

# Selenium in the Treatment of Thyroid Diseases: An Element in Search of the Relevant Indications?

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Selenium (Se) deficiency has been associated with a number of diseases [1], including thyroid diseases such as goiter, hypothyroidism, and autoimmune thyroiditis [2]. Se is an essential micronutrient that is incorporated into biologically active selenoproteins as the amino acid selenocysteine [3]. Among the most important are the iodothyronine deiodinases that are directly involved in thyroid hormone metabolism [3]. In healthy euthyroid individuals with marginal Se deficiency, Se supplementation has only minute, and clinically insignificant, effects on thyroid function [4]. However, Se levels have been found to be inversely correlated with thyroid size [5]. Furthermore, Se supplementation has been shown to decrease thyroid peroxidase antibodies (TPOAb) in autoimmune thyroiditis [6, 7]. Accepting that chronic autoimmune thyroid diseases are multifactorial diseases, and that environmental triggers are key components in their etiology [8], it is no surprise that Se deficiency has come into focus. It could be speculated that the above constitutes, in part, the inspiration for the massive use of Se, as revealed by an Italian questionnaire study focusing on the therapeutic use of Se in some well-characterized clinical situations [9]. Despite the inherent reservations in using such a questionnaire study, the survey seems to show that a number of specialists have adopted routine Se therapy in disease entities where the evidence is, to put it mildly, questionable.

From a web-based survey of 1,888 Associazione Medici Endocrinologi (AME) members, 778 (41%) provided

responses to all 23 questions. The vast majority of specialists, of whom >90% were endocrinologists, had used Se, and around 25% of them often or always. Let's look into the thyroid phenotypes investigated [9].

## Chronic Autoimmune Thyroiditis in Euthyroid Individuals

While 3 out of 4 respondents (72%) thought that there was evidence supporting Se use, 79% prescribed it sometimes, often, or always. Half of those who prescribed Se (49%) did it prophylactically to prevent serum TSH increase (49%) or to decrease thyroid antibody levels (39%). However, trials among individuals not receiving levothyroxine (LT<sub>4</sub>) have not reported these effects [10]. 59% of the respondents advocated use of >100 µg Se daily, without having knowledge of the pretherapy Se levels. Importantly, the scientific societies do not recommend Se supplementation for this indication.

## Hypothyroidism, with or without TPOAb

In case of subclinical hypothyroidism and positive TPOAb, 2 out of 3 respondents would (sometimes, often, or always) suggest use of Se. In case of negative TPOAb this propensity would decrease to 1 in 3 respondents. The

latter figures were also valid for hypothyroid individuals already on LT<sub>4</sub>. Systematic reviews and meta-analyses have shown that TPOAb levels, which we consider a surrogate activity marker, do decrease [6, 7] in patients receiving LT<sub>4</sub> treatment. However, this practice is not endorsed by any specialist society.

### **Chronic Autoimmune Thyroiditis and Pregnancy in Euthyroid Individuals**

Of the respondents who were proponents of Se use (40%), their aim was to (in descending order): prevent development of hypothyroidism (40%), reduce TPOAb levels (31%), or prevent postpartum thyroiditis (25%). Of the respondents who would suggest giving >100 µg Se daily (70%), 10% would use a dose >200 µg daily. The latter could have deleterious effects when pretherapy Se levels are not known. Again, it is important to recognize that guidelines do not support this practice [11].

### **Graves' Ophthalmopathy**

Given a case of a 42-year-old female with Graves' disease and no ophthalmopathy, 20% of the respondents would suggest adding Se to antithyroid drug therapy. In case she developed mild GO, 1 in 4 respondents would add Se, and 50% of respondents would continue with Se also after remission of her Graves' hyperthyroidism. Based on a single study by Marcocci et al. [12], which showed significantly improved quality of life, reduced eye involvement, and improved clinical activity score in the Se group, the European Thyroid Association suggests a 6-month trial of Se in patients with mild GO [13]. While some have found lower Se levels in Graves' hyperthyroidism with GO compared to without GO, others have not found an association between Se status and GO severity or activity [14]. Confirmation and clarification of potential mechanisms for the effect in GO are therefore eagerly awaited.

We are probably not the only ones confronted with the statement: 'You may be right about a questionable efficacy, but Se is then at least harmless.' However, this is incorrect. There is much to suggest a U-shaped link with Se status; whereas supplementation may benefit people with low Se status, those with adequate-to-high status might be affected adversely and should not take supplements [1]. This, as a minimum, requires that basal levels in a given individual or population is known before ad-

vocating Se supplementation. Recent studies have increasingly been focused on the potential side effects of Se, also when levels are within the ones reached by Se supplementation as low as 100–200 µg [15].

The current evidence of a clinically meaningful, cost-effective, durable, and safe implementation of Se supplementation is very sparse. Current use, at least in Italy, is not based on evidence and may well be harmful. The article by Negro et al. [9] is timely, important, and frightening. It teaches us an important message. Not implementing evidence-based medicine, needless to say, is unacceptable. However, implementing therapy, which potentially may turn out to be harmful, and for which there is no evidence is, in our view, much worse. Ongoing prospective, randomized, long-term studies, in both Graves' disease [16] and chronic autoimmune thyroiditis [17], will provide some answers concerning the value of supplemental Se to antithyroid drugs and LT<sub>4</sub>, respectively. Until the data from these studies have been properly analyzed, and to avoid the risks of medical reversal [18], use of Se supplementation should be restricted to indications for which there is evidence, namely the correction of Se deficiency [1]. Also, should indications for Se supplementation emerge, much work remains in order to define subpopulations who will benefit the most, the type and dose of Se preparation, and length of therapy.

From the data provided by Negro et al. [9], and given that they are truly representative of what Italian patients are advised to take, a number of pertinent questions arise. How have specialists in thyroid diseases come to these recommendations? Who has the responsibility for implementing therapy that is not endorsed by any relevant authority? Who has the responsibility to reverse inadvertent practice patterns? In our view, while Italian physicians and other authorities disseminate recommendations based on evidence, the present questionnaire should be followed by an in-depth global investigation of current practice patterns. If the present Italian data are representative of a widespread and mostly inappropriate use of Se, all our thyroid societies and their members have an obligation to correct this and make it clear what the current recommendations are when facing our patients.

### **Disclosure Statement**

The authors report no conflicts of interest.

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