant differences between the study groups in age, smoking, the body mass index, serum levels of thyrotropin, free thyroid hormones and 25-hydroxyvitamin D, serum titers of TPOAb and TgAb, as well as Jostel's thyrotropin, the SPINA-GT and the SPINA-GD indices (Table 1). No patient reported any significant adverse effects and all participants completed the study.

Both vitamin D and selenomethionine reduced serum titers of TPOAb and TgAb, as well as increased the SPINA-GT index (Table 2). Neither vitamin D nor selenomethionine had a statistically significant effect on serum levels of thyrotropin and free thyroid hormones. Moreover, selenomethionine increased the SPINA-GD index, while vitamin D increased serum levels of 25-hydroxyvitamin D. At the end of the study, both groups differed in circulating levels of 25-hydroxyvitamin D and the SPINA-GD index (Table 2).

The subgroup analysis revealed that the effect on vitamin D on thyroid antibody titers was stronger in men with 25-hydroxyvitamin D levels below 30 ng/mL than in men with 25-hydroxyvitamin D levels above this value (ΔTPOAb – patients with low 25-hydroxyvitamin D levels: −255 (112) U/mL, patients with normal 25-hydroxyvitamin D levels: −141 (94) U/mL, difference: 114 [17, 211] U/mL; ΔTgAb - patients with low 25-hydroxyvitamin D levels: −264 (123) U/mL, patients with normal 25-hydroxyvitamin D levels: −124 (108) U/mL, difference: 140 [31, 249] U/mL). The effect of selenomethionine on thyroid antibody titers did not differ between men with 25-hydroxyvitamin D levels below and above 30 ng/mL.

Baseline TPOAb titers correlated with baseline TgAb titers (vitamin D-treated men: r = 0.59, $p < 0.001$; selenomethionine-treated men: r=0.55, $p < 0.001$). Antibody titers inversely correlated with 25-hydroxyvitamin D levels (TPOAb: vitamin D-treated men – r=-0.37, $p < 0.01$; selenomethionine-treated men – r=-0.39, $p < 0.001$; TgAb: vitamin D-treated men – r=-0.30, $p < 0.05$; selenomethionine-treated men – r=-0.28, $p < 0.05$). Titers of TPOAb

Table 1
Baseline characteristics of patients.

Variable	Vitamin D-treated men	Selenomethionine-treated men	Difference [95% CI]
Number of patients [n]	20	17	–
Age [years; mean (SD)]	35 (8)	34 (7)	−1 [−6, 4]
Smokers [n/%]	Apr-20	Apr-24	–
Body mass index [kg/m^2; mean (SD)]	26.5 (3.7)	26.9 (3.4)	0.4 [−2.0, 2.8]
TPOAb [U/mL; mean (SD)]	836 (245)	878 (286)	42 [−135, 219]
TgAb [U/mL; mean (SD)]	756 (302)	783 (312)	27 [−178, 232]
Thyrotropin [mIU/L; mean (SD)]	2.9 (0.7)	2.8 (0.8)	−0.1 [−0.6, 0.4]
Free thyroxine [pmol/L; mean (SD)]	14.0 (2.2)	14.3 (2.0)	0.3 [−1.1, 1.7]
Free triiodothyronine [pmol/L; mean (SD)]	3.4 (0.6)	3.2 (0.7)	−0.2 [−0.6, 0.2]
Jostel's thyrotropin index [mean (SD)]	2.9 (0.3)	3.0 (0.2)	0.1 [−0.1, 0.3]
SPINA-GT index [pmol/s; mean (SD)]	2.07 (0.34)	2.15 (0.30)	0.08 [−0.14, 0.30]
SPINA-GD index [nmol/s; mean (SD)]	22.46 (3.51)	20.69 (3.01)	−1.77 [−3.97, 0.43]
25-hydroxyvitamin D [ng/mL; mean (SD)]	25 (10)	26 (12)	1 [−6, 8]
Patients with 25-hydroxyvitamin D below 30 ng/mL [n/%]	Oct-50	Sep-53	–

CI: confidence interval; IU: international unit; SD: standard deviation; SPINA: structure parameter inference approach; TgAb: thyroglobulin antibodies; TPOAb: thyroid peroxidase antibodies.

and TgAb correlated also with the SPINA-GT index (TPOAb – vitamin D-treated men: r=-0.30, $p < 0.05$; selenomethionine-treated men: r=0.32, $p < 0.05$; TgAb – vitamin D-treated men: r=-0.25, $p < 0.05$; selenomethionine-treated men: r=0.29, $p < 0.05$). The impact of vitamin D, but not of selenomethionine, on 25-hydroxyvitamin levels correlated with baseline 25-hydroxyvitamin levels (r=0.38, $p < 0.001$), as well as with treatment-induced changes in TPOAb (r=0.40, $p < 0.001$) and TgAb (r=0.37, $p < 0.01$). In both study groups, the impact of treatment on TPOAb titers correlated with the changes in TgAb titers (vitamin D-treated men: r=0.49, $p < 0.001$; selenomethionine-treated men: r=0.47, $p < 0.001$), while the impact on the SPINA-GT index correlated with the effect on antibody titers (TPOAb: vitamin D-treated men – r=0.35, $p < 0.01$; selenomethionine-treated men – r=0.38, $p < 0.01$; TgAb: vitamin

Table 2
Effect of exogenous vitamin D and selenomethionine on thyroid antibody titers, hormones, thyroid function tests and 25-hydroxyvitamin D levels in euthyroid men with Hashimoto's thyroiditis.

Variable	Vitamin D-treated men	Selenomethionine-treated men	Difference [95% CI]
TPOAb [U/mL; mean (SD)]			
Baseline	836 (245)	878 (286)	42 [−135, 219]
After 6 months	638 (211)[#]	649 (226)[#]	11 [−135, 157]
Change	−198 (86)	−229 (102)	−31 [−94, 32]
TgAb [U/mL; mean (SD)]			
Baseline	756 (302)	783 (312)	27 [−178, 232]
After 6 months	562 (267)[#]	570 (243)[#]	8 [−164, 180]
Change	−194 (104)	−213 (115)	−19 [−92, 54]
Thyrotropin [mIU/L; mean (SD)]			
Baseline	2.9 (0.7)	2.8 (0.8)	−0.1 [−0.6, 0.4]
After 6 months	2.7 (0.7)	2.6 (0.6)	−0.1 [−0.5, 0.3]
Change	−0.2 (0.2)	−0.2 (0.2)	0.0 [−0.1, 0.1]
Free thyroxine [pmol/L; mean (SD)]			
Baseline	14.0 (2.2)	14.3 (2.0)	0.3 [−1.1, 1.7]
After 6 months	15.5 (2.9)	15.2 (2.4)	−0.3 [−2.1, 1.5]
Change	1.5 (1.1)	0.9 (0.8)	−0.6 [−1.1, 0.1]
Free triiodothyronine [pmol/L; mean (SD)]			
Baseline	3.4 (0.6)	3.2 (0.7)	−0.2 [−0.6, 0.2]
After 6 months	3.6 (0.6)	3.8 (0.8)	0.2 [−0.3, 0.7]
Change	0.2 (0.4)	0.6 (0.5)	0.4 [−0.1, 0.9]
Jostel's thyrotropin index [mean (SD)]			
Baseline	2.9 (0.3)	3.0 (0.2)	0.1 [−0.1, 0.3]
After 6 months	3.1 (0.4)	3.0 (0.2)	−0.1 [−0.3, 0.1]
Change	0.2 (0.2)	0.0 (0.2)	−0.2 [−0.3, 0.1]
SPINA-GT index [pmol/s; mean (SD)]			
Baseline	2.07 (0.34)	2.15 (0.30)	0.08 [−0.14, 0.30]
After 6 months	2.38 (0.39)[#]	2.37 (0.32)[#]	−0.01 [−0.25, 0.23]
Change	0.31 (0.19)	0.22 (0.15)	−0.09 [−0.21, 0.03]
SPINA-GD index [nmol/s; mean (SD)]			–
Baseline	22.46 (3.51)	20.69 (3.01)	−1.77 [−3.97, 0.43]
After 6 months	21.48 (2.62)	23.12 (2.21)[#]	1.64 [0.01, 3.27][*]
Change	−0.98 (0.71)	2.43 (0.82)	3.41 [2.90, 3.92][&]
25-hydroxyvitamin D [ng/mL; mean (SD)]			
Baseline	25 (10)	26 (12)	1 [−6, 8]
After 6 months	42 (8)[#]	27 (9)	−15 [−21, −9][*]
Change	17 (8)	1 (2)	−16 [−20, −12][&]

CI: confidence interval; IU: international unit; SD: standard deviation; SPINA: structure parameter inference approach; TgAb: thyroglobulin antibodies; TPOAb: thyroid peroxidase antibodies.
[*] statistically significant difference between both groups.
[#] statistically significant difference between post-treatment and baseline values in the same group.
[&] statistically significant difference between the effects of vitamin D and selenomethionine.

D-treated men – r=0.28, $p < 0.05$; selenomethionine-treated men – r=0.26, $p < 0.05$). No other correlations were reported.

Discussion

This study has shown for the first time that both exogenous vitamin D and selenomethionine reduce thyroid antibody titers in untreated men with Hashimoto's thyroiditis, as well as that the strength of this effect does not differ between both treatment arms. Considering the association between thyroid antibody titers and the risk of the development of permanent hypothyroidism [24], the relative safety of vitamin D and selenomethionine at the doses used in the current study [25,26], as well as the fact that the effect of vitamin D and selenomethionine on TPOAb and TgAb correlated with their baseline values, it seems that men with very high titers of TPOAb and TgAb may gain particular benefits from treatment with 4000 IU of vitamin D or 200 μg of selenomethionine daily.

An interesting finding resulting from our study is that the effect of vitamin D on antibody titers was more pronounced in subjects with low than in subjects with normal vitamin D status. This may suggest that vitamin D-deficient patients with autoimmune thyroiditis may benefit more from vitamin D than subjects with 25-hydroxyvitamin D levels within the reference range. It means that the last group of men should be rather treated with selenomethionine, the effect of which was vitamin D-independent. Similarly to previous studies assessing the impact of selenium preparations on thyroid autoimmunity, we did not determine circulating levels of this micronutrient. Therefore, our study does not allow to answer the question whether thyroid-antibody-reducing effect of selenomethionine is selenium status-dependent. We intend to verify this issue in our future research.

Because of the inclusion criteria, serum thyrotropin and free thyroid hormones levels in all participants were within the reference range. Normal baseline activity of hypothalamic-pituitary-thyroid axis activity may explain no significant changes in serum hormone levels after vitamin D or selenomethionine treatment. However, both treatments increased the SPINA-GT index, estimating the maximum secretion rate under stimulated conditions [21,22], which correlated with a decrease in thyroid antibody titers. This finding indicates that vitamin D and selenomethionine, by inhibiting thyroid autoimmunity, increased secretory capacity of the thyroid gland. This action may, at least theoretically, delay the development of thyroid hypofunction. Moreover, selenomethionine increased the SPINA-GD index, measuring the maximum global activity of peripheral deiodinases per unit of time [21,22], the effect not observed in vitamin D-treated patients. Because iodothyronine deiodinases, converting the deiodination of thyroxine into triiodothyronine, belong to selenoproteins, their activity may be disturbed in selenium-deficient areas [27]. This explanation is supported by the study of Kłapcińska et al. [28] including men and women living in the Upper Silesia, the region of Poland, where also our research was carried out. These authors observed that although higher than in women, whole-blood selenium levels in men were markedly below the lower limit of the nutritional adequacy. Consequently, the increase in the SPINA-GD may reflect a stimulatory effect of an improvement in selenium status on deiodinase activities. No correlations with antibody titers and the presence only in one treatment arm indicate that this effect is not secondary to a reduction in thyroid autoimmunity. Finally, neither vitamin D nor selenomethionine affected Jostel's thyrotropin index, determining thyrotropic function of anterior pituitary on a quantitative level [23]. This means that neither vitamin D nor selenomethionine affect hypothalamic-pituitary-thyroid axis activity at the level of thyrotropes.

The beneficial effect of selenomethionine is probably associated with the role of different selenoproteins in antioxidant, redox and anti-inflammatory processes, involving T cells activity and reduced cytokine release [29]. In turn, activated cholecalciferol suppresses the adaptive immune system promoting immune tolerance [30]. It is, however, likely that molecular mechanisms of action of vitamin D and selenomethionine may to some extent overlap. In line with this explanation, calcitriol-induced expression of thioredoxin reductase (a selenoprotein protecting against oxidant injury, cell growth and transformation [31]) was potentiated by selenium treatment [32]; calcitriol enhanced selenium uptake by the duodenal brush border membrane vesicles [33]; while organoselenium increased 1α-hydroxylation of deltanoid, which is a vitamin D analog [34]. These findings may also suggest that vitamin D administered in combination with selenomethionine inhibits thyroid autoimmunity to a greater degree than each agent administered alone. The study protocol does not allow to confirm or reject this hypothesis. It should be, however, mentioned that the impact of selenomethionine on thyroid antibody titers in patients with Hashimoto's thyroiditis and subclinical hypothyroidism was potentiated by myo-inositol [35], as well as that myo-inositol administered together with selenomethionine strongly reduced thyroid antibody titers in euthyroid subjects with autoimmune thyroiditis [36], probably because of synergistic effects of myo-inositol and selenomethionine on inflammatory cell proliferation [37]. Taking into account that myo-inositol plays an important role in the phosphatidylinositol signal transduction pathway [35] and that phosphatidylinositol signal transduction pathway activity is regulated by calcitriol [38], similar benefits of vitamin D/selenomethionine combination therapy need to be considered and investigated in future studies.

There are some other shortcomings that may limit the generalizability of our findings. Because of the small sample size the results of the study must be interpreted with caution. Owing to low selenium status [28] and adequate iodine intake [39] in the Polish population, it cannot be ruled out that the impact of vitamin D and selenomethionine may be different in men inhabiting selenium-sufficient and iodine-depleted regions. Finally, the question whether vitamin D and selenomethionine affect serum titers of TPOAb and TgAb in hypothyroid and levothyroxine-treated men remains still open.

In conclusion, both vitamin D and selenomethionine are characterized by a favorable effect on thyroid antibody titers in men. This effect, correlating with baseline antibody titers and in the case of cholecalciferol with levels of 25-hydroxyvitamin D, may slightly improve secretory capacity of the thyroid gland. The obtained results should be confirmed in a larger clinical trial.

Author contributions

Robert Krysiak conceived of the study, participated in its design, performed the statistical analysis, as well as drafted and edited the manuscript. Witold Szkróbka conducted the literature search, carried out the assays and performed the statistical analysis. Bogusław Okopień participated in its design and coordination, and provided critical input during manuscript preparations. All authors read and approved the final manuscript.

Disclosure statement

The authors declare no conflicts of interest

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