Selenium and iodine: essential trace elements for the thyroid

Kristina Lossow, Tanja Schwerdtle, Anna Kipp

Abstract

Selenium and iodine are essential trace elements that work together to ensure that the thyroid functions optimally. A deficiency in one or both of these elements leads to fluctuations in thyroid hormone production, which have far-reaching consequences in terms of metabolic processes, neurological development, and disease. Iodine and selenium supply also play an important role in autoimmune diseases of the thyroid. Both the total selenium concentration in the serum and the concentration of selenoprotein P are suitable biomarkers for determining selenium status. Iodine concentration in the urine is the most commonly used method of determining iodine status. In order to improve assessment of supply status for these two essential trace elements plus an additional four, the TraceAge research group is identifying age- and sex-specific trace element profiles as well as new functional biomarkers for the individual trace elements. In addition, the research group will investigate interactions with other trace elements in more detail.

Keywords: selenium, iodine, thyroid gland, autoimmune diseases of the thyroid, selenoproteins, TraceAge

Introduction

Selenium and iodine are among the essential trace elements. Ensuring a comprehensive, adequate supply of these elements remains a challenge across the globe to this day, despite extensive efforts (such as the iodination of table salt). Factors that play a decisive role in the supply of these nutrients include not only soil conditions and traditional foods, but also the increasing spread of dietary trends, particularly in Europe.

A recently published study recorded the nutrient intakes of 32,423 study participants (EPIC-Oxford cohort) using diet questionnaires adapted to the participants' eating habits [1]. Both, this study and similar studies conducted in Germany showed that vegetarians had a lower selenium intake than people who consume meat and fish. Vegans are particularly at risk of inadequate iodine intake (exception: those who consume seaweed) [2]. The same conclusion was drawn by studies that used biomarkers to determine the status of both of these trace elements [3, 4].

In addition to diet, another cause of inadequate supply of trace elements are diseases such as inflammatory bowel disease or renal insufficiency, which can cause changes in the uptake or excretion of trace elements, respectively.

Selenium

The selenium content of plant-derived foods varies depending on the soil in which they grow. As a consequence, European plants are less rich in selenium than identical products from North America. Plant-derived foods that are relatively rich in selenium include Brazil nuts, legumes, cruciferous vegetables, and bulb vegetables. In Europe, adequate selenium intake is primarily achieved through the consumption of animal-derived foods such as meat, eggs, or fish. The selenium content of

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these products is ensured in EU member states through the widespread practice of feeding animals (especially pigs and poultry) with selenium-rich mineral mixtures. The recommended daily selenium intake for adults is 60–70 µg (◆ Table 1).
Ingested selenium compounds are metabolized in the body, resulting in the incorporation of selenocysteine into selenoproteins which mediate most selenium effects. The selenoproteins include enzymes such as glutathione peroxidases (GPx), which catalyze the reduction of peroxides, thioredoxin reductases (TR), which maintain the body's oxidation-reduction system, and deiodinases (DIO), which activate or deactivate the thyroid hormones.

Looking at the world as a whole, Germany has intermediate levels of selenium supply. Severe selenium deficiency-related diseases such as Keshan disease and Kashin-Beck disease (◆ Box), which have been described in China and in African countries, do not occur here.

Iodine

Iodine is an elemental component of the thyroid hormones triiodothyronine (T_3) and tetraiodothyronine (T_4). These hormones regulate growth and development, body temperature, and the metabolic processes for carbohydrates, proteins, and fats in the human body. Both plant and animal products generally contain only low amounts of iodine. The iodine content of these products varies depending on the soil and water in the region and depending on production processes (such as the use of plant fertilizer containing iodine, iodine-enriched animal feed, or table salt enriched with iodine). By contrast, seaweed, saltwater fish, and seafood naturally contain high levels of iodine.
According to the estimation of the World Health Organization (WHO), Germany has had an optimal intake of iodine since the introduction of iodized salt. However, this evaluation is in large part based on an erroneous iodine analysis by one of the three German laboratories where study-based iodine analyses were regularly performed on urine samples. The analytical error, which resulted in an iodine concentration that was 36% higher than the actual value, has now been identified [11] and corrected. This also explains why the two representative studies by the Robert Koch Institute – DEGS (German Health Interview and Examination Survey for Adults, 6,978 participants, 2008–2011) and KiGGS (German Health Interview and Examination for Children and Adolescents, > 14,000 participants, 2003–2006) – recorded lower iodine excretion values, resulting in the suggestion that about 30% of the subjects examined had an inadequate iodine supply [12, 13].

	Selenium [µg]	Iodine [µg]
Infants	10–15	40–80
Children (1–10 years)	15–30	100–140
Adolescents	45–70	180–200
Adults	60–70	200
Senior citizens	60–70	180
Pregnant women	60	230
Breastfeeding women	75	260
Upper limit (EFSA)	300	600

Tab. 1: **Estimated values for daily intake of selenium and recommended intakes of iodine from the German Nutrition Society (*Deutsche Gesellschaft für Ernährung* [DGE]) [5] and upper limits from the European Food Safety Authority (EFSA) [6, 7] for adults (including breastfeeding women and pregnant women, non-age-specific)**

Keshan disease

Keshan disease is a disease of the heart muscle (cardiomyopathy) that mainly affects growing children and pregnant women. It is thought to be due to an interaction between selenium deficiency and Coxsackie virus infection. Selenium supplementation significantly reduces the occurrence of the disease.

Kashin-Beck disease

Kashin-Beck disease is characterized by degenerative joint changes. It mainly occurs in children and manifests as deformation of hand and foot joints, inflammation of the nerves, internal bleeding, and stunting. Possible triggers of the disease that have been suggested include contamination of food with mycotoxins, selenium deficiency, and a high level of fulvic acid in drinking water.
Studies focussing on genetic aspects also came to the conclusion that in affected persons, the genes associated with apoptosis and selenium were expressed differently in the articular cartilage [8]. There are discussions about whether iodine deficiency may also be a cause alongside selenium deficiency. However, there is no direct evidence that iodine deficiency alone is a risk factor for Kashin-Beck disease. Selenium supplementation does indeed have a positive effect on the occurrence of the disease; however, it cannot prevent it completely [9, 10].

The daily intake recommended by the German Nutrition Society is 180–200 µg of iodine (◆ Table 1). During pregnancy and breastfeeding, intake should be around 10–20% higher. In the early stages of pregnancy in particular, a sufficient supply of iodine is essential for the neural development and maturation of the fetus. Therefore, the administration of iodized oil, particularly in the first and second trimester, could reduce the prevalence of neurological damage and improve child development [14]. Optimal iodine intake is also necessary for the critical phases of brain development later on. For instance, a randomized, double-blind, placebo-controlled study in school pupils in New Zealand aged 10–13 years showed that even a mild iodine deficiency hinders children in reaching their full intellectual potential [15].
Long-term undersupply leads to the exhaustion of iodine reserves, which in turn leads to reduced production of thyroid hormones (hypothyroidism). The consequence of this is tiredness, weight gain, lack of drive, and poor concentration. The thyroid reacts with hypertrophic and hyperplastic changes of the follicular epithelium (struma), often associated with the development of autonomous regions. If the iodine deficiency is suddenly resolved following a chronic deficiency, this can lead to excessive production of thyroid hormones in the autonomous nodules that is beyond the control of feedback regulation (◆ Figure 1), particularly in older adults with a nodular struma. The results of this include an increased metabolism together with weight loss, agitation, and muscle weakness. These long-term effects of undersupply of iodine are usually transient and they normally disappear after 1–10 years of adequate supply of iodine [16, 17].

How the interaction between iodine and selenium affects thyroid function

The thyroid has the highest tissue concentrations of selenium and iodine in the human body. The relevance of selenium for the proper function of the thyroid gland and the formation of thyroid hormones became clear in the 1980s when, for the first time, an increased T_4 concentration in the serum was observed in selenium-deficient animals at the same time as a T_3 deficiency [18].
The interaction of both trace elements in the thyroid gland is due to the fact that the selenoproteins of the DIO family are involved in the activation and inactivation of thyroid hormones. These are initially formed by stepwise iodination of the thyroglobulin scaffold by thyroperoxidase. If required, the thyroid hormones T_4 and (to a much lesser extent) T_3 are released through the breakdown of thyroglobulin. They then reach the target organs via the bloodstream. There, and in the thyroid gland itself, DIOs catalyze the formation of T_3 from precursor T_4, with T_3 being ten times more active (◆ Figure 1).
However, the half-life of the active T_3 is much shorter than that of T_4, so new thyroid hormones have to be produced continuously. DIO type III is responsible for the breakdown of T_4 and T_3. The iodination of thyroglobulin in the thyroid gland requires high concentrations of hydrogen peroxide, which leaves the thyroid gland vulnerable to oxidative cell damage. Along with other antioxidant enzymes, the selenoprotein families GPx and TR contribute to the breakdown of reactive compounds.
As selenium deficiency progresses, the activity of selenium-dependent DIOs is reduced, which in turn reduces both activation and breakdown of thyroid hormones. When an iodine deficiency and a selenium deficiency occur at the same time, this effect is getting stronger. Due to decreasing T_4 and T_3 concentrations and the absence of negative feedback regulation on the hypothalamic-pituitary axis, the thyroid gland is subject to constant stimulation. This leads to an excess of hydrogen peroxide in the thyroid follicles, which can be more difficult to neutralize than under conditions of a pure iodine deficiency due to a lack of selenoproteins.
Whereas iodine deficiency leads to enlargement (hyperplasia, hypertrophy) of the thyroid tissue, long-term deficiency in both trace elements results in oxidative tissue damage, which in turn leads to thyroid atrophy [19]. However, a mouse model with a complete loss of all selenoproteins in the thyroid demonstrated that the antioxidative protection of the thyroid gland does not appear to be limited to selenoproteins [20]. Nevertheless, the function of DIOs cannot be compensated for by other selenium-independent enzymes. Rare diseases caused by genetic defects in selenoprotein synthesis demonstrate this fact. A loss of expression of selenoproteins or greatly reduced expression in humans mainly affects thyroid hormone metabolism and leads to numbness and changes in bone metabolism – effects that are also described in association with iodine deficiency [21]. In order for the organ to function optimally, a sufficient supply of both trace elements is required.

Autoimmune diseases of the thyroid

The thyroid is the organ most often affected by autoimmune diseases. There are two main types of autoimmune disease of the thyroid.
Hashimoto's thyroiditis is caused by chronic inflammation of the thyroid, which eventually leads to increasing destruction of the tissue. The concomitant effects include a decrease in thyroid hormones, which cause

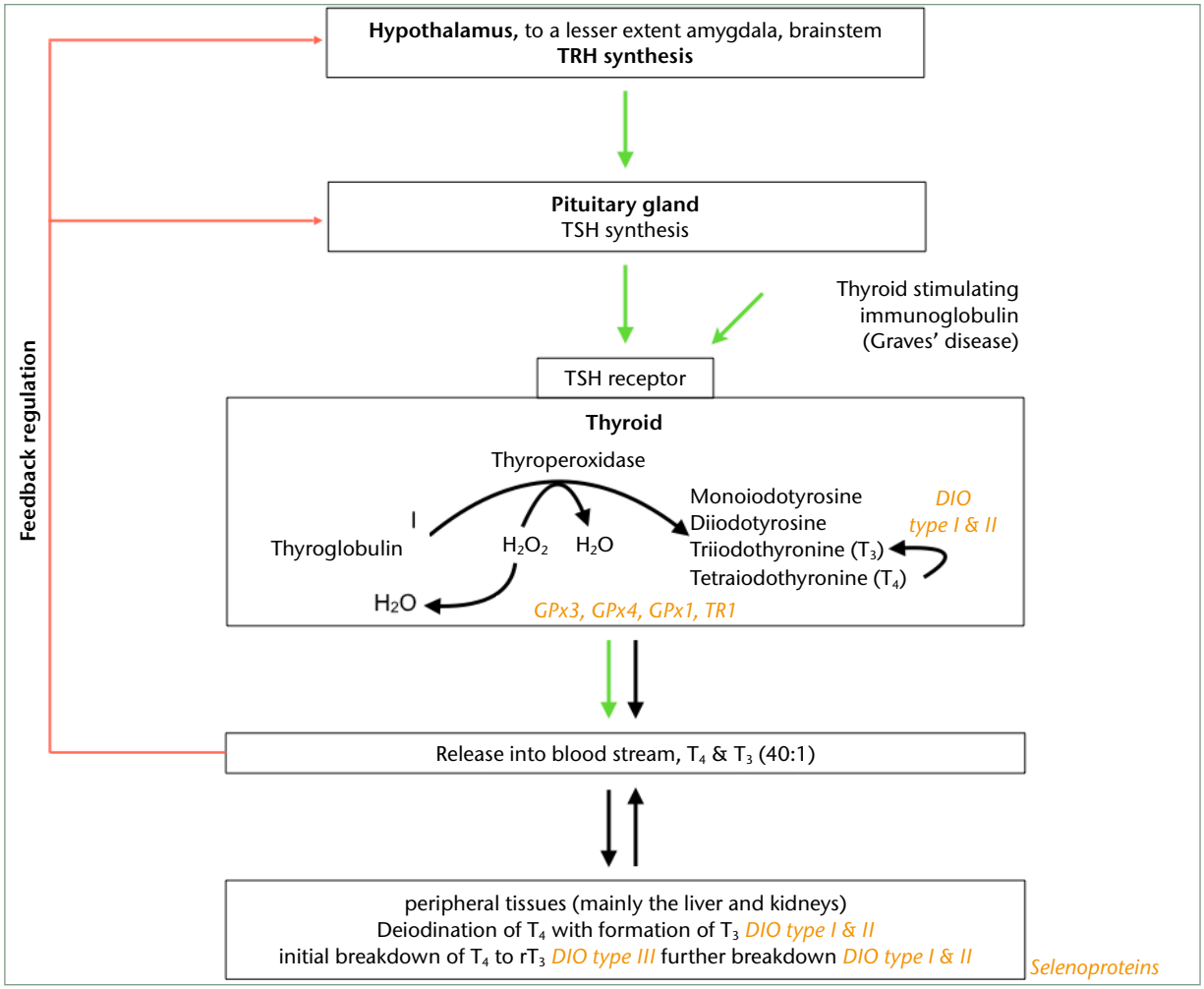

Fig. 1: **Regulation of thyroid hormone production**
DIO = deiodinase; GPx = glutathione peroxidase; H_2O = water; H_2O_2 = hydrogen peroxide; TR = thioredoxin reductases; rT_3 = reverse T_3; I = iodine; TRH = thyrotropin releasing hormone; TSH = thyroid stimulating hormone

symptoms such as exhaustion, weight gain, and muscle pain. It is estimated that 7–10% of the European population is affected, with women being diagnosed as positive twice as often as men [22]. In this disease, the body forms antibodies against thyroperoxidase or thyroglobulin.

In the case of Graves' disease (Morbus Basedow), the body's own defenses target the TSH receptor on thyroid cells (◆ Figure 1). This causes uncontrolled, high production of thyroid hormones. Clinical signs include struma, tachycardia, and bulging eyes with double vision and increased sensitivity to light.

The association between iodine and the occurrence of autoimmune reactions is complex; both inadequate supply and oversupply are associated with increases in autoantibodies [23–25]. Even in low-iodine regions, iodine supplementation can increase the short-term risk. In Denmark, a country that originally had a mild to moderate iodine deficit, iodine status had improved significantly five years after the introduction of iodized salt, but at the same time, the prevalence of antibodies against the thyroid also increased (possibly due to technical issues) by 14–20% [26]. However, once optimum iodine status is reached, the prevalence of autoimmune diseases reduces again in the long term [27]. Studies from Denmark and China also show that selenium levels in patients newly diagnosed with autoimmune disease of the thyroid, and especially in those diagnosed with Graves' disease, are significantly lower than in the corresponding controls [28–30]. An inverse correlation between selenium and antibodies directed against the thyroid is often observed [31]. However, it is not clear to what extent such observations are an indirect consequence of inflammatory processes. Since selenoproteins influence the adaptive and innate immune response [32], it is also conceivable that this might be a direct effect. A placebo-controlled study in patients with autoimmune disease of the thyroid showed a 36% reduction in autoantibodies after adminis-

tration of T_4 and 200 µg selenite compared to the placebo group (which received T_4 only). Patients with particularly high baseline values had reductions of up to 69% [33]. More recent studies also suggest that there may be additional genetic factors [34].

Biomarkers

Specific biomarkers that are easy to detect and that make it possible to identify a potential deficiency or intoxication (ideally before any clinical symptoms occur) are highly relevant as ways to determine the supply of trace elements.
For example, the concentration of selenium in the serum or plasma, or in the nails or hair is used to determine selenium supply. However, these parameters can vary widely even without any additional intervention. Selenoproteins are therefore a better option because they react with a high level of sensitivity to fluctuations in selenium supply and they also indicate the level of the selenium pool that is available for selenoprotein synthesis. Both determination of the activity of selenium-dependent GPx3, which accounts for over 90% of GPx activity in plasma, and determination of the concentration of selenoprotein P in blood are used for this purpose. Selenoprotein P is secreted by the liver in order to transport selenium to peripheral tissues, especially the brain. Based on current studies, selenoprotein P is the best biomarker for determining whether selenium supply is adequate.
By contrast, iodine concentration per g of creatinine in the urine (as an indicator of kidney function and the dilution of the urine) is often used to determine iodine exposure. This value is based on prior iodine intake and the amount of iodine that is absorbed by the thyroid gland and is thus retained in the body. Therefore, iodine concentration in the urine is a suitable biomarker for the supply status of the body as a whole, but does not provide any information about thyroid function specifically. In addition, other suitable biomarkers include the concentration of thyroid hormones (not suitable during pregnancy), thyroglobulin, or TSH in the serum. If the iodine supply deviates strongly from the reference value, the size of the thyroid gland can also provide information about the supply status.

TraceAge

The reciprocal interactions between trace elements in the human body are not limited to the aforementioned examples of selenium and iodine only. The body regulates trace elements to keep them within a narrow concentration range. Every human being has their own individual optimum supply of trace elements, which depends on the environment, habits, age, medications, and illnesses. In addition, imbalances are increasingly being identified as risk factors for the incidence or severity of diseases. However, biomarkers that are both easy to measure and robust are rare. In addition, it remains debatable whether the determination of a single, isolated parameter can provide a reliable picture of individual trace element and health status, or whether non-functional markers or the ratios of different trace elements to each other are a better alternative.
The mutual influence that six essential trace elements (selenium, copper, zinc, manganese, iron, and iodine) have on each other in healthy and diseased senior citizens will be investigated in more detail in the DFG (German Research Foundation) research group TraceAge. The investigations will focus on defining age- and gender-specific trace element profiles, but functional markers and stress indicators will also be recorded and evaluated at the same time. Such age- and gender-specific trace element profiles are currently being surveyed in human cohorts, mouse feeding studies, and analyses with the nematode *Caenorhabditis elegans*. The long-term aim of this is to improve the trace element status of senior citizens.

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Conflict of Interest
The authors declare no conflict of interest.

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