Inadequate supply of the essential trace element selenium (Se) has been associated with predisposition for, or manifestation of, various human diseases such as Keshan and Kashin–Beck disease, cancer, impaired immune function, neurodegenerative and age-related disorders and disturbances of the thyroid hormone axis. Se deficiency in combination with inadequate iodine contributes to the pathogenesis of myxedematous cretinism. The recent identification of various distinct selenocysteine-containing proteins, encoded by 25 human genes, provides information on the molecular and biochemical basis of beneficial and possible adverse effects of this trace element. The thyroid gland is among the human tissues with the highest Se content per mass unit similar to other endocrine organs and the brain. Selenoproteins involved in cellular antioxidative defence systems and redox control, such as the glutathione peroxidase (GPx) and the thioredoxin reductase (TrxR) family, are involved in protection of the thyroid gland from excess hydrogen peroxide and reactive oxygen species produced by the follicles for biosynthesis of thyroid hormones. In addition, the three key enzymes involved in activation and inactivation of thyroid hormones, the iodothyronine deiodinases (DIO1,2,3), are selenoproteins with development, cell- and pathology-related expression patterns. While nutritional Se supply is normally sufficient for adequate expression of functional Dio enzymes with exception of long-term parenteral nutrition and certain diseases impairing gastrointestinal absorption of Se compounds, the nutritional Se supply for the protection of the thyroid gland and synthesis of some more abundant selenoproteins of the GPx and the TrxR family might be limited their proper expression under (patho-)physiological conditions.
Introduction

The understanding of the essential role of selenium (Se) in thyroid hormone synthesis, metabolism, and action, as well as for normal thyroid function, increased substantially during the past decades. It has long been known that the thyroid belongs to the organs with the highest Se content due to the expression of several Se-dependent enzymes that are important in maintaining thyroid hormone metabolism such as the deiodinases (DIOs) and in preventing the thyroid cells from oxidative damage such as cytosolic and plasma glutathione peroxidases (cGPx and pGPx) as well as phospholipid-hydroperoxide glutathione peroxidase (PHGPx) (Fig. 1). The classical diseases linked to severe Se deficiency, the destructive osteoarthritis (Kashin–Beck disease) and the lethal myocarditis (Keshan disease), are not associated with a thyroid dysfunction. The first clinical evidence that severe Se deficiency in combination with other environmental factors is deleterious for the thyroid was found in Central Africa. Here, the supplementation of iodide alone was ineffective in restoring the thyroid function, and children developed myxedematous cretinism in a region with endemic iodine and/or Se deficiency. This form of cretinism is characterised by persistent postnatal hypothyroidism, despite iodine supplementation. The thyroid gland of these children is atrophic and firm, suggesting cell damage and fibrotic degeneration (for histology see Köhrle et al.). Further examinations revealed that in severe Se deficiency, the activity of thyroid glutathione peroxidases (GPx) is markedly decreased. This results in oxidative cell damage followed by necrosis and invasion of the thyroid tissue by macrophages and T lymphocytes. Chronic inflammation destroys the thyroid via TGF-dependent processes, resulting in an atrophy of the gland. It is now hypothesised that even mild–to-moderate nutritional Se deficiency might be responsible for the initiation or progression of autoimmune thyroid disorders in patients with the background of genetic susceptibility to develop autoimmune diseases.

Furthermore, Se has been shown to be important in the regulation of immune function (for review see refs. [14–16]). Se deficiency is accompanied by loss of immune competence. Both cell-mediated immunity and B-cell function can be impaired. This might be related to the fact that the Se-dependent

Fig. 1. Relevant Proteins and Factors involved in Thyroid Hormones Biosynthesis in Thyrocytes. Abbreviations: DAG, diacylglycerol; 5’DI, type I 5’-deiodinase; 5’DII, type II 5’-deiodinase; cGPx, cytosolic glutathione peroxidase, GPx1; pGPx, plasma glutathione peroxidase, GPx3; IP3, inositol trisphosphate; Sep15, selenoprotein 15; SePP, selenoprotein P; Tg, thyroglobulin; ThOx, thyrooxidase, dual oxidase (DuOx); TSH, thyroid stimulating hormone, thyrotropin.
enzymes GPx and thioredoxin reductase (TxnRd) exhibit antioxidative effects by reducing hydrogen peroxide, lipid and phospholipid hydroperoxides and thus decreasing formation of reactive oxygen species (ROS) and free radicals generated from their metabolism.\(^{17,18}\) In addition, both GPx and TxR modulate the respiratory burst and reduce superoxide anion production. Se compounds also reduce the nuclear translocation of the transcription factor NFκB in macrophages by interference with its cytosolic inhibitor IκB and the signalling cascade and hereby decrease inflammatory cytokine expression.\(^{19–22}\) Therefore, several prospective, randomised clinical trials were performed in patients with autoimmune thyroiditis (AIT) to examine whether a Se supplementation might reduce the inflammatory activity within the thyroid and prevent progression of this chronic disease affecting 10–15% of women in their reproductively active and postmenopausal years (for reviews see refs. \([13,23]\)). Several prospective, double-blinded studies examined the effects of various Se forms on AIT with different outcome.\(^{24–31}\)

A possible anti-inflammatory effect of Se compounds has already been demonstrated in a double-blind randomised trial in patients with rheumatoid arthritis, where the supplementation of 200 mg selenomethionine per day for 3 months significantly reduced pain and joint involvement.\(^{32,33}\) Se supplementation of 500–1000 mg has also been reported to improve survival in patients with severe sepsis.\(^{34,35}\)

**Experimental trials**

Se-dependent enzymes modulate the immune system not only within the thyroid but also within the other tissues.\(^{14–16}\) It has been shown that during severe Se deficiency, the lack of GPx activity may contribute to an oxidative damage of the thyroid cell and the initiation of thyroid damage and fibrosis.\(^{12,36}\) Increased fibroblast proliferation and decreased thyroid epithelial cell proliferation were observed. As activated macrophages infiltrating the thyroid gland express high amounts of TGFβ, it is assumed that TGFβ is responsible for fibroblast proliferation and inhibition of thyroid proliferation. The Se substitution in the rat model studied prevented this oxidative damage, necrosis and fibrosis.\(^{12}\) These effects, however, were not confirmed by other experimental approach, where combined iodine and Se deficiency was induced in dams, and either treated with high doses of iodine or Se.\(^{37}\) No fibrosis or necrosis could be detected in the foetus or pups under Se deficiency with or without iodine supplementation.\(^{3}\) In human thyroid follicles, apoptosis is induced by high doses of iodide, H₂O₂ or TGFβ. Pre-incubation of intact follicles with low doses of Se compounds increased GPx activity significantly and reduced the occurrence of apoptotic cells induced by all three substances.\(^{38}\)

**Se compounds in autoimmune thyroiditis: Clinical trials**

Until now, five randomised prospective clinical trials have been performed in patients with established AIT (Table 1). All of these studies have been performed in Europe (Germany, Greece, Italy and Austria) and Turkey, countries with known mild-to-moderate Se deficiency. The dosage of daily Se supplementation was 200 μg. The Se plasma levels at study entry were between 70–75 μg l⁻¹ and 86–125 μg l⁻¹ after 3 or 6 months' treatment. Thus, the Se levels were within the low normal range at study entry and within the recommended level after Se supplementation. Patients were randomised according to the TPOAb concentrations and treated with Se (200 μg) either as selenomethionine in three studies or with sodium-selenite in the two other studies\(^{23–31}\) (Fig. 2). The clinical endpoint of each study was the decrease in TPOAb concentrations after 3–12 months’ treatment. In all but one study, there was a significant decrease in the TPOAb concentrations after 3 months and a further decrease after 6 months has been reported.\(^{27}\)

During follow-up after stopping the Se supplementation, the TPOAb concentrations increased again nearly to the initial levels after 3 and 6 months’ observation. In one of the studies with a crossover design with reduction of Se from 200 μg per day to 100 μg per day, no decrease in the TPOAb concentrations after 3 months was observed.\(^{31}\) These studies clearly indicate that Se treatment results in reduced inflammatory activity, but it does not cure AIT.
<table>
<thead>
<tr>
<th>Selenium</th>
<th>N Verum/Placebo</th>
<th>TPOAb initial (U/L)</th>
<th>TPOAb 3 months (U/L)</th>
<th>TPOAb. after 6 months (U/L)</th>
<th>TPOAb after 12 months (U/L)</th>
<th>Significance</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na-selenite 200 μg/d</td>
<td>36/34</td>
<td>904 ± 205</td>
<td>575 ± 46</td>
<td>n.d.</td>
<td>n.d.</td>
<td>p = 0.013</td>
<td>Gärtnert, 2002 [24]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1090 ± 277</td>
<td>959 ± 267</td>
<td></td>
<td></td>
<td>p = 0.95</td>
<td></td>
</tr>
<tr>
<td>Na-selenite 200 μg/d</td>
<td>14/11</td>
<td>625 ± 470a</td>
<td>n.d.</td>
<td>354 + 321a</td>
<td>n.d.</td>
<td>p = 0.004</td>
<td>Gärtnert, 2003 [23]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1351 + 940</td>
<td></td>
<td></td>
<td></td>
<td>p = 0.55</td>
<td></td>
</tr>
<tr>
<td>Selenomethionine 200 μg/d</td>
<td>34/31</td>
<td>1875 + 1039</td>
<td>1013 + 382</td>
<td>844 + 227</td>
<td>n.d.</td>
<td>p &lt; 0.0001</td>
<td>Duntas, 2003 [25]</td>
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<tr>
<td></td>
<td></td>
<td>1758 + 917</td>
<td>1389 + 520</td>
<td>1284 + 410</td>
<td></td>
<td>p &lt; 0.005</td>
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<tr>
<td>Selenomethionine 200 μg/d</td>
<td>48/40</td>
<td>803 ± 483</td>
<td>572 ± 517</td>
<td>440 + 382</td>
<td>n.d.</td>
<td>p &lt; 0.01</td>
<td>Turk, 2006 [31]</td>
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<tr>
<td></td>
<td></td>
<td>770 ± 406</td>
<td>773 ± 372</td>
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<td></td>
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<tr>
<td>Selenmethionine 100 vs 200</td>
<td>20/20</td>
<td>544 ± 380b</td>
<td>694 ± 427b</td>
<td></td>
<td></td>
<td>p &lt; 0.01</td>
<td>Turk, 2006 [31]</td>
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<tr>
<td>μg/d</td>
<td></td>
<td></td>
<td>649 ± 628</td>
<td></td>
<td></td>
<td>p &lt; 0.01</td>
<td></td>
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<tr>
<td></td>
<td>20/20</td>
<td>524 ± 452</td>
<td>505 ± 464</td>
<td>n.d.</td>
<td>n.d.</td>
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<tr>
<td></td>
<td></td>
<td>521 ± 349</td>
<td>527 ± 354</td>
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</tr>
<tr>
<td>Selenmethionine 200 μg/d</td>
<td>A 40c</td>
<td>955 (530–2110)</td>
<td>905 (510–1990)</td>
<td></td>
<td></td>
<td>p &lt; 0.0001</td>
<td>Mazokopakis, 2007 [28]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>521 (340–1300)</td>
<td>710 (310–1280)</td>
<td></td>
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<td>p &lt; 0.001</td>
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<td>B 40c</td>
<td>770 (340–1300)</td>
<td>710 (310–1280)</td>
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<td></td>
<td>p &lt; 0.001</td>
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<tr>
<td></td>
<td></td>
<td>680 (200–1150)</td>
<td>694 (210–1180)</td>
<td></td>
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</tbody>
</table>

a From the group of patients in the first study [24] those who were already treated with 200 μg sodium-selenite or placebo were further treated with either with verum or placebo for 6 months [23].

b A subgroup of patients treated already with 200 μg selenomethionine for 3 months were either treated with 100 μg or 200 μg selenomethionine [31].

c All patients (group A and B) were treated with 200 μg selenomethion for 6 months, thereafter in group B selenium supplementation was stopped and group A continuously treated with 200 μg selenomethionine for further 6 months [28].
A successful causal cure of AIT by Se supplementation might indeed not be expected, as the disease is strongly influenced by an underlying genetic predisposition and triggered by stress or other environmental factors. Therefore, the rationale for the Se supplementation might be to treat patients in conditions when the inflammatory activity is high as in the postpartum condition, in the peri-menopausal state or during other stress situations. Since serum Se behaves as a negative acute-phase reactant, it appears reasonable to both correct the developing deficit and to strengthen the immune system by Se supplementation under these conditions of increased inflammatory activity.

In those studies, where ultrasound imaging of the thyroid was included as a secondary endpoint, patterns improved significantly under the Se supplementation. No Se-related side effects were seen in all treated patients. In one trial, quality of life had been monitored by short form (SF)-12 questionnaire before and after 3 months of treatment.24 Those patients in the serum group felt significantly better and no change was documented in the placebo group.

The rational background for using 200 mg of Se per day as the standard dosage in all these studies was the experience that this dosage seemed to be safe even if supplemented for many years, like in the large NPC cancer prevention trial.39 Until now, only one dose-finding study has been reported31, and it is also not known whether patients with initially high normal Se plasma levels will respond to the Se treatment. Observational studies where Se was measured in patients with different thyroid disorders revealed that the Se plasma levels are lower in AIT.40 Furthermore, women but not men with low Se plasma levels in the SUVIMAX study had decreased echogenicity of the whole thyroid gland and smaller volumes indicating AIT.41 These data clearly indicate that mild-to-moderate Se deficiency is associated with a higher incidence of AIT.

In all these trials, the patients were under l-thyroxine supplementation to keep TSH within the normal range. All of these studies included only low numbers of patients with a female preponderance, which might constitute an important bias. However, AIT is fivefold more frequent in women than in men,42 and therefore it is easier to recruit a sufficient number of women as study participants. In the study that did not show any effect of Se in patients with AIT27, the number of patients enrolled was lowest and the TPOAb concentrations were also lower compared to the other trials. Another critical point is that the duration of the disease in all studies is not known and also data on thyroid volume are
missing. Furthermore, although over the counter self-medication has been an exclusion criterion, this is not controlled in all of the trials.

The human thyroid gland is the organ most affected by tissue-specific autoimmune diseases, indicating the need for further studies. It would be important to perform randomised trials inAIT patients at the onset of the disease to show whether the thyroid dysfunction can be prevented with a Se supplementation.

The question arises whether a decrease in TPOAb concentrations really reflects a decreased inflammatory process within the thyroid or rather an improved functioning of the immune system. It has been assumed that the decrease in TPOAb is only a laboratory diagnostic indicator but not a clinical-relevant parameter. However, in another clinical trial, pregnant women with positive TPOAb were treated with 200 μg of selenomethionine per day from the first visit throughout pregnancy until 12 months after delivery. The TPOAb titres did not increase after delivery in contrast to the control group and significantly less postpartum thyroid dysfunctions occurred in the Se-supplemented group.43

Pregnancy and lactation are associated with an increased demand in thyroid hormones reflected in elevated thyroid hormone synthesis, secretion, serum binding and clearance as well as transfer to the foetus and newborn, respectively. It might well be that there is also an increased demand in Se supply during this period.

In another small intention-to-treat trial, six patients with subclinical hypothyroidism were treated with 200 μg selenomethionine per day for 6 months. The Se plasma levels were initially at 70 μg l⁻¹, and rose to 120 μg l⁻¹ after supplementation. The TPOAb concentrations decreased, TSH was normalised in all patients and ultrasound pattern improved substantially.29 This clearly indicates that the circulating TPOAb reflects the inflammatory activity within the thyroid, and this inflammation impairs thyroid function. In contrast to the TPOAb, the TgAb concentrations were not changed during the Se treatment. The TgAb are considered less specific for the inflammatory activity of AIT, as Tg in contrast to TPO is circulating in the blood and immune response might not directly be initiated within the thyroid.24

In all the studies performed so far, no alterations in thyroid hormone metabolism were detected during Se supplementation. This might be because the Se deficiency was only moderate and deiodinase activity decreases only in severe Se deficiency.3 In a previous study in a small cohort of patients with reduced thyroid iodine organification after subacute thyroiditis or postpartum thyroiditis30, a supplementation with 100 μg (1.26 μmol) per day Se had also no effect on thyroid hormone synthesis.

In a study with T4-substituted juvenile patients with congenital hypothyroidism, a 3-month supplementation with 20–60 μg selenomethionine per day normalised elevated serum TSH and decreased elevated serum thyroglobulin values while no changes in serum thyroid hormones were observed. This indicates that deiodinases are not limited in their activity under these conditions, while serum GPx activity increased after Se supplementation.44

### Se and immune response

The immune-modulatory effects of Se-dependent enzymes such as the GPx and TxR are involved in the organ-specific immune response.16,45 This could be demonstrated in mice under Se-deficient diet, where tissue damage of the lung was significantly increased after virus infection compared with mice under Se-adequate diet.46 Similar effects were seen in mice, infected with Coxsackie virus B that developed myocarditis.47,48 It is assumed that Keshan disease, a myocarditis linked to severe Se deficiency is probably caused by a Coxsackie virus infection and the viruses are more virulent when Se is low.

There are several prospective randomised trials done in patients with acute inflammatory response syndrome, where a higher dose of Se supplementation reduced morbidity and in some also mortality, especially in the most severely ill patients.49 As acute systemic inflammatory response syndrome is considered as an overreaction of the immune system, followed by tissue damage, Se obviously might attenuate this detrimental immune response.

The increased oxidative stress in all inflamed tissues increases NF-κB translocation, leading to an enhanced chemokine mRNA expression. Se exerts its immune-modulating effect by reducing NF-κB translocation and thereby prevents overreaction of the immune response.22,50–52 This might also be especially important in organ-specific autoimmune diseases, such as AIT, Crohn’s disease and others. Thus, Se-dependent enzymes are implicated in both antioxidative action by their intrinsic catalytic
activities and anti-inflammatory effects indirectly by modulating redox-dependent transcription. These combined effects are elicited because the GPx can reduce hydrogen peroxides, lipid and phospholipid hydroperoxides and thereby lowering the propagation of free radicals and reactive oxygen species. Lower hydroperoxide tissue concentrations diminish the production of inflammatory prostanoidals and leukotiennes. The respiratory burst is also dampened by Se-dependent enzymes as well as an overshooting superoxide production. These mechanisms additionally might contribute to a reduced inflammatory activity in organ-specific autoimmune response and may explain the improvement of the inflammatory activity in patients with AIT under Se treatment.

The anti-inflammatory effect of a Se supplementation of 200 μg (2.53 μmol) per day has also been shown in double-blinded studies in rheumatoid arthritis and asthma. In a small randomised trial, no changes in cytokine pattern or differences in CD4+ or CD8+ ratio were observed under 3-month treatment with 200 μg sodium-selenite in unselected patients with AIT.27 In this study, also TPOAb concentrations were unaffected. The reason might be that the study has not been performed in patients with active inflammatory activity.

Selenoproteins of the thyroid gland

Selenoprotein S has been suggested to be involved in the immune response, and single nucleotide polymorphisms associated with enhanced immune reaction and elevated cytokine release have been described. However, the relevance of these findings remains to be confirmed and contradicting observations have been published for patients with autoimmune diseases. Currently, no information is available, whether Selenoprotein S is expressed in the human thyroid, altered in autoimmune thyroid disease or responsive to Se supplementation in vivo. In the context of the high Se concentrations found in normal human thyroids, it comes as no surprise that most of the selenoproteins are found to be expressed in the gland and in thyrocytes (for review, see ref. [58]) (Fig. 1). While 5′-deiodinases Dio1 and Dio2 are involved in local activation of thyroid hormones, which are synthesised in the colloidal lumen as part of thyroglobulin or may be re-imported from the blood perfusing the highly vascularised gland, no clear evidence has yet been presented on thyroidal expression of functional Dio3, the enzyme mainly involved in degradation of the prohormone T4 and the biomimetically active T3. Thyroid hormone biosynthesis requires the (continuous, life-long) synthesis of H2O2 under control by the anterior pituitary hormone thyrotropin (TSH). This situation evidently needs an efficient antioxidative response against excessive H2O2 formed by the dual oxidase (DuOX or thyrooxidase, ThOx) and not completely consumed by the haemoprotein thyrooxidase (TPO) for TH synthesis. Therefore, several selenium-containing and non-selenium-dependent cellular redox-active and antioxidative enzymes and proteins are expressed in thyrocytes and partially secreted into the colloidal lumen. Among these is GPx3, which is one of the selenoproteins expressed at highest transcript and functional levels in thyrocytes, thus contributing significantly to the high selenium content of thyroids. Dio enzymes are of very low abundance and do not significantly contribute to the Se content of the gland. Hydrogen peroxide produced by thyrocytes as an oxidant for iodide at the apical luminal surface of the follicle may compromise cellular and genomic integrity of the surrounding cells, unless these are sufficiently protected by peroxidases. These peroxidases play two opposing roles in thyroid biology; on the one hand, they defend the follicular cells against H2O2 and ROS derived wherefrom; on the other hand, they might compete with TPO for H2O2, which is essential for TH biosynthesis. This scenario requires a distinct compartmentation and/or regulation by TSH and/or other signals. Apart from the GPx family, the TxnRd family and several peroxiredoxins are highly expressed in thyrocytes. Therefore, Se, the thioresolin and the peroxiredoxin network impact directly and indirectly on the function and integrity of this essential gland during the whole life time. For a detailed summary of expression patterns known so far, see ref. [58].

Se content in the thyroid gland does not directly reflect the Se status of the organism

Initially it was assumed that information on the Se status derived from serum, plasma or whole blood selenoprotein or Se parameters provides insight into the Se supply of tissues particularly...
depending on adequate Se supply such as testes, the brain and the endocrine tissues, such as the thyroid gland.\textsuperscript{3,59} However, systematic analysis in experimental animal models during nutritional Se depletion and repletion experiments and selective analysis of thyroid tissue removed during medical interventions (goitre, thyroid cancer, autoimmune thyroid disease) revealed a different picture.\textsuperscript{3,59–61} Se depletion of the serum or animals analysed, for example, in tissues such as liver, kidney, muscle and other organs had no or only minimal impact on thyroid Se content and expression of thyroid selenoproteins. Even higher than normal values were reported for Dio, GPx and TxnRd expression in the thyroid under conditions of Se depletion in the rest of the body, a situation parallel to that of the brain, which can only minimally be depleted from Se by nutritional interventions.\textsuperscript{62–66} These observations provided first evidence that the thyroid (and the brain) have an specific uptake or retention mechanism for Se even under conditions of severe nutritional and serum Se deficiency.\textsuperscript{1,67} This hypothesis was supported later on by the observation that thyroid Se content and expression of functional Se proteins, such as Dio, GPX and TxnRd, was even maintained at normal levels in the selenoprotein P knockout mouse model, where hepatic synthesis of the major Se transport and distribution protein for most other tissues (except the thyroid and the brain) has been interrupted leading to severe Se deficiency especially in male mice. Up to now, the biochemical nature of this selenoprotein P-independent uptake or retention mechanism for the thyroid gland has not been identified.

Marked differences between the ‘systemic Se status’ analysed by serum parameters and the Se content and functional expression of the selenoproteins Dio1, Dio2 and GPx-1 in human thyroid tissues from patients suffering from goitre, thyroid cancer or AIT have been reported.\textsuperscript{60} These and other observations raise some questions with respect to the explanation of beneficial effects of Se supply for adequate thyroid function, prevention of thyroid disease and positive effects of Se supplementation in AIT such as Hashimoto’s thyroiditis or postpartum thyroiditis. Beneficial effects of Se supplements for Graves’ disease have not been reported yet, but might be expected. It might well be that Se is not only beneficial for maintenance of thyroid integrity and antioxidative defence of thyroid follicles against continuous H$_2$O$_2$ production but also that protective effects of Se might be exerted through components of the humoral or cellular immune system, which might be less prone to autoreactive overreaction under conditions of adequate Se supply.\textsuperscript{14–16,18,68–70}

Various Se-containing compounds have different metabolic fates and might exert distinct actions

Currently, several chemical forms of Se are in medical use and nutritional sources for the essential trace element Se differ in their properties and bioavailabilities.\textsuperscript{69,71–74} Some low-molecular-weight Se compounds can reversibly bind to a group of selenium-binding proteins (SeBP) in serum and tissues, but these are not well defined with respect to their binding properties and their function is rather unclear. Mechanisms of cellular selenium uptake and gastrointestinal resorption of Se compounds are not well understood\textsuperscript{74}, including the hepatic organification of Se precursors, which are incorporated into the hepatically secreted Se transport and distribution protein selenoprotein P. Among the dietary available Se compounds, selenite can most directly be used for cotranslational incorporation into selenoproteins via the complex pathway involving the biosynthesis of the 21st proteinogenic amino acid selenocysteine\textsuperscript{75,76} (Fig. 2). Selenomethionine, the second Se-containing amino acid is incorporated into proteins at methionine positions. This reaction is not regulated and it occurs at random positions depending on the relative availability of Se-methionine versus normal sulphur-containing methionine. Higher supply of dietary selenomethionine thus increases the Se store in all proteins such as albumin and immunoglobulins, but has no direct impact on the selenocysteine-containing proteins encoded by the 25 human genes. Only the metabolism of Se-methionine containing proteins via trans-selenation or degradation fuels Se into the pool of selenocysteine-containing proteins synthesised \textit{de novo} and using Se in its H$_2$Se or Se-O intermediate form. As incorporation of Se into selenocysteine-containing proteins is a tightly regulated process, saturation is achieved in these pathways while selenomethionine incorporation occurring at random might create a Se storage pool, which might be available through time-consuming complete
degradation for subsequent biosynthesis of functional selenoproteins. Therefore, selenomethione-nine or yeast proteins containing this amino acid exhibit no acute toxicity but can lead to high Se levels, which are not directly bioavailable. By contrast, excessive intake of selenite might be toxic at chronic intake in concentrations beyond 800 μg per day, but Se in this form is directly bioavailable for synthesis of functional selenoproteins. Apart from these two forms of Se in nutrients or supplements, several Se compounds are currently tested in preclinical and clinical studies addressing preventive of therapeutic aspects of Se. Recently, a series of novel Se compounds have been synthesised and partially characterised as possible inhibitors of thyroidal TPO, GPx mimics or TrxRd inhibitors. Whether these compounds will be applicable for clinical purposes and will exhibit favourable toxicological profiles requires further studies.

Expression of the 5′-deiodinase selenoproteins in the thyroid contributes to T3 production

It has been known for long that thyroid expresses significant levels of the selenoprotein Dio1, which is stimulated by the TSH signalling cascade, and also directly by T3. However, its relative contribution to T3 secretion remains under debate. Under conditions of iodine deficiency, the T3/T4 ratio secreted by the gland is increased, probably due to an altered ratio of T3/T4 synthesis on the Tg scaffold. The identification of elevated Dio2 activity in some rare follicular thyroid tumours provided some explanation for hyperthyroidism occasionally occurring in the context of thyroid cancer, where, in the majority of cases, Dio1 expression is down regulated. Significant and considerable species differences have been observed for 5′-deiodinase expression in thyroid tissues, indicating the limits of extrapolations from animal experimental models in this respect for estimation of thyroid contribution to circulating T3. Clear evidence is available for elevated expression and activity levels of 5′-DIO in thyrocytes of patients with Graves’ disease and autonomous adenoma, both observations are compatible with the TSH receptor signalling mediated stimulation of Dio1 and Dio2 expression by TSH-receptor stimulating autoantibodies and activation of the cAMP-signalling cascade, respectively. Whether Se supply to the pathological thyroid gland is a limiting factor remains to be studied. Because single nucleotide polymorphisms with functional relevance have been described for the TSH receptor, Dio1 and Dio2 steady-state thyroid hormone and TSH level vary between the haplotypes but no links to Se supply have been reported yet for these subgroups, again suggesting that only very severe nutritional or disease-related Se deficiency will impact on T3 production and TH metabolism in animal experimental models and in humans. Rare mutations have been reported for Secis-binding protein 2 (SBP2), the key factor in cotranslational incorporation of selenocysteine into the various selenoproteins. Affected patients show alterations in the thyroid hormone axis caused by inappropriate T3 production through impaired 5′-DIO activity. Unfortunately, neither supplementation with selenite nor selenomethionine could rescue this defect, which probably requires TH supplementation for normal development and function of TH-dependent pathways in adults.

Summary

The essential trace element Selenium is required for thyroid hormone synthesis and metabolism. The thyroid gland has the highest Se content covalently incorporated into several selenoproteins such as the families of glutathione peroxidases, thioredoxin reductases and deiodinases. These contribute to thyroid hormone biosynthesis, antioxidative defense and redox control of thyrocytes as well as to thyroid hormone metabolism. Severe and persistent selenium deficiency impairs thyroid hormone biosynthesis and also exaggerates destruction of follicular structures and their replacement by fibrotic tissue (myxedematous cretinism). High iodide loads for the thyroid might have negative impact on a selenium depleted thyroid gland. Beneficial effects of selenium supplementation have been reported in several studies for the treatment of Hashimoto’s thyroiditis. Under these conditions both selenite and selenomethionine were effective at 200 μg / day. Mechanisms of action of this treatment remain as unclear as do possible preventive Se effects in thyroid cancer.
Conflict of interest

There are no conflicts of interest to be stated (KJ). RG received funding from biosyn Arzneimittel GmbH, Fellbach, Germany for studies on selenium treatment in ICU patients.

Acknowledgements

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