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ORIGINAL

Role of selenium and myo-inositol supplementation on autoimmune thyroiditis progression

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Abstract. Previous reports indicate that selenium supplementation may be useful to reduce cell oxidative stress. In particular, selenium may decrease the level of thyroid autoantibodies in patients with Hashimoto's thyroiditis (HT). Recent studies also indicate that myo-inositol may have beneficial effects on thyroid function in patients with HT. Hence, the aim of the present study is to evaluate whether myo-inositol may enhance the protective effect of selenium on HT progression to hypothyroidism. The study was designed as observational and retrospective. Thyroid hormones were evaluated in patients with HT who were either euthyroid or subclinically hypothyroid. These patients were subdivided into three groups: untreated, treated with selenomethionine alone (Se-meth: 83 μg/day) and treated with Se-meth plus myo-inositol (Se-meth + Myo-I: 83 μg/day + 600 mg/day). Outcome evaluation was performed at baseline and after 6 and 12 months of treatment. High-resolution ultrasound of the thyroid gland was performed to evaluate changes in thyroid echoic pattern during the study. Compared to baseline, levels of thyroid-stimulating hormone (TSH) increased significantly in untreated patients but decreased by 31% and 38%, respectively, in those treated with Se-meth and Se-meth + Myo-I. Moreover, in the latter group the TSH reduction was observed earlier than in the Se-meth-treated group. Densitometric analysis of thyroid ultrasonography showed an echoic pattern improvement in both treated groups compared to untreated patients, although this difference was not statistically significant. Thus, Se-meth treatment is effective in patients with HT and its effect may be improved in combination with Myo-I through earlier achievement of TSH levels closer to physiological concentrations.

Key words: Hashimoto's thyroiditis, Hypothyroidism, Selenomethionine, Myo-inositol, Thyroid autoantibodies

HASHIMOTO'S THYROIDITIS (HT) is the most frequent autoimmune disease arising from the interaction between genetic and environmental factors. While family history of thyroid disease may play a significant role in HT risk, environmental effects such as radiation exposure, pollutants and iatrogenic factors may trigger the autoimmune process [1, 2]. Specific autoantibodies—thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb)—against thyroid antigens are a serum hallmark of HT and may cause continuous damage to the thyroid tissue. Radiation, chemicals, excessive iodine and drugs (along with T and B lymphocyte activation), *via* increased hydrogen peroxide production, cause thyrocyte apoptosis and necrosis in HT [3-7]. The inflammation and oxidative stress is counteracted by antioxidant defense systems, such as increased serum levels of interleukin-37 [8]. Some studies have shown that selenium (Se) supplementation may be beneficial in autoimmune thyroid disorders but its clinical use is still under debate [9, 10]. In the last decade, several studies have shown that Se may protect thyroid cells from oxidative stress during autoimmune disease [11, 12]. Indeed, autoimmune thyroiditis incidence is higher in severe Se-deficient areas because of decreased activity in Se-dependent glutathione peroxidase. As Se-dependent enzymes regulate the general immune response, mild Se deficiency may also contribute to the development of several autoimmune diseases, including HT [13, 14]. Se supplementation may have potential immunomodulatory action due to its effect on the production of interferon gamma-inducible chemokines such as CXCL9, CXCL10 and CXCL11, which play a role in thyroid autoimmunity, although this effect is still controversial in the current literature [10, 15]. Inositols are hexahydroxycyclohexane compounds ($C_6H_{12}O_6$) that include nine stereoisomeric

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forms. The first identified is myo-inositol (Myo-I), a C6 sugar alcohol that plays a pivotal role in many metabolic pathways and whose derangement exerts negative effects on human health [16]. Inositol derivatives are important components in the cell's structural lipids and have several relevant functions, including morphogenesis, cytoskeleton rearrangement, regulation of cell proliferation and glucose metabolism [17, 18]. Inositols are also involved in the signaling of various hormones, including insulin, gonadotropins and thyroid-stimulating hormone (TSH) [19]. In particular, impaired inositol metabolism can negatively affect hormone biosynthesis, storage and secretion in mammalian thyroid. Myo-I is the precursor of phosphoinositides, which are mediators in the phosphatidylinositol signal transduction pathway. Phosphatidylinositol, *via* a second messenger of inositol 1,4,5-triphosphate, modulates intracellular Ca^{2+} release and acts as a docking molecule for several signal transduction proteins [20].

TSH signaling is based upon two different signaling branches: one branch involves cAMP production and the other is inositol-dependent. While cAMP mainly regulates cell growth, differentiation and thyroid hormone secretion, the inositol-dependent branch is involved in H_2O_2-mediated iodination [21, 22]. In particular, experimental evidence indicates that low TSH levels are able to stimulate the cAMP-mediated signal cascade whereas high TSH levels (up to 100-fold) are able to recruit the inositol-mediated signal cascade [23].

The aim of this study in HT patients is to evaluate the effect of combined selenomethionine (Se-meth) and Myo-I supplementation on disease evolution.

Materials and Methods

This is an observational and retrospective study on patients selected from our medical records with the following inclusion criteria: treatment with either oral Se-meth (83 μg Se in the form of L-Se-meth, Syrel®, IBSA Srl, Rome, Italy) or combined Se-meth plus Myo-I (83 μg Se in the form of L-Se-meth plus 600 mg Myo-I, Tiroxil®, Lo.Li. Pharma Srl, Rome, Italy) for at least 12 months; TSH levels between 2.5 and 10 mIU/L; normal free thyroxine (fT4) and free triiodothyronine (fT3) levels; positive serum TgAb and/or TPOAb; ultrasound pattern of chronic thyroiditis without the typical feature of nodular goiter; available data on serum TSH, fT3 and fT4 concentrations before treatment and thereafter at 6 and 12 months. Patients with the following criteria were excluded: previous treatment with levothyroxine; chronic debilitating diseases (*e.g.* severe hepatic and renal failure); malabsorption disorders (atrophic gastritis, celiac disease); patients under adjuvant treatment with trace elements, vitamins or antidepressant and antipsychotic drugs. An untreated control group of patients observed in the same period and who met the same above-mentioned criteria was selected. Medical records from a total of 101 patients were analyzed for this study (86 women and 15 men, mean age 45.4 ± 14.2 years). All patients were examined at our outpatient thyroid clinic and followed-up for a period of 12 months from July 2016 to June 2017. The study was carried out in accordance with the recommendations of our Institutional Review Board for retrospective study and with the 1964 Helsinki Declaration and its later amendments. Written informed consent was obtained from all participants. The primary endpoint was to compare the thyroid hormonal trend (TSH, fT4 and fT3) in the three groups of patients and the secondary endpoint was to evaluate the variations in thyroid echogenicity before and after therapy.

Laboratory and technical investigations

The study was performed over a period of 12 months. Blood samples were obtained from each patient and serum TSH, fT3 and fT4 levels were measured at baseline and at 6 and 12 months. TSH, fT3 and fT4 concentrations were measured by a third-generation chemiluminescent immunoassay (Abbott Architect TSH; Abbott, Wiesbaden, Germany) with inter- and within-assay coefficient of variation <10% and 5%, respectively, over the analytical range 0.02–88.0 μIU/mL. Two expert operators (M.R. and P.M.) in thyroid ultrasonography, who were both blinded to the treatment assigned to each group, performed high-resolution ultrasound through the MyLabSeven scanning platform (Esaote, Florence, Italy) at baseline and after 6 and 12 months. Definite elliptic areas were selected on ultrasound images of the thyroid gland in the right and left lobes. Changes in tissue density, evaluated as any gray-scale variations from the baseline value at 6 and 12 months, were compared by densitometric analysis (average densitometry between the two lobes was used) on acquired images processed through the NIH ImageJ software (https://imagej.nih.gov/ij/download.html).

Statistical analysis

Quantitative data are represented as mean ± standard deviation (SD), or as median and 25–75 interquartile range when appropriate, whereas qualitative data are represented as numbers and percentages. Percentages were compared by chi-square test and continuous variables by *t*-test. Repeated measurements of TSH values (baseline and after 6 and 12 months) were analyzed by multilevel linear regression analysis to compare the change over time between untreated patients and patients treated with either Se-meth alone or combined with Myo-I. All tests

Table 1 Clinical and laboratory characteristics of patients at study entry

Parameter		Control (n = 29)	Se-meth (n = 29)	Se-meth + Myo-Inositol (n = 43)	p value
Sex	Female	24 (83%)	26 (90%)	36 (84%)	0.72
	Male	5 (17%)	3 (10%)	7 (16%)	
Age, mean (SD)		50.3 (12.8)	47.3 (13.5)	40.8 (14.3)	0.012
TSH, median (IQR)		3.6 (2.9–4.3)	4.3 (3.5–4.7)	4.6 (4.1–5.3)	<0.001
fT3, median (IQR)		2.9 (2.5–3.3)	2.6 (2.3–3.0)	2.9 (2.4–3.2)	0.15
fT4, median (IQR)		1.1 (0.9–1.2)	1.0 (0.9–1.1)	1.0 (0.8–1.1)	0.14
TgAb, median (IQR)		288 (123–428)	152 (54–490)	110 (51–394)	0.19
TPOAb, median (IQR)		248 (161–633)	172 (80–600)	228 (68–645)	0.60

Table 2 Comparison of thyroid function tests between patients untreated and treated with either Se-meth or Se-meth + Myo-I, at baseline and after 6 and 12 months

	Control (n = 29)			Se-meth (n = 29)			Se-meth + Myo-Inositol (n = 43)		
	baseline	6 months	12 months	baseline	6 months	12 months	baseline	6 months	12 months
TSH (mIU/L)	3.7 ± 0.9	3.1 ± 1.3 (NS)	5.0 ± 2.6 (0.02)	4.5 ± 1.6	4.9 ± 2.0 (NS)	3.1 ± 1.0 (0.03)	4.7 ± 1.2	3.5 ± 1.3 (0.007)	2.9 ± 1.2 (<0.001)
fT3 (pg/mL)	2.9 ± 0.7	2.9 ± 0.6 (NS)	2.8 ± 0.6 (NS)	2.6 ± 0.7	2.7 ± 0.5 (NS)	2.9 ± 0.8 (NS)	2.8 ± 0.6	2.9 ± 0.6 (NS)	3.0 ± 0.3 (NS)
fT4 (ng/dL)	1.1 ± 0.2	1.1 ± 0.3 (NS)	1.0 ± 0.2 (NS)	1.0 ± 0.2	1.0 ± 0.2 (NS)	1.0 ± 0.2 (NS)	1.0 ± 0.2	1.0 ± 0.2 (NS)	0.9 ± 0.1 (NS)

Numbers shown in brackets are the p values relative to baseline. NS, not significant.

were two-sided and a p value of <0.05 was considered to be statistically significant. Statistical analyses were performed with Stata software version 16.1 (StataCorp, College Station, TX, USA).

Results

We selected 29 untreated patients (24 females and 5 males, mean age 50.3 ± 12.8 years), 29 patients receiving Se-meth alone (26 females and 3 males; mean age 47.3 ± 13.5 years) and 43 patients receiving oral combined treatment with Se-meth + Myo-I (36 females and 7 males; mean age 40.8 ± 14.3 years) (Table 1). Patients in the Se-meth + Myo-I group were younger than patients in the control group (p = 0.01), whereas there was no significant difference in age between Se-meth alone and the control group (p = 0.39). The male to female ratio was not significantly different between the three groups. Among the 101 selected patients, 60 (59.4%) had subclinical hypothyroidism: 10/29 (34.5%) in the control group, 15/29 (51.7%) in the Se-meth group and 35/43 (81.4%) in the Se-meth + Myo-I group. At baseline, the TSH level was 3.7 ± 0.9 mIU/L in the control group, which is significantly lower than the Se-meth (4.5 ± 1.6 mIU/L, p = 0.03) and Se-meth + Myo-I groups (4.7 ± 1.2 mIU/L, p < 0.001). At baseline, fT3 and fT4 levels were not significantly different between the three groups (Table 1).

After 6 months of supplementation, TSH did not change significantly in either the control or the Se-meth group (p = 0.50 and p = 0.45 *vs.* baseline, respectively), whereas a statistically significant TSH reduction was observed in the Se-meth + Myo-I group (p = 0.007 *vs.* baseline). Compared to baseline values, after 12 months of observation TSH increased significantly in untreated patients (mean TSH = 5.0 ± 2.6 mIU/L, p = 0.02). In contrast, a significant reduction of TSH was observed in both treated groups (Table 2, Fig. 1). Moreover, the TSH reduction was slightly more pronounced in the Se-meth + Myo-I group compared to the Se-meth group (38% *vs.* 31%, respectively). No changes were observed in the fT3 and fT4 values among the three groups (Table 2).

Along with the TSH increase in untreated patients during the 12 months of observation, the percentage of subclinical hypothyroidism also increased from 34.5% (at baseline) to 58.6% at 6 months (p = 0.07 *vs.* baseline) and 75.9% at 12 months (p = 0.002 *vs.* baseline). A similar, but not statistically significant, trend was observed in the Se-meth group, where the percentage of subclinical hypothyroidism was 51.7% at baseline, 58.6% at 6 months (p = 0.60 *vs.* baseline) and 75.9% at 12 months (p = 0.055 *vs.* baseline). Conversely, patients in the

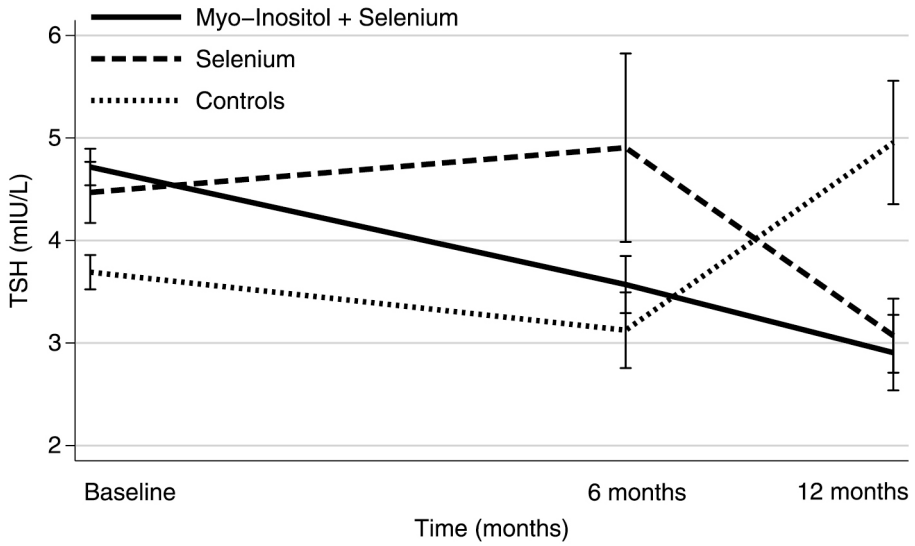

Fig. 1 Changes in thyroid-stimulating hormone (TSH) over time between selenomethionine + myo-inositol- and selenomethionine-treated groups with respect to the control group ($p < 0.001$).

Table 3 Variation in the percentage of subclinical hypothyroidism during the observation period in the three groups of patients

	n of patients	Baseline	6 months	*p* value	12 months	*p* value
Control	29	34.5%	58.6%	0.07	75.9%	0.002
Se-meth	29	51.7%	58.6%	0.60	75.9%	0.055
Se-meth + Myo-Inositol	43	81.4%	67.4%	0.14	79.1%	0.79

Se-meth + Myo-I group showed an initial reduction of the percentage of subclinical hypothyroidism from 81.4% at baseline to 67.4% ($p = 0.14$) after 6 months, but then an increase to the stable value of 79.1% at 12 months ($p = 0.79$ *vs.* baseline) (Table 3).

At baseline, 41 (40.6%) of the 101 patients had normal thyroid function. Among these 41 patients, the development of subclinical hypothyroid at 12 months was observed in 12/19 (63.2%) of the control group, 10/14 (71.4%) of the Se-meth group and 3/8 (37.5%) of the Se-meth + Myo-I group ($p = 0.28$).

At baseline, ultrasound examination in all patients revealed a variable degree of typical hypoechoic pattern in thyroid tissue. As expected, thyroid echogenicity decreased during follow-up in all patients; however, a lower reduction of thyroid echogenicity was observed in both treated groups (–8% in Se-meth group and –7.4% in Se-meth + Myo-I group) compared to the control (–11%), although this difference was not statistically significant.

Discussion

Several trials described the impact of Se-meth on inflammatory activity in thyroid-specific autoimmune disease, suggesting a possible therapeutic effect in reducing TPOAb levels in patients with HT. Moreover, meta-analyses on this topic raised several issues due to the heterogeneity among different studies, including the absence of specific clinical endpoints, the Se status in the examined population and the properties of the different Se formulations employed. In this respect, the previous reports indicate that Se-meth is better adsorbed than sodium selenite, as the absorption of selenite is approximately two-thirds that of Se-meth. However, no conclusive results from randomized controlled trials are available to date in HT. Hence, the current evidence does not support the use of Se supplementation in HT treatment [10, 24-26]. Se supplementation in patients with HT has been investigated also in combination with Myo-I. A prospective randomized double-blinded study demonstrated that combined therapy (Se-meth + Myo-I) results in greater reductions of TSH level (by 31%) and antibody titer (by 10%) than with Se-meth alone. This study concluded that only combined therapy (Se-meth + Myo-I) is able to significantly reduce TSH levels in HT patients [27]. A second study [28], performed by the same research group in a larger cohort of patients, showed a significant reduction in TSH level and significant decreases in both TgAb and TPOAb. Furthermore,

quality of life was significantly improved in all treated patients at the end of this study. Even fT3 and fT4 levels were significantly higher at the end of the study compared to baseline values. In our study, the differences between Se-meth and Se-meth + Myo-I are not so pronounced as the previous reports but are still present. Our results indicated an earlier serum TSH reduction in the group receiving combined supplementation (Se-meth + Myo-I) than with Se-meth alone. We did not investigate changes of quality of life, including the occurrence of female sexual dysfunction that has been documented in patients with thyroid disorders [29].

On the other hand, fT4 and fT3 levels did not significantly change in response to the different treatments and no data were analyzed on TPOAb levels because in our study we considered as endpoints the changes in both TSH level and thyroid ultrasound echogenicity evaluated over a period of 12 months.

The effect of Myo-I may be explained by its role in TSH receptor (TSH-R) signaling [19]. TSH-R is a G-protein receptor that couples to Gαs and Gαq proteins. Gαs activation activates the cAMP-protein kinase A signal transduction pathway and, along with adenylate cyclase, stimulates iodine uptake, thyroglobulin gene transcription, thyroid peroxidase activity and the sodium-myo-iodine symporter in thyrocytes [21-23]. Higher TSH levels bind to the high-affinity binding site on both protomers of the TSH-R homodimer, thereby activating Gs and Gq/11 to increase both cAMP and IP1 (inositol monophosphate) production [30]. Derangement of the inositol-dependent TSH signaling pathway may contribute to hypothyroidism development, hence it is possible to hypothesize that Myo-I supplementation may enhance thyrocyte sensitivity to TSH stimulation in terms of IP1 production, thereby preventing thyroid insufficiency to a certain degree [31]. We are aware that in our cohort the rate of developing hypothyroidism is higher than previously reported in the general population [32]. However, in our series the higher prevalence of subclinical hypothyroidism may be influenced by several factors, including adult age, antibody titer, ultrasound pattern and TSH in the upper range [33, 34]. As our study is observational and performed in an Endocrinology Unit, these patients are not representative of the general population but are selected for thyroid disease.

In conclusion, our data indicate that combined Se-meth + Myo-I is helpful in restoring and maintaining the euthyroid state in patients with HT, with or without subclinical hypothyroidism, and that this effect occurs earlier than with Se supplementation alone. However, HT remains a complex and ever-expanding disease of unknown pathogenesis that awaits prevention and planning more prospective studies to investigate novel forms of treatment.

Disclosure Statement

None of the authors have any potential conflicts of interest associated with this research.

References

1. Weetman AP (2009) The genetics of autoimmune thyroid disease. *Horm Metab Res* 41: 421–425.
2. Duntas LH (2008) Environmental factors and autoimmune thyroiditis. *Nat Clin Pract Endocrinol Metab* 4: 454–460.
3. Ajjan RA, Weetman AP (2015) The pathogenesis of Hashimoto's thyroiditis: further developments in our understanding. *Horm Metab Res* 47: 702–710.
4. Chakrabarti SK, Ghosh S, Banerjee S, Mukherjee S, Chowdhury S (2016) Oxidative stress in hypothyroid patients and the role of antioxidant supplementation. *Indian J Endocrinol Metab* 20: 674–678.
5. Ates I, Yilmaz FM, Altay M, Yilmaz N, Berker D, *et al.* (2015) The relationship between oxidative stress and autoimmunity in Hashimoto's thyroiditis. *Eur J Endocrinol* 173: 791–799.
6. Ruggeri RM, Vicchio TM, Cristani M, Certo R, Caccamo D, *et al.* (2016) Oxidative stress and advanced glycation end products in Hashimoto's thyroiditis. *Thyroid* 26: 504–511.
7. Di Dalmazi G, Hirshberg J, Lyle D, Freij JB, Caturegli P (2016) Reactive oxygen species in organ-specific autoimmunity. *Auto Immun Highlights* 7: 11.
8. Ruggeri RM, Cristani M, Vicchio TM, Alibrandi A, Giovinazzo S, *et al.* (2019) Increased serum interleukin-37 (IL-37) levels correlate with oxidative stress parameters in Hashimoto's thyroiditis. *J Endocrinol Invest* 42: 199–205.
9. Nacamulli D, Mian C, Petricca D, Lazzarotto F, Barollo S, *et al.* (2010) Influence of physiological dietary selenium supplementation on the natural course of autoimmune thyroiditis. *Clin Endocrinol (Oxf)* 73: 535–539.
10. Esposito D, Rotondi M, Accardo G, Vallone G, Conzo G, *et al.* (2017) Influence of short-term selenium supplementation on the natural course of Hashimoto's thyroiditis: clinical results of a blinded placebo-controlled randomized prospective trial. *J Endocrinol Invest* 40: 83–89.
11. Köhrle J (2015) Selenium and the thyroid. *Curr Opin Endocrinol Diabetes Obes* 22: 392–401.
12. Ruggeri RM, D'Ascola A, Vicchio TM, Campo S, Giani F, *et al.* (2020) Selenium exerts protective effects against oxidative stress and cell damage in human thyrocytes and

fibroblasts. *Endocrine* 68: 151–162.
13. Bulow Pedersen I, Knudsen N, Carle A, Schomburg L, Kohrle J, *et al.* (2013) Serum selenium is low in newly diagnosed Graves' disease: a population-based study. *Clin Endocrinol (Oxf)* 79: 584–590.
14. Wu Q, Rayman MP, Lv H, Schomburg L, Cui B, *et al.* (2015) Low population selenium status is associated with increased prevalence of thyroid disease. *J Clin Endocrinol Metab* 100: 4037–4047.
15. Pirola I, Rotondi M, Cristiano A, Maffezzoni F, Pasquali D, *et al.* (2020) Selenium supplementation in patients with subclinical hypothyroidism affected by autoimmune thyroiditis: results of the SETI study. *Endocrinol Diabetes Nutr* 67: 28–35.
16. Di Paolo G, De Camilli P (2006) Phosphoinositides in cell regulation and membrane dynamics. *Nature* 443: 651–657.
17. Halet G, Tunwell R, Balla T, Swann K, Carroll J (2002) The dynamics of plasma membrane PtdIns(4,5)P(2) at fertilization of mouse eggs. *J Cell Sci* 115: 2139–2149.
18. Papaleo E, Unfer V, Baillargeon JP, Chiu TT (2009) Contribution of myo-inositol to reproduction. *Eur J Obstet Gynecol Reprod Biol* 147: 120–123.
19. Benvenga S, Antonelli A (2016) Inositol(s) in thyroid function, growth and autoimmunity. *Rev Endocr Metab Disord* 17: 471–484.
20. Kutateladze TG (2010) Translation of the phosphoinositide code by PI effectors. *Nat Chem Biol* 6: 507–513.
21. Ohye H, Sugawara M (2010) Dual oxidase, hydrogen peroxide and thyroid diseases. *Exp Biol Med (Maywood)* 235: 424–433.
22. Grasberger H, Van Sande J, Hag-Dahood Mahameed A, Tenenbaum-Rakover Y, Refetoff S (2007) A familial thyrotropin (TSH) receptor mutation provides *in vivo* evidence that the inositol phosphates/Ca2+ cascade mediates TSH action on thyroid hormone synthesis. *J Clin Endocrinol Metab* 92: 2816–2820.
23. Parma J, Van Sande J, Swillens S, Tonacchera M, Dumont J, *et al.* (1995) Somatic mutations causing constitutive activity of the thyrotropin receptor are the major cause of hyperfunctioning thyroid adenomas: identification of additional mutations activating both the cyclic adenosine 3',5'-monophosphate and inositol phosphate-Ca2+ cascades. *Mol Endocrinol* 9: 725–733.
24. Winther KH, Wichman JE, Bonnema SJ, Hegedus L (2017) Insufficient documentation for clinical efficacy of selenium supplementation in chronic autoimmune thyroiditis, based on a systematic review and meta-analysis. *Endocrine* 55: 376–385.
25. Toulis KA, Anastasilakis AD, Tzellos TG, Goulis DG, Kouvelas D (2010) Selenium supplementation in the treatment of Hashimoto's thyroiditis: a systematic review and a meta-analysis. *Thyroid* 20: 1163–1173.
26. Wichman J, Winther KH, Bonnema SJ, Hegedus L (2016) Selenium supplementation significantly reduces thyroid autoantibody levels in patients with chronic autoimmune thyroiditis: a systematic review and meta-analysis. *Thyroid* 26: 1681–1692.
27. Nordio M, Pajalich R (2013) Combined treatment with Myo-inositol and selenium ensures euthyroidism in subclinical hypothyroidism patients with autoimmune thyroiditis. *J Thyroid Res* 2013: 424163.
28. Nordio M, Basciani S (2017) Treatment with Myo-inositol and selenium ensures euthyroidism in patients with autoimmune thyroiditis. *Int J Endocrinol* 2017: 2549491.
29. Pasquali D, Maiorino MI, Renzullo A, Bellastella G, Accardo G, *et al.* (2013) Female sexual dysfunction in women with thyroid disorders. *J Endocrinol Invest* 36: 729–733.
30. Allen MD, Neumann S, Gershengorn MC (2011) Occupancy of both sites on the thyrotropin (TSH) receptor dimer is necessary for phosphoinositide signaling. *FASEB J* 25: 3687–3694.
31. Grafton G, Baxter MA, Sheppard MC, Eggo MC (1995) Regulation of myo-inositol transport during the growth and differentiation of thyrocytes: a link with thyroid-stimulating hormone-induced phospholipase A2 activity. *Biochem J* 309: 667–675.
32. Vanderpump MPJ, Tunbrldge WMG, French JM, Appleton D, Bates D, *et al.* (1995) The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham survey. *Clin Endocrinol (Oxf)* 43: 55–68.
33. Ragusa F, Fallahi P, Elia G, Gonnella D, Paparo SR, *et al.* (2019) Hashimotos' thyroiditis: epidemiology, pathogenesis, clinic and therapy. *Best Pract Res Clin Endocrinol Metab* 33: 101367.
34. Redford C, Vaidya B (2017) Subclinical hypothyroidism: should we treat? *Post Reprod Health* 23: 55–62.