European Thyroid Journal (2024) **13** e240038
https://doi.org/10.1530/ETJ-24-0038

Received 11 February 2024
Accepted 20 February 2024
Available online 20 February 2024
Version of Record published 8 March 2024

COMMENTARY

The intermediary between the brain and the immune system is likely to be the thyroid

Leonidas Duntas

Evgenideion Hospital, Unit of Endocrinology, Diabetes and Metabolism, National and Kapodeistrian University of Athens, Greece

Correspondence should be addressed to L Duntas: lduntas@eugenideion.uoa.gr or leonidas@duntas.gr

The essential trace element selenium (Se) is present in the form of selenocysteine in at least 25 selenoenzymes, these including the three deiodinases (DIOs) that regulate the monodeiodination of thyroxine (T4) to 3,5,3'-triiodothyronine (T3) and the glutathione peroxidases (GPXs), all of which act as the guards of bodily homeostasis (1). Se is thus indispensable for optimal thyroid function and for human health (2). Given that low Se has been associated with several thyroid diseases a Se-rich diet is recommended, particularly in regions with low-Se soils (3). The thyroid gland has the highest Se content as compared to all other tissues, with the brain being, in cases of severe Se deficiency, the last organ to be depleted. The latter indicates that, in conditions of severe Se deficiency, Se levels in the brain tend not to be influenced by dietary intake since, according to the biological adaptation theory (4), Se may be transferred to the brain from less critical organs. This has been suggested in a few reports showing, in the context of a low-Se diet and/or of extreme stress, increased affinity of the brain for selenoprotein P (SELENOP), the Se transport protein, as well as for high selenoprotein W (SELENOW) concentrations in contrast to reduced levels in all other tissues (5). In rats fed a low-Se diet, thioredoxin reductase activity was decreased in all tissues but not in the brain (6). Hashimoto's thyroiditis (HT), the most common thyroid disease and a frequent cause of hypothyroidism, has been strongly associated with clinical decline and impaired quality of life (QoL) (7). Apart from some small cross-sectional studies, the role of Se in brain function and in the modulation of psychological states via large cohort studies has largely not been studied.

In a recent issue of the *European Thyroid Journal*, Larsen *et al.* (8) report on a multicenter double-blinded randomized clinical trial (CATALYST) whose aim was to investigate the effects of Se supplementation on QoL, thyroid hormone concentrations, and titers of autoantibodies in patients with chronic autoimmune thyroiditis (CAIT). The authors are to be congratulated on the excellent planning and conduction of this randomized controlled trial (RCT), which has provided several important findings and increased our knowledge concerning Se supplementation in CAIT.

The study included 412 patients, with serum thyroid peroxidase antibody (TPOAb) levels ≥100 IU/mL, who randomly received Se 200 μg as yeast or placebo added to levothyroxine (LT4) treatment over a period of 12 months. Se is naturally accumulated by yeast, while selenomethionine, organic Se, is the basic form of selenium in yeast cells. QoL was assessed by the Thyroid-related Patient-Reported-Outcome-39 questionnaire (ThyPRO-39). Although QoL improved during the trial, no difference in any scale of the ThyPRO-39 was observed between the Se group and the placebo group after 12 months of intervention. In contrast, the placebo group exhibited better QoL as compared to the Se group. The fact that QoL was not significantly different among the study groups points to a positive effect of LT4 treatment not related to Se intake. By decreasing thyroid-stimulating hormone (TSH) level, LT4 may open the way to stimulating Se's regulation of intracellular levels of hydrogen peroxide (H_2O_2). Basal Se levels were borderline low, a state that could possibly favor a high degree of effectiveness of administered Se through its boosting of the function of mainly SELENOP, GPX1, and thioredoxin reductase (TRXR).

Se can additionally activate selenoprotein S (SELENOS) and enhance its anti-inflammatory performance, leading to a decrease in proinflammatory chemokines and cytokines, such as IFN-γ and TNF-α, from the activated T cells (9).

Se possibly acts alone or in synergy with other nutrients to beneficially influence brain function and the nervous system, thereby improving mood and QoL (4), although this was not shown in this study. Nevertheless, it should be borne in mind that certain lifestyle factors, such as smoking and deficiencies of folate, vitamin B12, iron, and zinc as well as of Se, which tend to be

Published by Bioscientifica Ltd.
https://etj.bioscientifica.com

European Thyroid Journal (2024) **13** e240038
https://doi.org/10.1530/ETJ-24-0038

more common among patients with mood swing and depression, can also lead to poor QoL (10).

TPOAb titers were found to be lower in the Se than in the placebo group, but Se did not affect LT4 dosage or FT3/FT4 ratio nor did the duration of disease modify any parameter. The statistically significant reduction ($P < 0.016$) of the pathognomonic TPOAb titers in this study confirms similar results reported in other papers from various parts of the world with different soil Se concentrations (11). Of note, the decrease in TPOAb is thought to have been more pronounced in patients with low Se level at baseline.

The considerable diminishment of TPOAbs indicates a possible modulatory effect on oxidative stress, likely leading to co-regulation of TPOAb generation. It is an extremely important finding demonstrating that Se provides health benefits to patients with inflammatory diseases, such as CAIT, who are exposed to high oxidative stress.

As stated by the authors, however, it remains questionable whether CAIT patients on LT4 treatment should be routinely Se supplemented as the benefit is not clear. Clearly, large, RCTs need to be conducted in patients not on LT4 treatment to establish whether Se administration attenuates the inflammatory process. As a rule, physicians need to advise patients with autoimmune thyroiditis (AIT) and other autoimmune diseases as well as with infections as to the necessity for adequate dietary Se intake. Regarding pregnancy since low serum Se levels have been found in women with preeclampsia, it has been hypothesized that low maternal Se status during early gestation may be an indicator of preterm birth (12). In pregnant women with CAIT, Se intake decreased TPOAb titers only in postpartum thyroiditis (13). However, due to the lack of measurable biomarkers to assess the effect of Se supplementation, current studies do not currently recommend the use of Se in pregnancy.

In conclusion, the results of the CATALYST not only add to the rich Se databank regarding treatment of CAIT, but they also incentivize further studies designed to explore Se's effect on other immune parameters while also replying to the question of whether long-term Se supplementation can reverse the progression of disease in early-stage autoimmune thyroiditis.

It has long been known that the thyroid is essential for the maintenance of overall body homeostasis, in which 'selenostasis' plays an essential role. Se being fundamental for selenoenzyme activity is likely to be a crucial intermediary between the thyroid and the immune system.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of this commentary.

Funding

This work did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

References

1 Schomburg L. Selenium, selenoproteins and the thyroid gland: interactions in health and disease. *Nature Reviews. Endocrinology* 2011 **8** 160–171. (https://doi.org/10.1038/nrendo.2011.174)

2 Duntas LH & Benvenga S. Selenium: an element for life. *Endocrine* 2015 **48** 756–775. (https://doi.org/10.1007/s12020-014-0477-6)

3 Wu Q, Rayman MP, Lv H, Schomburg L, Cui B, Gao C, Chen P, Zhuang G, Zhang Z, Peng X, *et al.* J Low population selenium status is associated with increased prevalence of thyroid disease. *Journal of Clinical Endocrinology and Metabolism* 2015 **100** 4037–4047. (https://doi.org/10.1210/jc.2015-2222)

4 Benton D. Selenium intake, mood and other aspects of psychological functioning. *Nutritional Neuroscience* 2002 **5** 363–374. (https://doi.org/10.1080/1028415021000055925)

5 Raman AV, Pitts MW, Seyedali A, Hashimoto AC, Bellinger FP & Berry MJ. Selenoprotein W expression and regulation in mouse brain and neurons. *Brain and Behavior* 2013 **3** 562–574. (https://doi.org/10.1002/brb3.159)

6 Hill KE, McCollum GW, Boeglin ME & Burk RF. Thioredoxin reductase activity is decreased by selenium deficiency. *Biochemical and Biophysical Research Communications* 1997 **234** 293–295. (https://doi.org/10.1006/bbrc.1997.6618)

7 Rigó A, Malkov K, Szabó A, Bognár VK & Urbán R. Adaptation and validation of the Hungarian version of Thyroid-Related Patient-Reported Outcome-39 (ThyPro-39) questionnaire: testing factor structure, known-group validity with the comparison of quality of life in Hashimoto's thyroiditis and Graves' disease. *Journal of Patient-Reported Outcomes* 2023 **7** 60. (https://doi.org/10.1186/s41687-023-00606-7)

8 Larsen C, Winther KH, Cramon PK, Rasmussen ÅK, Feldt-Rasmusssen U, Knudsen NJ, Bjorner JB, Schomburg L, Demircan K, Chillon TS, *et al.* Selenium supplementation and placebo are equally effective in improving quality of life in patients with hypothyroidism. *European Thyroid Journal* 2024 **13** e230175. (https://doi.org/10.1530/ETJ-23-0175)

9 Ralli M, Angeletti D, Fiore M, D'Aguanno V, Lambiase A, Artico M, de Vincentiis M & Greco A. Hashimoto's thyroiditis: an update on pathogenic mechanisms, diagnostic protocols, therapeutic strategies, and potential malignant transformation. *Autoimmunity Reviews* 2020 **19**. (https://doi.org/10.1016/j.autrev.2020.102649)

10 Bodnar LM & Wisner KL. Nutrition and depression: implications for improving mental health among childbearing-aged women. *Biological Psychiatry* 2005 **58** 679–685. (https://doi.org/10.1016/j.biopsych.2005.05.009)

11 Köhrle J. Selenium in endocrinology—selenoprotein-related diseases, population studies, and epidemiological evidence. *Endocrinology* 2021 **162** bqaa228. (https://doi.org/10.1210/endocr/bqaa228)

12 Silva I, Bracchi I & Keating E. The association between selenium levels and hypertensive disorders of pregnancy: a systematic review of the literature. *British Journal of Nutrition* 2023 **130** 651–665. (https://doi.org/10.1017/S0007114522003671)

13 Negro R, Greco G, Mangieri T, Pezzarossa A, Dazzi D & Hassan H. The influence of selenium supplementation on postpartum thyroid status in pregnant women with thyroid peroxidase autoantibodies. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 1263–1268. (https://doi.org/10.1210/jc.2006-1821)