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Multiple nutritional factors and thyroid disease, with particular reference to autoimmune thyroid disease

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Hashimoto's thyroiditis (HT) and Graves' disease (GD) are examples of autoimmune thyroid disease (AITD), the commonest autoimmune condition. Antibodies to thyroid peroxidase (TPO), the enzyme that catalyses thyroid-hormone production and antibodies to the receptor for the thyroid-stimulating hormone, are characteristic of HT and GD, respectively. It is presently accepted that genetic susceptibility, environmental factors, including nutritional factors and immune disorders contribute to the development of AITD. Aiming to investigate the effect of iodine, iron and selenium in the risk, pathogenesis and treatment of thyroid disease, PubMed and the Cochrane Library were searched for relevant publications to provide a narrative review. *Iodine*: chronic exposure to excess iodine intake induces autoimmune thyroiditis, partly because highly-iodinated thyroglobulin (Tg) is more immunogenic. The recent introduction of universal salt iodisation can have a similar, although transient, effect. *Iron*: iron deficiency impairs thyroid metabolism. TPO is a haem enzyme that becomes active only after binding haem. AITD patients are frequently iron-deficient since autoimmune gastritis, which reduces iron absorption and coeliac disease which causes iron loss, are frequent co-morbidities. In two-thirds of women with persistent symptoms of hypothyroidism despite appropriate levothyroxine therapy, restoration of serum ferritin above 100 µg/l ameliorated symptoms. *Selenium*: selenoproteins are essential to thyroid action. In particular, the glutathione peroxidases remove excessive hydrogen peroxide produced there for the iodination of Tg to form thyroid hormones. There is evidence from observational studies and randomised controlled trials that selenium, probably as selenoproteins, can reduce TPO-antibody concentration, hypothyroidism and postpartum thyroiditis. Appropriate status of iodine, iron and selenium is crucial to thyroid health.

Autoimmune thyroid disease: Autoimmune thyroiditis: Nutrition: Iodine: Iron: Selenium

The thyroid gland is the organ most commonly affected by autoimmune disease[1]. Lymphocytic infiltration of the thyroid is a frequent post-mortem finding in some 40 % of white females and 20 % of white males in the USA, with similar percentages of British white males and females being affected[2]. In black Americans and Japanese, the occurrence of lymphocytic thyroid infiltration was less than half that in Caucasians[2]. Autoimmune thyroid disease (AITD) was probably first described in 1912 when a Japanese physician, Hakaru Hashimoto, reported a condition where the thyroid was infiltrated by lymphocytes resulting in the production of anti-thyroid antibodies[3].

AITD, also known as autoimmune thyroiditis, has a multifactorial aetiology involving both genetic, environmental and nutritional factors[4]. It includes a spectrum of thyroid conditions ranging from hypothyroidism, most notably Hashimoto's thyroiditis (HT) at one end,

Abbreviations: AITD; autoimmune thyroid disease; DIO; deiodinases; GD; Graves' disease; GPX; glutathione peroxidases; HT; Hashimoto's thyroiditis; ID; iron deficiency; L-T4; levothyroxine; RCT; randomised controlled trial; T3; tri-iodothyronine; T4, thyroxine; Tg; thyroglobulin; TPO; thyroid peroxidase; TSH; thyroid-stimulating hormone.

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to hyperthyroidism, most commonly Graves' disease (GD) at the other end[4]. In HT, the thyroid gland is gradually destroyed resulting in reduced production of thyroid hormones and triggering symptoms that include fatigue, weight gain, constipation, increased sensitivity to cold, dry skin, depression, muscle aches and reduced exercise tolerance[5]. HT affects more than 15 % of females over 60 years and 2 % of males[6]. It is defined by the presence of antibodies to thyroid peroxidase (TPO), the thyroid enzyme that oxidises iodide to iodine for thyroid hormone synthesis[4]. In addition, antibodies to thyroglobulin (Tg), the protein on which thyroid hormones are synthesised by iodination of its tyrosine residues, are frequently present[4]. In GD, the major autoantigen (thyroid-stimulating hormone (TSH)-antibody) is to the receptor for the TSH, which causes overproduction of thyroid hormones, resulting in symptoms such as irritability, rapid heartbeat, weight loss, poor tolerance of heat and bulging eyes (Graves' orbitopathy)[4,7,8].

Nutritional factors that affect thyroid function include the micronutrients iodine, iron and selenium[9]; these will be discussed later. Though vitamin D has been postulated to affect thyroid function, the evidence is insufficient[9] to include it in the present review.

PubMed and the Cochrane Library were searched for publications up to March 2018 using the search terms 'autoimmune thyroiditis' OR 'autoimmune thyroid disease' in combination with 'iodine', 'selenium', 'iron' and 'nutrition OR diet'. Articles were filtered by the relevance of the title, abstract and finally the full text. Relevant conclusions or results were extracted from each article to provide a narrative review.

Iodine

Role of iodine in the thyroid

Iodine is a key constituent of the thyroid hormones, thyroxine (T4, pro-hormone) and tri-iodothyronine (T3, active hormone), as shown in Fig. 1, which also depicts the key players in thyroid hormone synthesis that takes place in the thyroid follicular cells[10].

Iodine and autoimmune thyroid disease

The association between iodine intake and the presence of circulating thyroid antibodies is complex with iodine intake both below and above the recommended level being associated with an increase in circulating antibodies[11]. Circulating TPO-antibodies and Tg-antibodies are common both in populations with a stable high iodine intake and those with mild and moderate iodine deficiency (ID)[12]. Deficient iodine intake can lead to nodular goitre in which thyroid antigens are released from the abnormal gland, resulting in the presence of thyroid antibodies in the circulation[13]. However, excess iodine intake or a rise in intake following iodine fortification of an iodine-deficient population also gives an increased risk of thyroid autoimmunity, as attested by studies in many countries[14–24]. In China, for instance, 3 years after the introduction of salt iodisation in 1996, the prevalence of AITD was 0·5 % in an area of mildly deficient iodine intake, 1·7 % in an area of more-than-adequate iodine intake and 2·8 % in an area of excessive iodine intake[14]. In Denmark, formerly a region of mild-to-moderate ID (median urinary iodine concentration 61 μg/l), 5 years after the mandatory iodine fortification of salt, iodine status had significantly improved (median urinary iodine concentration 101 μg/l), but the prevalence of thyroid antibodies had risen, i.e. TPO-antibody >30 IU/ml increased from 14 to 24 % and Tg-antibody >20 IU/ml increased from 14 to 20 %[18]. However, despite the short-term adverse effects on thyroid autoimmunity, raising iodine intake from a deficient to an optimal intake-level ultimately results in the decreased prevalence of AITD; Denmark is an example of this[11,25].

Potential mechanisms by which high or increased iodine intake raises autoimmune thyroid disease risk

The increase in circulating antibodies associated with iodine fortification is probably due to a number of factors including the strong immunogenicity of highly iodinated Tg which may trigger an immune reaction against the thyroid gland[25,26]. An additional factor may be that excess iodine intake increases the expression of the intercellular adhesion molecule-1, on the thyrocyte causing accelerated mononuclear cell infiltration and inflammation[26]. This has been demonstrated in the NOD.H2^{h4} mouse model of autoimmune thyroiditis where iodide treatment enhanced the transcription of intercellular adhesion molecule-1 triggered by reactive oxygen species and, in particular, by hydrogen peroxide generated in the thyrocyte for the organification of iodine[26,27]. Other likely effects of high iodine intake in susceptible individuals are an increased production of thyroid-infiltrating T helper 17 cells, inhibition of T regulatory cell development and an abnormal expression of TNF-related apoptosis-inducing ligand in thyrocytes, resulting in apoptosis and tissue destruction[28].

Iodine-intake recommendations to reduce autoimmune thyroid disease risk

With regard to autoimmune thyroiditis, as can be seen from the earlier section, there is more evidence for an association with iodine excess than with deficiency, especially in genetically susceptible individuals[14,28,29]. It is therefore important to ensure, as far as possible, that iodine intake falls within the recommended levels[11] (see Table 1[30–32]). On a population basis, this would be represented by a median urinary iodine concentration in adults of 100–200 μg/l. Authorities introducing iodine fortification of the food supply in a country (e.g. universal salt iodisation) need to ensure that such fortification is introduced very cautiously; Denmark provides an excellent example of how this can be done[33]. Individuals living in a country that does not have an iodine-fortified food supply who avoid the main food sources of iodine, i.e. milk and dairy products, seafood, most notably haddock, cod, crab, large/Dublin-bay prawns (often called scampi) and eggs, and do not use iodised salt, should be advised to take a daily supplement containing 140–150 μg iodine for thyroid protection, particularly if

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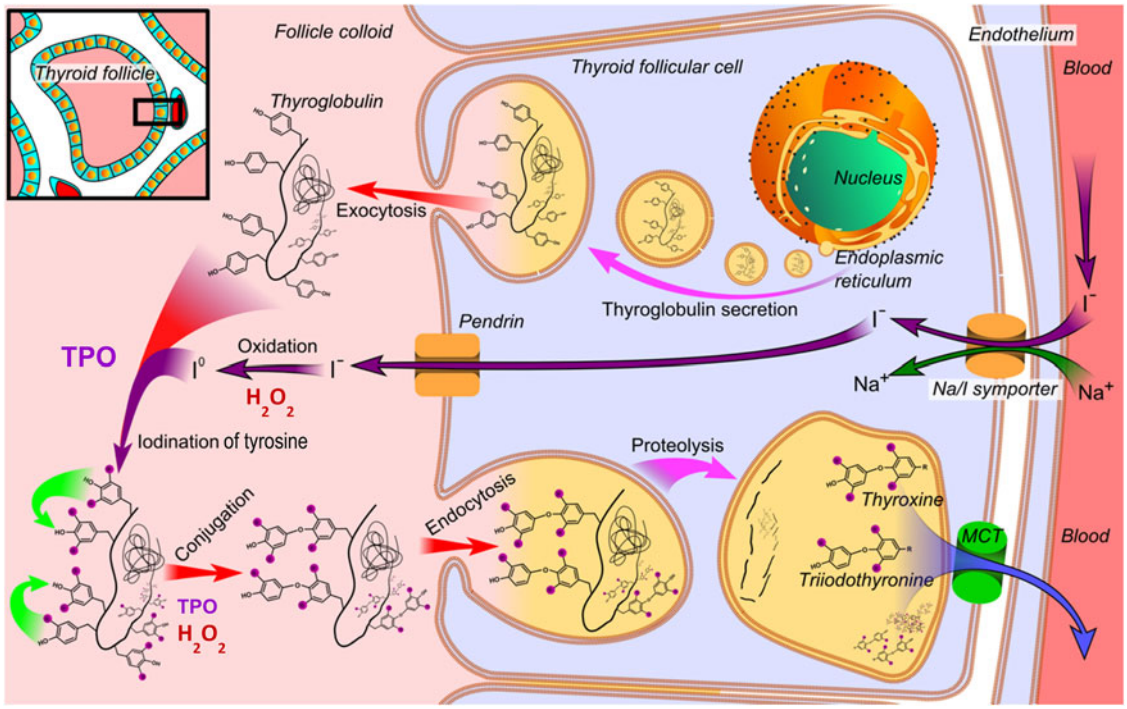

Fig. 1. (Colour online) Synthesis of the thyroid hormones in the thyroid follicle (modified from Häggström 2014[10]). Thyroglobulin is synthesised in the rough endoplasmic reticulum and follows the secretory pathway to enter the colloid in the lumen of the thyroid follicle by exocytosis. Meanwhile, a sodium-iodide (Na/I) symporter pumps iodide (I^-) actively into the cell, which previously has crossed the endothelium by largely unknown mechanisms. This iodide enters the follicular lumen from the cytoplasm by the transporter pendrin, in a purportedly passive manner. In the colloid, iodide (I^-) is oxidised to iodine (I^0) by hydrogen peroxide (H_2O_2) with the help of an enzyme called thyroid peroxidase (TPO). Iodine (I^0) is very reactive and iodinates the thyroglobulin at tyrosyl residues in its protein chain (in total containing approximately 120 tyrosyl residues). In conjugation, adjacent tyrosyl residues are paired together, again under the influence of TPO and H_2O_2. The entire complex re-enters the follicular cell by endocytosis. Proteolysis by various proteases liberates thyroxine and triiodothyronine molecules, which enter the blood *via* a monocarboxylate transporter (MCT).

planning pregnancy[34–36]. Although high in iodine, intake of brown seaweed (e.g. kelp/kombu), or brown-seaweed supplements should be avoided as it may result in excessive intake[37].

Iron

Role of iron in the thyroid

A haem-dependent enzyme, TPO, that has iron at its active centre, is required for thyroid hormone synthesis, as illustrated in Fig. 1[38,39]. TPO becomes active at the apical surface of thyrocytes only after it binds a prosthetic haem group[40], hence an adequate iron status is required for the synthesis of thyroid hormones.

Co-morbidity of autoimmune thyroid disease and other autoimmune conditions

It is not always appreciated that ID is common in people with AITD owing to the frequent co-morbidity of other autoimmune conditions such as coeliac disease[41–43] and autoimmune gastritis[44–47] that often cause ID. Patients with subclinical hypothyroidism or HT frequently have lower serum iron concentration and a higher prevalence of ID than do healthy controls[48,49]. A symbiotic relationship exists between active thyroid hormone concentration and the formation of erythrocytes; T3 is needed to stimulate the proliferation of erythrocyte precursors, both directly and by enhancing the production of erythropoietin[50].

Table 1. Iodine intake requirements by life stage according to various authorities

Age	EFSA AI (μg/d)[30]	USA RDA (μg/d)[31]	ICCIDD/UNICEF/ WHO RNI (μg/d)[32]
0–6 month	–	110 (AI)	90
7–12 month	70	130 (AI)	90
1–6 year	90	90	90
7–10 year	90	90–120	120
11–14 year	120	120–150	120–150
15–17 year	130	–	–
15–50 year	–	150	150
≥18 year	150	–	–
Pregnancy	200	220	250
Lactation	200	290	250

AI, adequate intake; RNI, recommended nutrient intake.

Dependence of thyroid function on iron status

ID reduces thyroid hormone production by decreasing the activity of TPO[38–40]. Evidence of the dependency of thyroid function on iron status comes from both animal and human studies. In rodents, ID, with or without anaemia, decreased serum T4 and T3 concentrations, lowered 5′-deiodinase (DIO) activity and reduced the ability to thermoregulate in response to a cold environment[39,51–53]. In US women with mild ID anaemia (Hb, 110 g/l), serum T3 and T4 were significantly lower than in iron-sufficient controls[54]. Furthermore, ID predicts poor maternal thyroid status in pregnancy; in a study on 365 Swiss pregnant women in the second and third trimesters with borderline ID (median urinary iodine concentration 139 μg/l), concentrations of TSH, total T4 and urinary iodine were measured. Body iron stores, calculated from blood Hb concentration, mean corpuscular volume, serum ferritin, and transferrin receptor were highly significant predictors of TSH and total T4 ($P < 0{\cdot}0001$)[55]. We also know that ID is associated with hypothyroxinaemia; serum free T4 concentrations were significantly lower in both 3340 pregnant and 1052 non-pregnant Chinese women with ID than in iron-adequate women[56].

Effect of low iron stores on the efficacy of treatment for hypothyroidism

It is important to recognise that low iron stores may contribute to symptom persistence in patients treated for hypothyroidism in 5–10 % of whom symptoms remain despite being treated with levothyroxine (L-T4)[57]. An example is afforded by a small study in twenty-five Finnish women with persistent symptoms of hypothyroidism, despite appropriate L-T4 therapy, who became symptom-free when treated with oral iron supplements for 6–12 months[58]. None of the women had anaemia or erythrocyte indices outside the reference range although all had serum ferritin <60 μg/l. Restoration of serum ferritin above 100 μg/l ameliorated the symptoms in two-thirds of the women. At least 30–50 % of hypothyroid patients with persisting symptoms despite adequate L-T4 therapy may, in fact, have covert ID[58].

Supplementation with thyroid hormone can improve iron status

An interesting fact is that supplementation with thyroid hormone in patients with subclinical hypothyroidism improves iron status. Early experiments in hypothyroid rats showed diminished gastrointestinal iron absorption that was restored to normal on supplementation with T3[59]. In iron-deficient women with subclinical hypothyroidism treated for 1 year with T4, the frequency of anaemia decreased ($P = 0{\cdot}001$) while ferritin, iron and Hb levels slightly increased ($P > 0{\cdot}05$)[49]. In untreated women, a further decrease in ferritin level and increase in anaemia occurred[49]. In two randomised controlled trials (RCT) in patients with coexisting ID anaemia and sub-clinical hypothyroidism, treatment with iron and L-T4 together was considerably more effective in improving iron status than was treatment with iron alone[60,61].

Recommendations for iron intake in thyroid patients

Patients with AITD or hypothyroidism should be routinely screened for ID. If either ID or serum ferritin below 70 μg/l is found[58], coeliac disease or autoimmune gastritis may be the cause and should be treated. Medication that reduces the acidity of stomach contents (e.g. proton pump inhibitors) may also cause reduced iron absorption[62]. If ID anaemia is present, haematological testing can be used to rule out the anaemia of chronic disease as the cause. In the absence of the latter, supplementation should be begun to restore iron sufficiency and prevent its deleterious effects on thyroid function[54,63].

Once iron sufficiency is restored, assuming there is no underlying clinical cause of the deficiency, patients need to be told how to optimise their dietary iron intake. Foods with relatively high iron concentration include meat, fish, cereals, beans, nuts, egg yolks, dark green vegetables, potatoes and fortified foods[64]. However, iron is inefficiently absorbed, its bioavailability from different foods being markedly variable; bioavailability has been estimated to be in the range of 14–18 % for mixed diets and 5–12 % for vegetarian diets in individuals with no iron stores[65]. Absorption depends on a number of dietary and host-related factors; haem iron (from animal tissues) is considerably better absorbed than non-haem iron, although the latter constitutes 90 % of the iron in a mixed diet. Dietary factors that reduce non-haem iron absorption include phytate, polyphenols and calcium, while those that increase it include ascorbic acid and muscle tissue[65]. Following dietary advice, iron status should be checked regularly.

Selenium

Role of selenium in the thyroid: selenoproteins

The thyroid contains the highest concentration of selenium in the human body and is able to retain it even under conditions of severe deficiency[66]. A number of selenoproteins are expressed in thyrocytes[67], those named later being particularly important to thyroid function.

The deiodinases. DIO1 and DIO2 can activate T4 by transforming it into T3 by removal of the 5′-iodine, while DIO1 and DIO3 can prevent T4 from being activated by converting it to the inactive reverse T3[68] (Fig. 2). DIO3 can also inactivate T3 by 5-deiodination to diiodothyronine. DIO2 is largely responsible for the local conversion of T4 to T3 in extrathyroidal target tissues[69]. A major role of DIO3 is to protect sensitive cells, such as fetal tissue, the placenta and central nervous system, from excessive concentrations of the active hormone, T3[69,70].

The glutathione peroxidases. Extracellular glutathione peroxidase (GPX)3 is the only actively secreted GPX isozyme that is abundantly expressed in the thyroid gland[70]. It is secreted at the apical side of the thyrocyte membrane where it converts excess hydrogen peroxide that has not been used by TPO for the iodination of tyrosyl residues of Tg or for iodotyrosine coupling, into harmless water[71].

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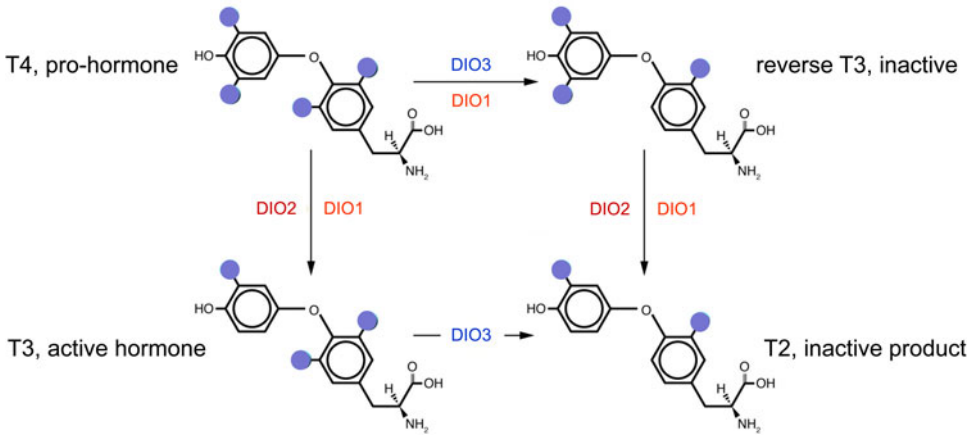

Fig. 2. (Colour online) Action of the iodothyronine deiodinases, DIO1, DIO2 and DIO3, to produce the active and inactive forms of thyroid hormone.

Selenoprotein S. Selenoprotein S (SELENOS) is involved in the control of the inflammatory response in the endoplasmic reticulum by retrotranslocation of misfolded proteins from the endoplasmic reticulum lumen to the cytosol[72]. In a Portuguese study, the *SELENOS* – 105G/A promoter polymorphism (rs28665122) was strongly associated with circulating levels of cytokines such as IL-1β, IL-6, and TNF-α, known to be involved in the pathogenesis of HT[71,73]. Those with the *SELENOS* GA and AA genotypes were significantly more likely to have HT: OR (95 % CI) for HT was 2·22 (1·67, 2·95) and in male A-allele carriers, 3·94 (1·43, 10·84).

Effect of selenium status on thyroid disease

Selenium deficiency has been associated with a number of adverse thyroid conditions, including hypothyroidism, subclinical hypothyroidism, enlarged thyroid[74–77], thyroid cancer[67,77–79] and AITD, including HT[75,77] and GD[77,80].

A study of thyroid disease prevalence in more than 6000 people from two counties of Shaanxi Province, China, of very different selenium status, adequate and low, showed the protective effect of selenium adequacy[75]. Median (interquartile range) serum selenium concentration differed almost 2-fold (103·6 (79·7, 135·9) *v.* 57·4 (39·4, 82·1) μg/l; $P = 0·001$) between the two counties although iodine status was comparable[75]. After adjustment for potential confounders, the prevalence of pathological thyroid conditions was significantly lower in the adequate-selenium than in the low-selenium county (18·0 *v.* 30·5%; $P < 0·001$). Higher serum selenium was associated with significantly lower odds (OR (95 % CI)) of autoimmune thyroiditis (0·47 (0·35, 0·65)), hypothyroidism (0·75 (0·63, 0·90)), subclinical hypothyroidism (0·68 (0·58, 0·93)) and enlarged thyroid (0·75 (0·59, 0·97))[75]. The iodine intake was more-than-adequate[14,75,81] in both counties which may have accounted to some extent for the high prevalence of thyroid disease[15,82].

Selenium status has been found to be significantly lower in patients with GD than in normal controls in Danish[80] and Chinese studies[83]. In the latter, serum selenium was negatively correlated with serum titre of TPO-antibodies ($r = -0·161$, $P = 0·021$), and Tg-antibodies ($r = -0·237$, $P = 0·001$)[83]. In a prospective, case–control study in an Australian population, mean serum selenium decreased in parallel with increasing severity of Graves' orbitopathy: 94·0 (SD 15·8) μg/l in GD, 86·9 (SD 15·0) μg/l in moderate-to-severe Graves' orbitopathy and 86·1 (SD 13.4) μg/l in sight-threatening Graves' orbitopathy ($P = 0·003$)[84]. However, these data may simply reflect the presence of inflammation in GD and more especially in Graves' orbitopathy; the expression of selenoproteins including plasma selenoprotein P is reduced by inflammatory cytokines resulting in a fall in plasma selenium[85,86].

Randomised controlled trials of selenium in thyroid disease

Several trials of selenium supplementation have been carried out in AITD/HT and mild Graves' orbitopathy.

In a large, multicentre, RCT with selenium, patients with mild Graves' orbitopathy significantly improved on treatment with 100 μg selenium twice/d (as sodium selenite) for 6 months[7]. Patients on selenium treatment had improved quality of life ($P < 0·001$), less eye involvement ($P = 0·01$) and slower disease progression ($P = 0·01$). The benefit persisted at the 12-month follow-up. A protocol for an RCT of selenium in patients with Graves' hyperthyroidism (the GRASS trial) was published in 2013[87]. The primary outcome is the proportion of participants with anti-thyroid drug treatment failure at the end of the intervention period (24–30 months). Secondary outcomes include thyroid-specific quality of life and eye symptoms during the first year after randomisation[87]. The results of the trial have not yet been reported.

There have been a number of systematic reviews/meta-analyses of controlled trials of selenium treatment in patients with AITD/HT[70,88–90]. The most recent is a 2016 meta-analysis of sixteen trials that found that selenium supplementation reduced serum TPO-antibodies levels after 3, 6 and 12 months in a population with chronic autoimmune thyroiditis treated with L-T4[88]. However, in an untreated autoimmune thyroiditis

population, the effect was significant only after 3 months[88]. Some of these studies also saw a reduction in Tg-antibody titre at 12 months, an improvement in thyroid echogenicity and an increase in subjective well-being. Unfortunately, the methodology of many of the studies was flawed; underpowered, not double-blinded, not placebo-controlled and disparities in iodine intake were not considered[88,89,91]. The beneficial effect in some studies and not in others cannot easily be explained on the basis of baseline selenium status, stage of disease, baseline TPO-antibody titres, form or dose of selenium used[4]. Later studies not included in these meta-analyses have been too small to contribute meaningful data[92,93]. Well designed, properly powered, RCT of selenium in the treatment of AITD/HT are therefore still needed before we can confidently recommend selenium supplementation in these patients. The protocol for a new, high-quality, trial of selenium supplementation (Catalyst Trial) in patients with chronic autoimmune thyroiditis has been published[94]. We await the results with interest.

The presence of thyroid autoantibodies is relatively high in women of childbearing age[95]. One notable RCT has been carried out in pregnant women positive for TPO-antibodies. Up to 50 % of such women develop postpartum thyroiditis of whom 20–40 % subsequently become hypothyroid[96]. In an Italian study, 151 TPO-antibody positive women were randomly assigned to supplementation with 200 µg selenium/d (as selenomethionine) or placebo during pregnancy and the postpartum period[97]. TPO-antibodies fell significantly during gestation in both groups but the reduction was significantly greater in the selenium-supplemented group ($P = 0{\cdot}01$) and remained so in the postpartum period ($P = 0{\cdot}01$) (see Fig. 3). Compared with women on placebo, those on selenium had a significantly lower incidence of post-partum thyroid disease (28·6 *v.* 48·6 %; $P < 0{\cdot}01$) and permanent hypothyroidism (11·7 *v.* 20·3 %; $P < 0{\cdot}01$). In contrast to women on placebo, ultra-sound echogenicity did not fall in those supplemented with selenium. At the end of the postpartum period, grade 2–3 thyroiditis had developed in 44·3% of women on placebo but only in 27·3% of women on selenium ($P < 0{\cdot}01$)[97].

The only other RCT that investigated the effect of selenium supplementation on AITD in pregnancy found no difference in the magnitude of TPO-antibody decrease between selenium and placebo groups[98]. However the median baseline TPO-antibody concentrations in the women were much lower than in the earlier study, the selenium dose was less than one third as high (60 µg/d) and the trial was not adequately powered[98]. Clearly, there is a need for a further, high-quality, adequately powered RCT in the TPO-antibody-positive pregnant population to see if the results of the Italian study can be replicated[97].

Is selenium intake adequate to reduce the risk of thyroid disease?

Selenium intake differs vastly from one part of the world to another owing to differences in the selenium content of the soil on which crops and fodder are grown, selenium speciation, soil pH and organic-matter content[99]. Intake ranges from deficient (7 µg/d) to toxic (4990 µg/d) as shown in Fig. 4[100,101]. A vertical band in Fig. 4 shows the level of intake believed to be needed to optimise the activity of GPX3[101], the main selenoenzyme that removes excess hydrogen peroxide from the thyroid. It is clear that the mean intake in many countries, notably those in Europe, does not achieve that level.

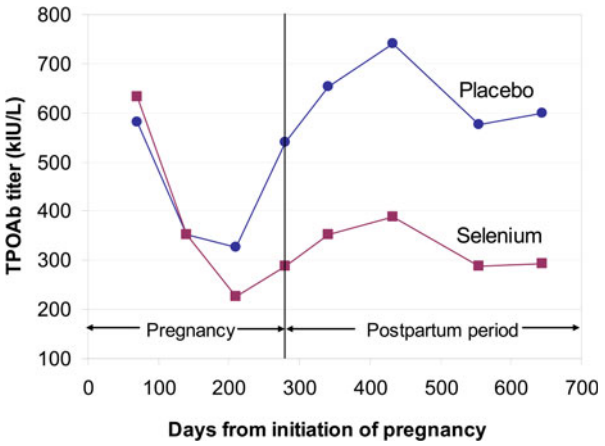

Fig. 3. (Colour online) Selenium protects against postpartum autoimmune thyroid disease (adapted from Negro *et al.*[97] with permission 0. TPOAb, thyroid peroxidase antibodies.

Recommendations for selenium intake

Although we lack evidence that selenium supplementation results in clinical improvement in autoimmune thyroiditis (other than in mild Graves' orbitopathy), it still makes sense to ensure that selenium intake is adequate, given the roles played by selenoproteins in human health[100] and particularly in the thyroid[70,71]. Regions of deficient, more-than-adequate or high iodine intake may have more need for selenium owing to the capacity of selenoproteins to protect the thyroid from excessive hydrogen peroxide[71] and from inflammation[71] (see earlier). Hence, in such locations, clinicians need to ensure that selenium intake/status is adequate. Women are at greater risk of thyroid disorders and may thus have a higher requirement for additional selenium, particularly in pregnancy. Geographical location will give a good indication of selenium adequacy or otherwise (see Fig. 4).

It is also important to enquire into the dietary habits of a given patient and see if he/she eats foods that supply selenium[100]. Although Brazil nuts are the richest selenium food source they cannot be recommended as a main source as the content is very variable, ranging from 0·03 to 512 mg/kg fresh weight, and they are high in barium, which can be toxic[102]. Otherwise, organ meats and seafoods are the best sources, followed by muscle meats, cereals and grains, although the selenium content of the latter varies widely with location, being towards or at the bottom of the range in the UK and Europe but at the top in North America, most notably in Canada (see Fig. 5)[100,102]. In China, selenium-enriched tea is an option[75]. Given the sources described, vegans and vegetarians in the West are particularly at risk of inadequate selenium intake.

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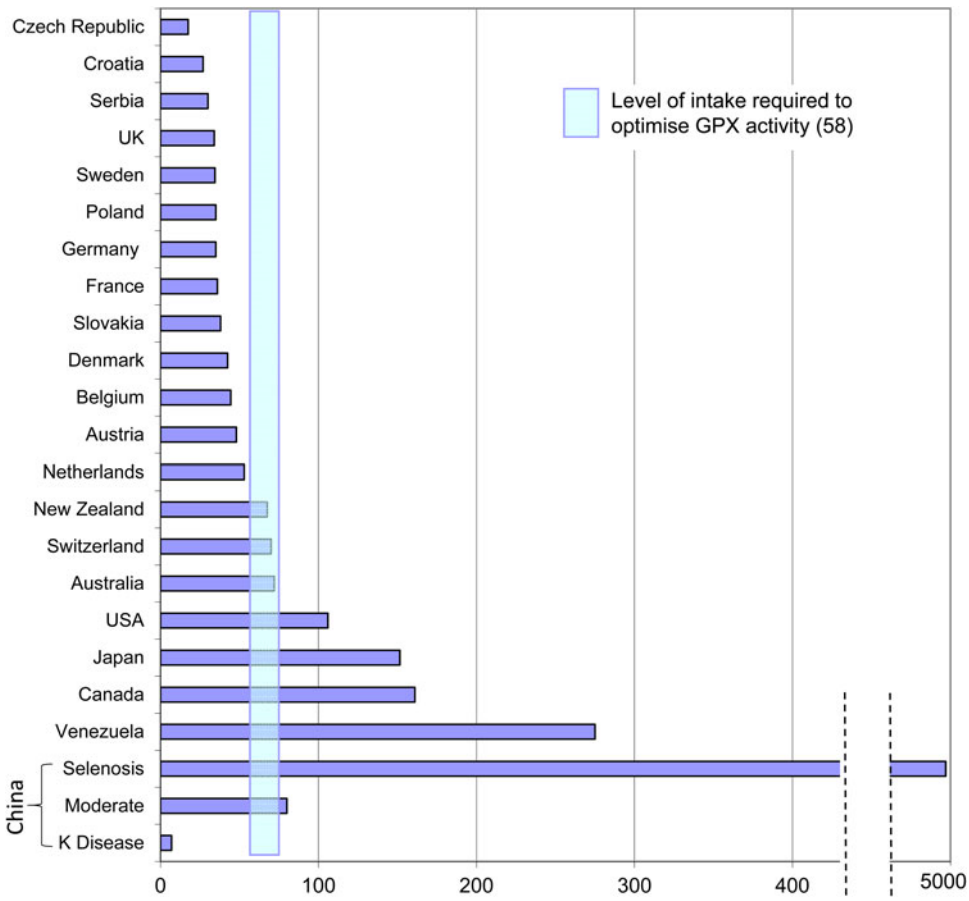

Fig. 4. (Colour online) Mean selenium intake levels (μg/d) in different countries and the range of selenium intake (55–75 μg/d) believed to be required for optimal activity of plasma glutathione peroxidase (GPX3) (adapted from Rayman[101]).

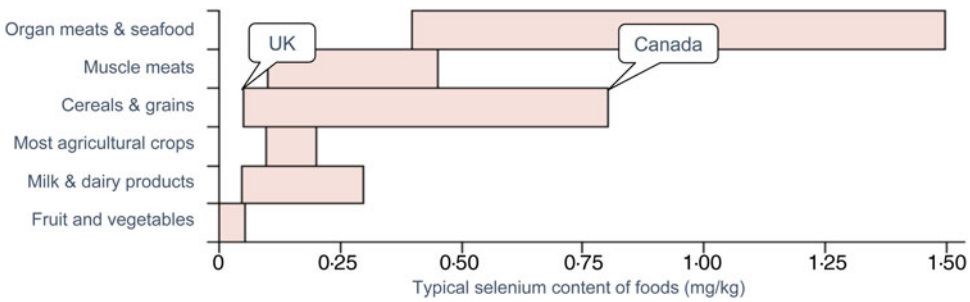

Fig. 5. (Colour online) Typical selenium content of food sources, adapted from WHO. Selenium. A report of the International Programme on Chemical Safety. Environmental Health Criteria number 58. Geneva: WHO, 1987 (reproduced from Rayman[100]).

If a patient's diet in a country of low-to-moderate selenium intake contains few, or no, selenium-rich sources, low-dose selenium supplementation can be advised although no more than 50–100 μg selenium/d is advisable. Multi-vitamin/mineral tablets may contain 50 μg selenium, a daily amount that will generally be adequate, particularly for women. A dose of 100 μg selenium/d (as selenium-yeast) given to someone in the UK will raise plasma selenium to about 140 μg/l which is more than enough to optimise the synthesis of all the selenoproteins[103]. Either selenium-yeast (which behaves in the body such as wheat-selenium) or sodium selenite which the body can readily use for selenoprotein synthesis without increasing the build-up of selenium, will do[102].

Clinicians should be aware that even if a hypothyroid patient is being treated with L-T4, a number of studies have found that giving selenium as well as L-T4 resulted in a greater reduction in TPO-antibodies, inflammatory cytokines and C-reactive protein[104,105].

Although selenium is essential, excessive intake is toxic; supplements of selenium of 200 μg/d (as selenium yeast or selenomethionine), generally considered to be safe, have been associated with toxic effects (alopecia, dermatitis, squamous cell carcinoma, type-2 diabetes mellitus, high-grade prostate cancer) in North Americans[106–108]. If selenium concentration reaches or exceeds 122 μg/l in plasma, as in the top tertile of the Nutritional Prevention of Cancer trial[109] or is already 137 μg/l in serum, as in SELECT[106], supplementation should be avoided[106–108,110]. Furthermore, mortality was found to be increased in a European population of relatively low selenium status (plasma selenium 89 μg/l) on long-term supplementation with 300 μg/d (as selenium-yeast)[111]. As for many nutrients, there is a U-shaped relationship between selenium status and risk of a number of adverse conditions[100]. The aim should, therefore, be to have an intake sufficient to reduce the risk of thyroid disease without risking toxicity[100].

Conclusion

As explained in detail earlier, the appropriate status of iodine, iron and selenium is crucial to thyroid health. Nutritional status of these micronutrients is frequently inadequate: iodine status is often low in countries without iodine fortification of the food supply; selenium status is generally fairly poor in Europe and many parts of China; iron status is frequently low in women of childbearing age, particularly towards the end of pregnancy. Clinicians need to be aware of these dietary risk factors and to treat thyroid patients accordingly.

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Conflicts of Interest

None.

Authorship

M. P. R. is the sole author of the review.

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