Review

On the importance of selenium and iodine metabolism for thyroid hormone biosynthesis and human health

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The trace elements iodine and selenium (Se) are essential for thyroid gland functioning and thyroid hormone biosynthesis and metabolism. While iodine is needed as the eponymous constituent of the two major thyroid hormones triiodo-L-thyronine (T3), and tetraiodo-L-thyronine (T4), Se is essential for the biosynthesis and function of a small number of selenocysteine (Sec)-containing selenoproteins implicated in thyroid hormone metabolism and gland function. The Se-dependent iodothyronine deiodinases control thyroid hormone turnover, while both intracellular and secreted Se-dependent glutathione peroxidases are implicated in gland protection. Recently, a number of clinical supplementation trials have indicated positive effects of increasing the Se status of the participants in a variety of pathologies. These findings enforce the notion that many people might profit from improving their Se status, both as a means to reduce the individual health risk as well as to balance a Se deficiency which often develops during the course of illness. Even though the underlying mechanisms are still largely uncharacterised, the effects of Se appear to be exerted via multiple different mechanisms that impact most pronounced on the endocrine and the immune systems.

Keywords: Autoimmune / Gender / Selenoprotein / Thyroiditis / Trace element

Received: November 15, 2007; revised: February 1, 2008; accepted: February 8, 2008

1 Selenium (Se) intake, Se availability and Se metabolism

The distribution of selenium (Se) varies widely in the environment and in different countries. While the soils of central Asian regions and most European countries are generally low in both iodine and Se concentrations, no such deficiencies are observed in other parts of the world including most regions of the USA or Japan. The Se concentrations in plants and farm animals largely depend on these local availabilities [1]. During the biosynthesis of the amino acids methionine and cysteine, the plants make use of both sulfur (S)- and Se-containing substrates. Depending on the plant, large amounts of Se can thereby enter the food chain [2]. Depending on the type of plant and relative concentration of Se over S in the soil, considerable quantities of selenomethionine (SeMet) and also variable amounts of Se-methylselenocysteine, selenocystathionine, selenocysteine (Sec) and γ-glutamyl-Se-methylcysteine are synthesised by plants and taken up through the diet by animals and humans. To avoid adverse health effects because of Se deficiency, the feed of farm animals is often supplemented with adequate Se sources [3]. This supplementation strategy is believed to be responsible for improved fertility, immune system functioning and meat quality in comparison to non-supplemented animals.

In higher mammals, two interconnected cycles of Se-containing proteins are found. SeMet is taken up mainly from plants, i.e. vegetables, fruits or cereals, and enters all proteins in response to AUG codons, albeit at a marginal
rate which reflects the relative amount of SeMet over Met in the diet. Depending on this relation, the fraction of SeMet residues compared to Met in, e.g. human albumin has been determined to range in the order of 1:8000–1:2800, indicating that only around 1 in 1000 albumin molecules harbours a single SeMet in its primary sequence [4].

In contrast, biosynthesis of the Sec-containing selenoproteins represents a stringently regulated, mRNA-encoded and highly specific process [5]. Biostatistical algorithms have been developed and used to predict that the human genome contains only very few genes that specify Sec-insertion at precisely predefined positions [6]. Labelling experiments with 75-Se in rats have indicated the presence of about 50 differently-sized Se-containing proteins [7], consistent with the number of 25 human or 24 rodent genes identified by these elegant in silico analyses. Albeit, not all of these proteins are synthesised at constant rates; it appears as if very essential selenoproteins implicated in vital functions of the cell or the organism become preferentially synthesised, even in times of Se-shortage. These proteins include the isozymes of the thioredoxin reductase (TxnRd) family, i.e. TxnRd-1 and -2, and the phospholipid-hydroperoxide-specific glutathione peroxidase (PH-GPx), i.e. GPx-4. These selenoproteins have been demonstrated to be essential for the development and survival, for their genetic inactivation in mice proved to be lethal [8]. Some of the other selenoproteins appear to represent less vital components of the proteome, including the ubiquitously expressed GPx-1 or the extracellular mainly kidney-derived plasma isozyme, i.e. GPx-3. Surprisingly, the recent characterisation of the first identified human patients suffering from a general deficit of selenoprotein biosynthesis because of inherited mutations in the Sec-Insertion Sequence Binding Protein 2 (SBP2) gene displayed a defective thyroid hormone feedback axis [9]. Both the analysis of mRNA and protein concentrations from these patients and the consecutive in vitro characterisation of the mutant proteins indicated that the deiodinase isozymes belong to the less-well supplied selenoproteins in times of insufficient biosynthetic capacity.

In healthy individuals, supplementation with different Se-forms yields a complex picture of effects on the Se status (Fig. 1). SeMet can directly be funnelled into all proteins at Met-specific positions in direct relation to its relative abundance. Thus, enriching one's diet with large amounts of SeMet over regular Met intake leads to an increasing value for total blood Se concentration because of increased fractions of SeMet-containing serum proteins [10]. The overall effect, i.e. an increased serum or plasma Se concentration, is largely independent from the original Se status of the individual. In contrast, the effect of increased intake of inorganic Se sources like sodium-selenite or -selenate differs decisively between well-supplied and marginally-supplied individuals. In general, inorganic Se sources can only be used for the biosynthesis of Sec-containing but not of SeMet-containing selenoproteins. This fact represents the fundamental difference between these two supplementation forms that are sometimes used without detailed description and further discrimination in human, experimental animal or in vitro studies. Only the use of SeMet will always result in increased serum Se concentrations. In serum or plasma, there are two soluble selenoproteins that account for the largest fraction of blood Se, i.e. GPx-3 mainly from kidney and selenoprotein P (SePP) mainly from liver. Biosynthesis and circulating levels of these two selenoproteins can apparently be saturated, albeit at slightly different Se intake levels [10]. SePP responds over a larger range of supply and is therefore considered to represent the better and more reliable indicator of Se status and Se intake [11]. Nevertheless, once saturated levels of both proteins have been reached, which appears to need less than 80–100 μg Se/day in humans or 50–100 nM Se in cell culture, no further increase in SePP or GPx-3 concentrations is usually observed.

![Figure 1](image-url)
However when SeMet is chosen as Se source for supplementation, total Se concentration in blood increases even in well-supplied individuals [10]. No mechanism is known to limit this gradual increase in the biosynthesis of SeMet-containing proteins. This lack of control has given rise to concern and questioned the choice of SeMet as a suitable supplementation form in human trials. In view of the aforementioned marginal fraction of actually affected proteins such effects appear negligible and have generally not been observed in the respective human studies. Still, the recent re-analysis of the large NPC trial in which more than 1000 participants received either 200 μg SeMet-containing yeast per day or placebo over several years has revitalised the fear of some adverse side effects by the chronic use of this organic Se-containing supplement in already well-supplied individuals [12]. This notion has been strengthened by a cross-sectional analysis from participants in the NHANES III survey but the effects were relatively small and limited to the highest quintile of Se status [13]. Whether SeMet-containing proteins show different properties such as higher sensitivity towards spontaneous oxidation compared to their normal sulphur versions remains an open issue.

Inorganic Se sources like sodium-selenate or -selenite are not linearly used for selenoprotein biosynthesis. Their metabolism strongly depends on the Se status of the consumer; a marginally supplied individual will take full advantage of the offered Se-source and steadily increase selenoprotein biosynthesis according to the dietary supply [11]. This is in contrast to individuals who are already Se-replete and present with saturated concentrations of plasma GPx-3 and SePP. Here, the surplus Se is not taken up for protein biosynthesis but rather secreted in the form of Se-containing sugar derivatives, or once a presumably toxic level has been passed, such excessive Se can be exhaled as dimethyl-selenide or lost as trimethylselenonium in urine [14]. In how far healthy and diseased individuals, young and older people, or male and female patients differ in their metabolic routes of dietary-derived Se is currently a matter of intensive research and scientific discussion [15]. Unfortunately, large-scale and long-time supplementation studies with inorganic Se sources are missing, therefore direct comparisons of both the beneficial and potentially adverse effects appear impossible at present [16].

2 Se status, Se-dependent diseases and supplementation studies

The relative amount of SeMet-containing and ‘real’ selenoproteins, and the metabolism of dietary-derived Se is not constant but depends largely on the actual nutritional and health status of the individual. This complex system of interactions is responsible for the lack of unanimous consensus on the recommended Se intake per day or the optimal Se concentration in blood [17]. Current assessments have mainly relied on the average Se concentrations found in areas where no deficiency symptoms are observed, the amount needed to prevent the development of Se deficiency symptoms, or the amount needed to saturate circulating levels of GPx-1 in erythrocytes, GPx-3 or SePP in plasma or serum. Some consensus is reached in suggesting that a daily intake of around 1 μg Se/kg body weight is definitely safe to prevent symptoms related to Se deficiency without carrying the apprehension of any adverse side effects.

Most inhabitants of the USA do easily reach or even exceed this recommended intake while many Europeans and people from Central China are usually slightly or considerably below this value [18]. Still, this suboptimal intake cannot easily be made responsible for obvious health issues.
in those marginally supplied areas. On the contrary, a daily supplementation of 200 µg Se proved of chemopreventive potency in the large aforementioned NPC trial and appears thus advisable to even the well-supplied North Americans that participated in this study and displayed Se blood concentrations largely exceeding average European values [19]. These effects are unlikely to be mediated by those selenoproteins that we can measure easily from serum or plasma for they have likely already been saturated at the beginning of the supplementation period in both verum- and placebo-treated individuals.

The question whether there were further bioactive Se-containing metabolites present in the yeast preparations chosen, or whether such metabolites have been generated in vivo in the participants, or whether those selenoproteins that we can not readily measure from human blood do need a higher Se supply than GPx-1, GPx-3 or SePP to become saturated can not be answered, yet. Thus, with our knowledge on the common final pathway of inorganic and organic Se sources in marginally supplied individuals, i.e. the improved biosynthesis of Sec-containing selenoproteins, we can easily and confidently recommend how to avoid or treat conditions of Se deficiency – but we have not yet reached solid scientific, experimental or empirical ground to finally decide on the optimal intake level of Se or the most suitable form to be used [20].

Yet, some very recent clinical trials have given further support to the well-appreciated notion that most people should benefit from increased Se intake. The follow-up analyses from the NPC trial convincingly verified the chemopreventive potential of 200 µg Se-enriched yeast per day to decrease, e.g. prostate cancer risk especially for participants that resided in the lowest tertile of baseline Se concentrations at the beginning of the study [21]. In Europe, a recently published case-control study indicated a pronounced inverse association of bladder cancer risk and serum Se concentrations [22]. Besides cancer, cardiovascular events represent the other major mortality reason in humans. An inverse association of Se blood levels with systolic and diastolic blood pressure has been reported in marginally supplied Europeans [23]. Interestingly, this effect was only observed in men but not in women [24]. In addition, activity of GPx-1 from erythrocytes was found strongly associated with cardiovascular event risk in patients with coronary artery disease [25]. Even though we do not yet understand the underlying mechanisms or whether GPx-1 was actively involved in the physiological effects or rather represented a convenient surrogate marker from blood to estimate the Se status, these clinical findings also support the claim for an increased daily Se intake.

A third major health risk is often encountered when by chance or surgery the immune system becomes activated beyond its regular extent. Infection, inflammation or traumas can induce vivid acute phase responses that reduce serum Se concentrations depending on the strength and the duration of the stimuli [26]. In sepsis patients, a clear correlation of mortality risk and blood Se concentrations has been established [27]. In a recent randomised, double-blind multiple-centre study, Se supplementation after the onset of severe sepsis has proven effective to improve health and reduce mortality [28]. Even when at present some similar trials failed to confirm the beneficial outcome upon acute supplementation with high Se dosages, there is consensus that patients with low Se concentrations have a poorer prognosis compared to well-supplied individuals. Neither the mechanisms by which Se concentrations decline during the acute phase response, nor the fate of the Se that disappears from blood are currently unequivocally resolved. Nevertheless, the clinical observations still argue for a preventive upregulation of the personal Se stores to be well prepared to survive such accidental or surgery-related challenges.

A last example for the potentially beneficial effects of increased Se supply to combat a premature mortality risk is given by recent results from a clinical trial on patients with HIV infections. In general, AIDS patients tend to develop Se deficiency during the course of the disease, and Se blood concentrations negatively correlate to AIDS mortality. Outcome from a respective double-blinded Se supplementation trials with AIDS patients has just been published [29]. Strong concerns had been raised against such trials before based on the identification of a Se-containing isozyme from the GPx family in the viral genome [30]. It was argued that not only the immune system of the patient but also proliferation rate and agility of the virus might become strengthened by Se supplementation. Fortunately, these fears have not come true, and both CD4-positive cell counts increased and viral RNA titres decreased in response to Se supplementation [29]. Further trials are needed to work out the impact of antiviral therapy on these effects. Still, increasing the Se status might represent a new promising adjuvant therapy option especially in Se deficient AIDS patients.

But as mentioned above, the long-term results from the NPC trial with those participants from the highest tertile of baseline plasma selenium level that appeared to carry an increased diabetes risk indicate that an upper limit of daily Se intake should not be exceeded [12]. Yet, most patients in hospital or under chronic ambulant therapy are unlikely to reside among the best supplied individuals and this risk can almost be completely excluded for people living in marginally supplied areas, i.e. large parts of Europe, Asia or Africa.

Taken together, it is obvious that disease impacts strongly on the Se metabolism in both men and women and their resulting Se status. Especially those patients with an activated immune response are in danger of developing a Se deficiency and might profit over-proportionally from Se supplementation. Still, cautious use of Se-containing supplements is indicated, especially if already a high Se status has been reached. The potential interaction of Se supple-
metabolism with the regular medications has often not been characterised, as mentioned above for AIDS and antiviral therapy. Moreover, potential interference with other widespread used pharmaceuticals like statins [31] or aminoglycoside antibiotics [32] have been described in vitro but are at present of unknown importance for Se metabolism in humans.

3 Thyroid gland functioning and thyroid hormone biosynthesis

Adequate function of the thyroid hormone axis critically depends on the essential trace elements iodine, Se and iron. The thyroid gland contains the highest iodine and Se concentration among the human tissues [33]. Biosynthesis of thyroid hormones, which are key regulators of brain development, body growth and intermediary metabolism, utilises iodine as building block for iodinated tyrosine residues of thyroglobulin (Tg). Iodide uptake is mediated against a concentration gradient via the sodium–iodide symporter (NIS), which is located in the basolateral membrane of thyrocytes (Fig. 2). NIS expression and activity are under thyroid stimulating hormone (TSH, thyrotropin) control and the energy required for this import is provided by the activity of the Na-K-ATPase [34]. The organification of iodide is catalysed by the hemoprotein thyroperoxidase (TPO), which uses H2O2 as cosubstrate [35]. TPO catalyses both the iodination of tyrosyl residues of Tg and the H2O2-dependent coupling of iodinated tyrosyl residues to generate the iodothyronines, which exhibit the typical diphenylether structure of thyroid hormones. Thyrooxinidase 1 and 2 (Thox) also named dual oxidase 1 and 2 (Duox), the G-protein coupled TSH receptor signals via the Gq/G11 coupled stimulation of phospholipase C. While most of the thyrocyte-specific processes such as iodide uptake and expression of genes relevant for thyrocyte-specific functions are under control of the cAMP pathway, albeit with several species differences, recent data generated in transgenic and knockout mouse models suggest that the reactions relevant for iodine organisation and thyroid hormone secretion are depending on the Gq/G11-signalling cascade [41]. This indicates that TSH-dependent proliferation and adaptive growth in response to goitrogen exposure are dependent on phosphoinositol, diacylglycerol and Ca2+ signalling. This recent information also suggests that at least some of the Se-dependent reactions of thyrocytes might be controlled by the Gq/G11-pathway.

4 The role of Se in thyroid hormone metabolism

Iodide accumulation and thyroid hormone biosynthesis commence at the end of the first trimester in the foetal thyroid gland and continue throughout the whole life. This
implies life-long TSH-regulated generation of H$_2$O$_2$ inside of the thyroid follicular lumen. As H$_2$O$_2$ represents a highly reactive cytotoxic metabolite, its generation would be difficult to control and to tailor to the particular demand of thyroid hormone biosynthesis if it was generated within the cytosol of thyrocytes. Therefore, the unique follicular organisation of the monolayer of epithelial thyrocytes that forms the extracellular colloid luminal space as a well-defined biological containment, and the dense microvascular supply with iodide, nutrients and blood on the basolateral side provide a logistic masterpiece of evolution. This unique compartmentation enables the use of a rather strong chemical, i.e. H$_2$O$_2$, for iodination and coupling, which can now proceed in a radical-mediated reaction mode [33]. In contrast to some outdated textbook statements, the production of H$_2$O$_2$ by Duox, its utilisation by TPO for iodination of tyrosyl residues and the coupling of iodinated tyrosyl side chains to iodothyronines in the Tg protein occur extracellularly at the surface of the apical plasma membrane facing the colloid space. In this ‘thyroxisome’ organisation [35], the extracellular active site of Duox delivers H$_2$O$_2$ to the extracellular active site of TPO, which uses both extracellular H$_2$O$_2$ and extracellular Tg as its two substrates. Reaction control is exerted by recently identified intracellular Duox activator proteins [42]. Still, additional precautions are required to protect thyrocytes from any excess of extracellularly-generated H$_2$O$_2$. This task cannot be fulfilled by the intracellular catalase alone, which displays a Km value for H$_2$O$_2$ that is too high to be efficient in its degradation. Here, members of the family of Se-dependent GPx display the appropriate Km values, and particular isoforms react efficiently with H$_2$O$_2$ to generate H$_2$O, e.g. the secreted isoform GPx-3. High expression of GPx-3 transcripts in the thyroid gland, production and secretion of functional GPx enzyme by thyrocytes and thyroid cell lines and noncovalent attachment of GPx-3 to Tg globules in the colloid has recently been demonstrated [43]. Previous studies indicated that production and secretion of GPx-3 by thyrocytes is under negative control of Ca$^{2+}$ signalling pathways [44]. This regulation is compatible with the above mentioned Gq/G11-mediated control of iodination and thyroid hormone secretion pathways. Otherwise, a concomitant parallel generation and degradation of H$_2$O$_2$ would not allow for optimal control of efficient thyroid hormone biosynthesis, and the maintenance of the integrity of thyrocytes and their follicular organisation would be at risk.

The high expression of the selenoprotein GPx-3 in thyrocytes and its secretion into the closed and protected colloid lumen (Fig. 2) might be one explanation for the high Se content of the thyroid gland observed in humans and many other species. Apart from GPx-3, several other members of the selenoprotein family are expressed in thyrocytes, e.g. TxnRd1 and TxnRd2, additional GPx family members (GPx-1, GPx-4), both 5'-deiodinase isoforms (Dio1, Dio2), Sep15, SePP, selenoproteins M and S [43]. To what extent these selenoproteins contribute to the Se content of the thyroid gland and whether they are also involved in antioxidant defence and redox control of thyrocytes remains to be studied. However, even if secreted GPx-3 was capable of degrading excess H$_2$O$_2$ efficiently, additional precautions are required to protect both the cell membrane and the intracellular compartments from any H$_2$O$_2$ diffusing into the thyrocytes. These functions might be elicited by both the GPx-1 and GPx-4 isozymes, the Se-dependent TxnRd enzymes and peroxiredoxins in addition to intracellular catalase.

Currently no detailed information is available on the modes of entry of Se compounds into thyrocytes (see below) but all available data hint towards an unparalleled priority of the thyroid gland over the other tissues with respect to Se supply and Se retention. An isolated Se deficiency does not necessarily lead to any obvious destruction of the highly active gland structure or to an increased death of H$_2$O$_2$-producing thyrocytes. In contrast, even elevated thyroid deiodinase expression levels and activities have been reported in Se deficient animal models [45, 46]. Further dedicated transgenic animal models will be needed to elucidate the function of a thyroid gland that has been deprived of specific selenoproteins, and its consequences for thyroid hormone biosynthesis and secretion.

### 5 Privileged supply of the thyroid gland by Se

Among all the tissues, the thyroid gland contains the highest Se concentration in the human body [33]. This feature is largely independent from the Se status of the organism, i.e. even in experimental animal studies where Se supply was strongly reduced by feeding diets that were almost completely deprived of every Se source, the brain and the endocrine glands, especially the thyroid, retained almost normal concentrations of the essential trace elements. Se concentrations and GPx activities in plasma, liver or kidneys become almost undetectable under these conditions [45]. Several recent transgenic mouse models have sharpened our ideas on the molecular metabolism of dietary-derived Se and its transport routes within the organism [47].

Since its first identification, the Se-rich plasma protein SePP has been assumed to be involved in Se transport and Se storage. Indeed, upon cloning of the SePP-encoding mRNA, 10 separate Sec-insertion codons were identified within the ORF, and they are largely conserved between rodents and humans [48]. Se isotopes injected into mammals appear fast in SePP-specific serum fractions and point towards the liver as the likely origin of circulating SePP molecules. This model for SePP biosynthesis and function was verified when transgenic SePP deficient mice were generated and analysed. On regular chow, SePP-KO mice displayed strongly reduced Se concentrations in plasma and almost all the other organs except for liver and thyroid.
Liver obviously still retained its Se uptake mechanisms, but instead of channelling the available Se into SePP biosynthesis and secretion, SePP-KO mice accumulated surplus hepatic Se amounts mainly in the form of GPx-1, the most abundant hepatic selenoprotein. Accordingly, other Se- and SePP-dependent compartments including serum, kidney, brain or testis displayed reduced Se contents [49, 50]. These results demonstrated the importance of Se and SePP for brain function and development for the first time, since purely dietary restrictions had never been successful before to reduce brain Se concentrations [47].

In this model, the impaired Se organification and transport via SePP led to Se-dependent neurological deficits including ataxia and seizures. Interestingly, these phenotypes were successfully rescued by increasing the diet with either sodium-selenite or SeMet. Thus, a regular SePP metabolism was important to guarantee privileged brain Se status. It remained to be determined whether hepatically-derived SePP or locally produced brain SePP was responsible for preferential Se supply into the CNS. Inactivation of all hepatic selenoproteins including hepatic SePP revealed that under these conditions of again strongly-reduced plasma Se concentrations, brain Se content was surprisingly only slightly affected [51]. The results indicated that heptatically produced and secreted SePP was not necessary for Se status in brain, in contrast to e.g. supply of plasma or the kidney. Locally expressed SePP mRNA and the Se-dependent translation and biosynthesis of mature SePP within the brain appeared indispensable for regular brain Se concentrations [52]. The uptake and turnover in brain may be related to the presence of specific SePP-receptors, as recently identified and described in testis [53]. Interestingly, both under Se-restricted nutrition and upon genetic SePP inactivation, the thyroid gland contained largely unaffected high concentrations of the essential trace element. The direct comparison to other organs places the thyroid gland even on the very top of the hierarchical Se supply among the organs, definitely on top of brain since thyroid Se levels remained unaffected even in the complete absence of SePP biosynthesis [46]. Whether this priority is affected in illness, by medical manipulation of thyroid hormone bioavailability, H2O2 generation. Due to inadequate iodide availability, H2O2 will accumulate and start to damage thyrocytes and follicular integrity and result in enhanced necrosis of epithelial tissue, which is replaced by fibrotic structures. The concomitant Se deficiency might impair the regular degradation of excess H2O2 via reduced GPx activity resulting in inadequate protection of thyrocytes and follicular structure from radical damage. Additional goitrogen exposure exaggerates this vicious circle by inhibiting NIS-mediated iodide uptake and TPO activity, both well known targets for several goitrogens. Whether inadequate Fe supply additionally impairs synthesis and function of the central hemoprotein TPO has not been studied in detail, yet [58].

Three observations are of particular note in this context. Firstly, mild Se deficiency results in a partial protection of the thyroid hormone axis and thyroid hormone metabolic pathways, because decreased activity of the Se-dependent deiodinase isozymes in Se deficient peripheral tissues reduces turnover of thyroid hormones, prolongs their biological half-lives and enhances enterohepatic recycling of iodothyronines and their conjugates [59]. This leads to an iodine-sparing effect, which relieves the pressure on the thyroid gland to supply more hormones. Evidence for this reasoning came from a supplementation trial in an iodine- and Se deficient and probably also goitrogen-exposed myxedematous cretin in Zaire. In contrast to initial expectations, Se supplementation resulted in disruption of his thyroid hormone status and led to myxedematous coma. Apparently, the chronically damaged thyroid gland of this patient was unable to efficiently utilise the offered iodide anymore that was liberated by the restored activity of the Se-dependent deiodinase enzymes [56]. From this study it was concluded that an adequate iodine status has to be restored first before Se supplementation can be initiated, at least under conditions of combined severe nutritional deficiencies of both trace elements.

6 Inadequate Se supply results in a vulnerable thyroid gland

First evidence for a vital role of Se in thyroid gland function came from observations in animal experiments and epidemiologic studies in some parts of Zaire, where endemic myxedematous cretinism has been observed [56]. This form of cretinism is characterised by mental and developmental retardation (dwarfism), severe hypothyroidism, myxedema but no goitre. Experimental animal, interventional and clinical studies suggest, that combined iodine and Se deficiencies in conjunction with nutritional exposure to goitrogens precipitate this disease, in which an inadequate iodine supply and lack of thyroid hormone biosynthesis lead to enhanced TSH stimulation of the gland via an impaired negative hypothalamic-pituitary feedback control [57]. Enhanced TSH receptor activation stimulates among other targets Duox activity and H2O2 generation. Due to inadequate iodide availability, H2O2 will accumulate and start to damage thyrocytes and follicular integrity and result in enhanced necrosis of epithelial tissue, which is replaced by fibrotic structures. The concomitant Se deficiency might impair the regular degradation of excess H2O2 via reduced GPx activity resulting in inadequate protection of thyrocytes and follicular structure from radical damage. Additional goitrogen exposure exaggerates this vicious circle by inhibiting NIS-mediated iodide uptake and TPO activity, both well known targets for several goitrogens. Whether inadequate Fe supply additionally impairs synthesis and function of the central hemoprotein TPO has not been studied in detail, yet [58].

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Interestingly, myxedematous cretinism has also been observed in other regions than central Zaire such as in some parts of India or Tibet [33]. Though also in these areas, a combination of severe iodine and Se deficiency has been described as an underlying reason, there are no indications that the phenotype is associated with a specific goitrogen. Instead, other precipitating factors such as toxins in grain (aflatoxin) or drinking water (fulvic acid) appear more likely to be involved in disease development. In addition, this type of cretinism seems to be associated with Kashin-Beck disease ("big joint disease"), a severe, irreversible chondro-osteopathy, which apparently can be prevented by adequate Se (and iodine?) supply [60]. In model systems, fulvic acid exposure leads to excessive superoxide formation [61], which might explain a protective effect of adequate Se supply and GPx activity for the degradation of H₂O₂.

In otherwise healthy and well-supplied humans, an isolated mild Se deficiency does not alter measurable thyroid hormone concentrations, and no evidence for an impaired or altered activity level of deiodinase isozymes has been found in regions with moderate or low Se intake [62]. Similar results have been observed in critical care patients who display strongly reduced serum Se levels but failed to respond with altered serum thyroid hormone concentrations upon Se supplementation [63]. These results indicate that the deiodinase isozymes are sufficiently expressed to maintain regular steady-state thyroid hormone concentrations under normal or even moderately Se deficient conditions. Only severe or chronically-reduced Se availability, potentially in combination with unfavourable genetic predisposition, will lead to impaired Dio expression and insufficient function in humans. Such conditions are difficult to be mimicked in cell culture or animal models, but their consequences leading to reduced thyroid hormone metabolism might be of fundamental importance to explain certain pathophysiological settings, e.g. the increased frequency of goitres in the EU or the still enigmatic low-T₃ syndrome in severe illness [64].

The issue of excessive iodine intake (e.g. by nutritional overload, the application of iodinated X-ray contrast agents or the antiarhythmic drug amiodarone) under conditions of inadequate Se supply is probably even more problematic. Chronic high nutritional intake of iodine in humans (>500 µg/day) leads to a substantial increase in thyroid size and an impaired thyroid hormone biosynthesis. Such situations are not uncommon in e.g. northern Japan, where local diet frequently contains more than 1000 µg iodine/day. Several observational and epidemiological studies indicate that successful table salt iodination programmes in regions of iodine deficiency or inadequate iodine supply (which still applies for 2/3 of our populated world!) lead to a significant but transient increase in autoimmune thyroid diseases (AITDs) in the respective population [65]. This effect is accompanied by an altered pattern of thyroid cancer forms in the long run. Here, a shift from the more problematic follicular to the less aggressive and treatable papillary forms is reported [66]. Successful table salt iodination programmes also reduce the incidence and prevalence of nodular alterations of the thyroid gland and reduce goitre growth, thereby improving the health status in both short and long term perspective. Whether Se – iodine, Fe – iodine, or even Se – Fe – iodine interactions and imbalances contribute to the transient increase in AITD accompanying such successful iodination programmes is still unclear and needs to be taken into account in future programme planning for micronutrient supplementation.

From these considerations, we would like to support the notion that an increased iodine supply to a thyroid gland which has been adapted to mild, moderate or even severe iodine deficiency requires concomitant improvement of its Se (and Fe?) intake to protect the organ from its increased iodising activity. Enhanced Se supply is needed to equip the thyrocytes and colloidal lumen with adequate amounts of functionally active GPx, TxnRd, Dio, Sep15 and other redox-active selenoproteins in order to optimally protect this vulnerable structure from any excessive iodide-derived oxidation products or H₂O₂-derived reactive oxygen species. Support for this hypothesis derives from a number of in vitro, experimental animal and human studies. In cells in culture, inadequate Se supply leads to decreased GPx activity and a parallel aberrant intracellular iodination of proteins [67]. Exposure to iodide excess results in severe necrosis and destruction of integral follicular organisation in Se deficient and combined Se- and iodine-deficient animals [57], whether or not concomitant exposure to goitrogens further aggravates this condition. These observations have been interpreted as being due to excessive H₂O₂ and ROS production by thyroid cells which result in, e.g. liberation of TGFβ, a strong inductor of fibrosis. Pretreatment with TGFβ-immunoneutralising sera was able to prevent this deleterious condition, and adequate Se supply proved to be beneficial in preventing necrosis and fibrosis, possibly by supporting apoptotic repair events [57]. Whether only GPx or also TxnRd and other selenoproteins and selenoenzymes contribute to thyroid protection from excess iodide, H₂O₂ and oxidative reactive products remains to be studied. So far, no distinctions between different Se species or nutritional forms have been made in their potential to exert these protective actions and a molecular link between Se protective effects and mechanism of fibrotic destruction of thyroid tissue has not been provided, yet.

7 Se deficiency and autoimmune thyroid disease

During the last years, several studies (Table 1) have reported on beneficial or preventive effects of Se supplementation in AITD. AITD is not uncommon in females dur-
ing their childbearing years. Pathophysiology of various forms of AITD is still not understood and so far no causative treatment is available for any of the major disease forms or its variants. Graves’ disease (m. Basedow) is caused by autoantibodies stimulating the TSH receptor on thyrocytes and retroorbital fibroblasts and leads to severe hyperthyroidism and in most cases endocrine orbitopathy. Antithyroid medication is clinical routine in AITD, and sometimes surgical or radiiodine intervention is necessary and may be accompanied by anti-inflammatory treatments or agents blocking the β-adrenergic receptors. Determination of stimulating TSH receptor autoantibodies (TRAK) is the main diagnostic procedure. M. Hashimoto, a destructive autoimmune disease, leads to hypothyroidism, which requires lifelong substitution of L-thyroxine, one of the most often prescribed drugs worldwide. Pathogenesis of m. Hashimoto is still unclear, but TPO and Tg autoantibodies are found and determined in patients. While only limited data have been reported for adjuvant treatment of Graves’ disease with Se compounds in combination with ‘other antioxidants’ [68], remission and outcome has been linked to adequately high serum Se levels (>120 μg/L) and low TRAK values [69]. In contrast to Graves’ disease, much more information is available on positive effects of Se supplementation in the treatment of m. Hashimoto.

Several observational and three prospective, double-blind controlled studies [70–73] reported on beneficial effects of Se supplementation in patients with m. Hashimoto and autoimmune thyroiditis. The effects after 3–12 month of supplementation were remarkably independent on the Se compound used, i.e. selenite, SeMet or Se-enriched yeast. Titres for TPO autoantibodies (TPOab) decreased (not those for Tg), the ultrasound pattern of the thyroid gland improved and in one study a standardised questionnaire on quality of life indicated improved contentedness of Se-treated patients [71]. Since all these Se-containing supplements funnel ultimately into the common final path of selenoprotein biosynthesis, it is conceivable that the beneficial effects are mediated by Se-responsive selenoenzymes. The nature of these selenoproteins involved in autoimmune disease and the site of effect, i.e. within the thyroid gland or via the immune system, remain to be established. Unfortunately, no clear evidence has yet been presented for a supplementation-induced conversion of m. Hashimoto or autoimmune thyroiditis to normal euthyroidism, which would not require further concomitant L-thyroxine replacement medication. Thus, Se supplementation can currently only be regarded as an adjuvant option to complement L-thyroxine replacement at best.

A very recent prospective controlled blinded study provided surprising results on positive Se-dependent treatment of postpartum thyroiditis and hypothyroidism, again a very frequent serious complication during pregnancy associated with AITD [74]. TPOab and thyroid inflammatory activity were decreased and the incidence of hypothyroidism in the postpartum period was reduced by the Se supplementation. If this result can be verified and confirmed by further independent studies, a systematic screening for TPOab and the adjuvant treatment to increase the Se status of the women will provide a major progress in preventing and treating the deleterious effects of maternal thyroid disease for both the mother and the developing child.

### Table 1. Clinical studies on adjuvant Se-based treatment of AITD

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Study type</th>
<th>Form of Se</th>
<th>Major outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune thyroiditis, Hashimoto’s thyroiditis</td>
<td>Observational treatment</td>
<td>Selenite</td>
<td>Decreased TPOab titres, improved patient status</td>
<td>[70]</td>
</tr>
<tr>
<td>Autoimmune thyroiditis, Hashimoto’s thyroiditis; females</td>
<td>Prospective, placebo controlled, double blind, crossover</td>
<td>200 μg Selenite</td>
<td>Decreased TPOab titres, improved patient well being, normalised echogenicity in thyroid ultrasound</td>
<td>[71]</td>
</tr>
<tr>
<td>Autoimmune thyroiditis, Hashimoto’s thyroiditis</td>
<td>Prospective, placebo controlled, double blind</td>
<td>SeMet</td>
<td>Decreased TPOab titres, improved patient well being</td>
<td>[72]</td>
</tr>
<tr>
<td>Autoimmune thyroiditis, Hashimoto’s thyroiditis; females</td>
<td>Prospective, placebo controlled, double blind</td>
<td>100/200 μg SeMet</td>
<td>Decreased TPOab titres</td>
<td>[73]</td>
</tr>
<tr>
<td>TPOab positive pregnant women</td>
<td>Prospective, placebo controlled, double blind</td>
<td>200 μg SeMet</td>
<td>Decreased incidence of both postpartum thyroiditis and permanent hypothyroidism</td>
<td>[74]</td>
</tr>
</tbody>
</table>
supplied areas like everywhere in Europe or in most parts of Asia or Africa. The positive supplementation effects described and verified to date clearly highlight the enormous potential of actively controlling and increasing a person's Se status. Beneficial effects have been observed on the cancer risk of several organ systems, on cardiovascular parameters, on the immune system, the endocrine axes with a special emphasis on thyroid gland function and thyroid hormone metabolism. Epidemiological analyses have indicated that a large fraction of goitres can be prevented in endemic areas by improving the Se status of the inhabitants – provided that adequate iodide supply is established before Se intervention, and recent Se supplementation studies proved effective to treat two forms of AITD. Clearly, more prospective and monitoring studies with larger cohorts of patients and longer durations are needed to confirm the surprisingly efficient health effects. Nevertheless, it appears as if both the molecular research and the clinical trials have finally come of age to be taken serious and to receive the attention and sometimes even the funding that is needed to verify the findings and broaden the promising application fields of this potent trace element.

Supported by grants from the Deutsche Forschungsgemeinschaft (Kö 922/8-2/3, Scho 849/2-1), Deutsche Krebshilfe (10-1792 Scholl), EnFürCé, and EFRE TSB Zukunftsfonds Berlin (#10182000).

The authors have declared no conflict of interest.

9 References


