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The Effect of Micronutrient Deficiencies on Iodine Nutrition and Thyroid Metabolism

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Introduction

The risk of multiple, coexisting micronutrient deficiencies is high in developing countries, due to monotonous diets based on staple foods of low nutrient density [1]. Dietary deficiencies are compounded by increased turnover and/or losses due to endemic infectious diseases, such as intestinal parasites and malaria. Infants, children and pregnant women are particularly vulnerable because of increased needs during growth and pregnancy. Inadequate intake of iodine impairs thyroid function and results in a spectrum of disorders – goiter, cognitive impairment, and congenital abnormalities – collectively referred to as the iodine deficiency disorders (IDD). Along with iodine, other micronutrient deficiencies may adversely affect the thyroid. Deficiencies of iron and selenium can act in concert with iodine deficiency to impair thyroid function and modify the response to prophylactic iodine [2, 3]. Limited data from animal studies also suggests vitamin A and zinc deficiencies influence thyroid metabolism. This paper reviews the influence of these four micronutrient deficiencies on thyroid metabolism and IDD.

Abbreviations: DIT, Diiodothyronine; Hb, Hemoglobin; Hct, Hematocrit; IDA, Iron deficiency anemia; IDD, Iodine deficiency disorders; MIT, Monoiodothyronine; RBP, Retinol-binding protein; SF, Serum ferritin; T_3, Triiodothyronine; T_4, Thyroxine; TBG, Thyroxine-binding globuline; Tg, Thyroglobulin; TPO, Thyroid peroxidase; TSH, Thyrotropin, Thyroid-stimulating hormone; TT_3, Total triiodothyronine; TT_4, Total thyroxine; TTR, Transthyretin; Tvol, Thyroid volume; VAD, Vitamin A deficiency.

Iron

Deficiencies of iron and iodine are major public health problems in Africa, and many children are at high risk of both goiter and iron deficiency anemia (IDA). In regions of West and North Africa, 23 to 35% of school-aged children suffer from both goiter and IDA [4, 5]. Iron deficiency with or without anemia can have adverse effects on thyroid metabolism. IDA may have a greater impact on IDD than previously described goitrogens because of its high prevalence in vulnerable groups [6].

Evidence from rat studies

Initial studies on thyroid hormone metabolism in iron-deficient anemic rats focused on thermoregulation. Iron deficiency decreased plasma triiodothyronine (T_3) and thyroxine (T_4) concentrations compared with those of control rats, and the normal increase in plasma levels of T_3 and T_4 observed in control rats after cold exposure (4°C)

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was not seen in iron-deficient rats [7–9]. Additionally, the thyroid-stimulating hormone (TSH) response to cold in iron-deficient anemic rats was lower than in the controls [8]. Overall, although iron-deficient rats were able to increase thyroid hormone production and utilization when challenged with a cool environment, iron deficiency limited their ability to fully up-regulate thyroid hormone metabolism to the degree observed in iron-replete rats [10]. Normal animals whose hematocrits (Hct) were lowered by exchange transfusion showed the same responses as iron-deficient animals who were chronically anemic, whereas transfusion of iron-deficient rats to normal Hct improved the defect [11]. Injecting iron-deficient anemic rats with T_3 improved the ability of rats with IDA to maintain body temperature at 4°C, but injections of T_4 had no such beneficial effects [9]. These findings led the authors to conclude that IDA blunts the TSH response to cold temperature, impairs the conversion of T_4 to T_3, and that anemia, rather than tissue iron deficiency, is the critical factor in causing an impaired thyroid response to low temperature [12].

Severely iron-deficient anemic animals (Hct 16%) showed a blunted TSH response despite lower T_3 and T_4 concentrations [13], whereas no effect was found in less severely iron-deficient rats (Hct 31%) [8]. Beard *et al* [13] reported the T_3 turnover rate from the plasma pool and its irreversible loss from the system is significantly lower in iron deficiency. These results were confirmed in a second kinetic study, which showed lower T_4 and T_3 disposal rates in iron-deficient rats than in control rats (by 48% and 28%, respectively) at 15°C temperature [10]. Smith *et al* [14] demonstrated decreased nuclear T_3 binding in iron deficiency. In addition, IDA leads to decreased hepatic 5'-deiodinase activity, which catalyzes the conversion of T_4 to T_3 [13, 15, 16]. The depression of 5'-deiodinase activity is greater in more severely iron-deficient anemic rats (72%) than in the less severely anemic rats (25%) [15]. Although the lowered hepatic 5'-deiodinase activity observed in iron deficiency may be partly due to low plasma T_4 concentrations, normalizing plasma T_4 did not normalize hepatic 5'-deiodinase activity. These observations suggest that the mechanisms that control hepatic 5'-deiodinase activity (e.g. enzyme synthesis, allosteric regulation of enzyme activity) are directly affected by iron deficiency, regardless of thyroid hormone status [15].

Evidence from human studies

Lukaski *et al* [17] observed no differences in thyroid hormone and TSH concentrations between iron-depleted and iron-repleted women at room temperature. However, the relative increases in TSH, T_4, and T_3 after cold exposure were smaller (18, 16, and 18% respectively) when iron balance was negative than when it was positive (23, 23, and 25%, respectively). Martinez-Torres *et al* [18] reported a nonsignificant 10% decrease in T_3 concentrations in both moderate to severe IDA [hemoglobin (Hb) 75 g/L] and iron deficiency without anemia compared to control subjects. Beard *et al* [19] found a highly significant difference in T_3 concentrations between anemic (Hb 110 g/L) and control women. This discrepancy might be due to a smaller within-group variance in the latter study because only women with a certain body fatness and during particular days of their menstruation cycle were included [19]. In the same study, plasma TSH concentrations of anemic women were within the normal range at baseline and were unaffected by iron status. The subsequent iron supplementation corrected anemia, but only partially normalized thyroid hormone concentrations [19].

Studies have also demonstrated a relationship between anemia and hypothyroidism. Anemia has been reported in 25–50% of hypothyroid patients [20, 21], but anemia was due to iron deficiency only in a few cases. However, a recent study found significant differences in serum ferritin (SF) concentration and total iron-binding capacity when comparing 57 hypothyroid patients and 61 euthyroid controls [22]. Moreover, in a group of hypothyroid patients with low serum iron levels, Hb concentrations increased in response to T_4, but the increase was greater in response to T_4 given with iron [20]. In thyroidectomized rats, gastrointestinal iron absorption was decreased compared to intact control rats and it increased in response to thyroid hormone therapy [23]. Poor iron absorption in hypothyroidism may be due to achlorhydria [24, 25]. The reduced erythrocyte mass in the hypothyroid state may be an adaptive process, a result of reduced need for delivery of oxygen to peripheral tissues, one consequence being a decrease in serum erythropoietin concentration [24].

Public health significance

Evidence from cross-sectional studies

Data from the few available cross-sectional studies that have investigated the correlation between IDD and IDA are equivocal. A survey in Ethiopian children found no correlation in goiter rate or thyroid hormone levels and iron status [26]. Also, no significant difference was found in the prevalence of anemia between goitrous and nongoitrous subjects in the Philippines [27]. However, in severely vitamin A-deficient Ethiopian children, low levels of T_3 were associated with serum iron and low transferrin saturation [28]. A national screening in 2917 children in Iran reported a highly significant difference in goiter rates by palpation between children with low and normal SF levels [29]. Goiter was 3.8 times more prevalent in school children with low SF levels than in children with normal

SF concentrations. Moreover, Zimmermann *et al* in 1997 [4] assessed iron status and goiter rate by palpation in 419 children aged 6–15 years in two villages in western Côte d'Ivoire and found a relative risk of 1.9 (confidence interval 1.5–2.3) for goiter for children with IDA.

Evidence from intervention studies

Zimmermann *et al* [4] investigated the effect of a 200 mg oral dose of iodine as iodized oil in non-anemic (n = 51) and iron-deficient anemic (n = 53) children with goiter in western Côte d'Ivoire. At 15 and 30 weeks, thyroid volume (Tvol) was significantly reduced in the non-anemic group compared to the anemic group ($p < 0.001$). A clear difference in goiter prevalence was apparent at 15 and 30 weeks, when goiter rates were 62% and 64% in the anemic group and only 31% and 12% in the non-anemic group, respectively. After 30 weeks, TSH and T_4 concentrations improved significantly in the non-anemic group compared to the anemic group. Beginning at 30 weeks, the anemic children were given 60 mg oral iron as ferrous sulfate four times/week for 12 weeks [30]. Change in Tvol, which had reached a plateau at weeks 10 through 30 in the iron-deficient anemic children, began to fall again after iron supplementation. Goiter prevalence in the anemic group, which had remained at 62% to 64% from weeks 10 through 30, was reduced after iron supplementation to 31% and 20% at 50 and 65 weeks [30].

A randomized, double-blind, placebo-controlled trial in 5- to 14-year-old children in Côte d'Ivoire confirmed that iron supplementation (60 mg iron/day, 4 days/week for 16 weeks) improves the efficacy of iodized salt in goitrous children with iron deficiency [31]. The mean reduction in Tvol in the iron-treated group was approximately twice that of the placebo group: $-22.8 \pm 10.7\%$ compared to $-12.7 \pm 10.1\%$. In a 9-month fortification trial in Moroccan children comparing dual-fortified salt (containing iodine and iron) with iodized salt alone [32], greater improvement in thyroid function was found in the group receiving the dual-fortified salt. The prevalence of goiter and hypothyroidism was significantly reduced in the dual-fortified salt group compared to the iodized salt group. Overall, these results suggest that a high prevalence of iron deficiency among children in areas of endemic goiter may reduce the effectiveness of iodized salt programs.

Potential mechanisms of the iodine and iron interaction

As described above, certain aspects of thyroid metabolism in iron deficiency overlap with those observed in hypothyroid states. The plasma concentrations of T_4 and T_3 are lower and thyroid response to several different input stimuli is blunted in IDA. However, it is not clear how iron deficiency exerts its effects on thyroid and iodine metabolism.

Beard *et al* [10] suggested that IDA induces alterations in central nervous system control. The lowered $[I^{125}]T_3$ binding to hepatic nuclei shown in rats could be a contributory mechanism as well [33]. Normalization of plasma T_4 kinetic parameters in iron-deficient anemic rats provided with exogenous T_4 suggests that low plasma T_4 concentrations contribute to the altered thyroid hormone kinetics associated with iron deficiency [10]. Presumably, in iron-deficient anemic rats, a smaller portion of T_4 is converted to T_3 and a larger portion is converted to reverse T_3, a physiologically inactive metabolite. This is in agreement with a study by Smith *et al* [14] who concluded that iron-deficient rats are functionally hypothyroid, with a tendency toward thyroid hormone inactivation versus activation. According to Beard *et al* [10] the effect of iron deficiency on either the hepatic 5'-deiodinase or the brown fat deiodinase II observed in rats is rather minimal. Moreover, using an in vitro method, outer ring deiodinase activity is not affected by either ferric or ferrous iron [34].

Thyroid metabolism could also be impaired by iron deficiency through anemia and lowered oxygen transport, similar to the thyroid impairment of hypoxia found in animals [35, 36]. Thyroid impairment was also found in chronically hypoxic children, who had not only increased levels of reverse T_3, but also decreased concentrations of T_4 and T_3, whereas in acutely hypoxic children, mean serum T_4 and T_3 concentrations were not altered, but mean serum reverse T_3 concentration was significantly elevated [37]. However, in healthy subjects, hypoxic stress led to marked elevations in plasma T_4 and T_4 within 4 hours and the increased levels were maintained during the entire period of exposure [38, 39]. This indicates that in the healthy subject, hypoxia cannot entirely explain hypothyroidism associated with IDA.

The association between anemia and hypothyroidism may be physiologic to some extent; that is, a result of reduced need for delivery of oxygen to peripheral tissues in hypothyroidism [24]. On the other hand, a widely recognized effect of thyroid hormones is their influence over energy metabolism [40]. As food intake is reduced in anemia, falling thyroid hormone concentration may be in part a physiologic adaptation. This has been confirmed by reduced thyroid hormone concentrations in modified fasting of rats [41, 42].

An additional mechanism that could induce increased Tvol in IDA is the interaction of nitric oxide with Hb. Nitric oxide is a potent vasodilator that is produced in endothelial cells and has been assumed to act exclusively at its site of synthesis [43]. McMahon *et al* [44] recently showed that binding of nitric oxide to hemes and thiols of Hb varies as a function of HbO_2 saturation, suggesting that Hb is involved in the systematic transport and delivery of nitric oxide to tissues. Moreover, red blood cell/thiol-me-

diated vasodilator activity was inversely proportional to HbO_2 saturation [44]. Theoretically, this inverse relationship could cause enlarged Tvol in IDA due to vasodilatation and explain the blunted Tvol response to iodine prophylaxis in IDA. According to Lane & Gross [43] it is widely appreciated that nitric oxide bioactivity is scavenged by heme-iron in Hb [45, 46], and that animal and human blood contains low micromolar concentrations of nitric oxide-Hb. However, the suggestion that Hb actually delivers nitric oxide bioactivity is highly controversial and further investigation is needed [43, 47].

Another potential mechanism for reduced thyroid hormone concentration in IDA is impairment of thyroid peroxidase (TPO) activity. TPO is a glycosylated heme-enzyme bound to the apical membrane of the thyrocytes [48]. It plays a key role in thyroid hormone synthesis as it catalyzes the two initial steps, iodination of the thyroglobulin (Tg) and coupling of the iodotyrosine residues [49]. While the thyroid hormone synthesis occurs at the apical membrane of the thyrocytes, TPO is localized in the endoplasmic reticulum and in the perinuclear membrane [50–52]. Only about 30% of the synthesized TPO is able to fold correctly and to reach the apical cell surface [52, 53]. Fayadat *et al* [54] investigated whether heme had to be inserted into TPO for its exit from the endoplasmic reticulum and found that hemin, a chemical derivative of Hb, increased the quantity of human TPO at the apical cell surface level by 20% and increased TPO activity at the cell surface by 120%. The authors concluded that some of the human TPO molecules at the cell surface of the thyrocytes are inactive because they lack heme; this result agrees with the conclusions of earlier studies [55, 56]. It has been shown in the case of lactoperoxidase, a mammalian peroxidase similar to TPO, that no other enzyme system is required to modify heme before incorporation into the enzyme [57]. Using a monolayer technique with an apical pole oriented toward the culture medium, Fayadat *et al* [54] showed that adding hemin had an increasing effect on cell surface TPO activity of 30%.

We have recently shown that TPO activity is significantly reduced in IDA [58]. Male weanling Sprague-Dawley rats (n = 84) were assigned to seven groups. Three groups (ID-3, ID-7, ID-11) were fed iron-deficient diets containing 3, 7, and 11 μg iron/g. An iron-sufficient diet was fed to three pair-fed groups and an iron-sufficient diet was consumed *ad libitum* by one control group. After four weeks, Hb, T_3, and T_4 were significantly lower in the iron-deficient groups than in the control group ($p < 0.001$). TPO activity (by both guaiacol and iodide assays) was markedly reduced by iron deficiency ($p < 0.05$). Compared to the *ad libitum* control group, TPO activity per total thyroid determined by the guaiacol assay in the ID-3, ID-7, and ID-11 groups was decreased by 56, 45, and 33%, respectively ($p < 0.05$). These data provide a possible explanation for the observed impairment in thyroid response to iodine repletion in goitrous, iron-deficient children [58].

Selenium

Selenium functions largely through an association with proteins, known as selenoproteins. It is an essential component of several major metabolic pathways, including thyroid hormone metabolism, antioxidant defense systems, and immune function [59]. The effects of selenium status on the thyroid derive from two aspects of its biological function: 1) three selenium-containing deiodinases regulate the synthesis and degradation of the biologically active thyroid hormone T_3, and 2) selenoperoxidases and possibly thioredoxin reductase protect the thyroid gland from H_2O_2 produced during the synthesis of thyroid hormones [2].

Evidence from rat studies

During severe selenium depletion, the brain and endocrine glands have priority on supplies of this element [60]. In rats, 5'-deiodinase I activity in the thyroid is highly resistant to selenium depletion [61]. In contrast, 5'-deiodinase I in peripheral tissues like liver and kidney is strongly decreased by selenium deficiency in both short-term [62,63] and long-term rat studies [64].

In rat studies, it has been shown that selenium deficiency can further compound the adverse effects of iodine deficiency [65, 66]. Male weanling rats fed on diets deficient in selenium and iodine for seven weeks showed lower concentrations of T_4, T_3, and depleted amounts of iodine in thyroid than in selenium or iodine deficiency alone [66]. Furthermore, rats deficient in both trace elements had larger thyroid glands, higher plasma TSH concentrations, and higher cerebral deiodinase II activities than rats deficient in iodine alone. However, Hotz *et al* [63] reported that in rats, low dietary iodine reduced serum T_4, low dietary selenium raised serum T_4 concentrations, and diets deficient in both selenium and iodine did not significantly affect serum T_4 concentrations. The reduced synthesis of T_4 during iodine deficiency was potentially masked by the lower deiodination of T_4 as a result of concurrent selenium deficiency. Other feeding trials, however, found no significantly different plasma T_4 or TSH concentrations between rats with combined selenium and iodine deficiency and those with iodine deficiency alone [64, 66, 67]. Whether concurrent selenium deficiency aggravates iodine deficiency may depend on the acuteness and the severity of the deficiency [63, 68].

Glutathione peroxidases containing selenium are found in different cell fractions and tissues of the body [69]. In selenium-deficient rats, lower activities of glutathione peroxidases were found in liver, kidney, and erythrocytes, but not in the thyroid [63]. Thyroid glutathione peroxidase activity may be maintained due to its important function in the thyroid to neutralize H_2O_2 and prevent cytotoxicity, as large amounts of H_2O_2 are generated during the biosynthesis of thyroid hormones. However, the negligible differences in plasma T_3 concentrations comparing iodine-deficient, and selenium- and iodine-deficient, rats suggests that the thyroid gland is able to retain sufficient selenium to produce T_3 either by *de novo* synthesis or by deiodination of T_4 by 5'-deiodinase I [2]. This may be at the expense of increased peroxidative damage to the gland. It has been shown that thyroid cells from severely selenium-deficient rats were more necrotic on iodine re-feeding than were those from selenium-adequate rats [70]. Furthermore, the thyroid gland morphology was restored to normal within 15 days of iodide administration in selenium-sufficient, but not in selenium-deficient, rats [71].

Evidence from human studies

Selenium deficiency and cretinism

Severe deficiencies of selenium and iodine coexist in China, Southeast Asia, Russia, Egypt, and Central and West Africa [72, 73]. Interactions between those two trace elements have been associated with different diseases, such as Kashin-Beck disease in Tibet [74] and myxedematous cretinism in Central Africa [75–77].

In iodine deficiency, TSH concentration is increased and consequently the production of H_2O_2 in thyroid cells is elevated. Selenium deficiency results in reduced levels of glutathione peroxidase leading to an accumulation of H_2O_2. This excess H_2O_2 could induce thyroid cell damage, resulting in myxedematous cretinism that is caused by severe hypothyroidism [78]. Although this hypothesis has not been proven, it is clear that myxedematous cretinism and its consequences are due to a failure of the thyroid in the cretin, while neurological cretinism is principally due to the failure of the mother to provide enough T_4 to the fetus resulting in extreme mental retardation [79].

Selenium deficiency may also protect the fetus from brain damage despite severe iodine deficiency in the mother. In selenium deficiency, T_4 is preserved because of decreased deiodination by peripheral 5'-deiodinase I, a selenium-containing enzyme, and thus T_4 remains available for the fetus. As brain deiodinase II is not a selenium-containing enzyme [80], the conversion of T_4 to T_3 in the brain remains intact. These mechanisms may protect fetal brain from the deleterious consequences of maternal T_4 deficiency [79].

However, some studies have failed to provide convincing support for the hypothesis that selenium deficiency is the only compounding factor responsible for endemic cretinism seen in some iodine-deficient areas [2]. Ngo *et al* [81] reported that the prevalence of cretinism varied widely in different regions of Zaire, whereas the severity of combined selenium and iodine deficiency was uniform. Similarly the distribution of myxedematous cretinism is not related to selenium deficiency in China [82]. According to Arthur *et al* [2] other additional factors in endemic cretinism, besides selenium deficiency, must be considered.

Evidence from cross-sectional studies

Two studies have investigated the association of selenium deficiency and goiter prevalence in school children in Turkey. One found an association between low antioxidant enzymes (glutathione peroxidase, catalase, and superoxide dismutase) and low selenium status and goiter [83], whereas the other study found that low serum selenium had little or no impact on goiter endemia [84]. In a study in Poland, no association was found between selenium status and free T_4 and TSH concentrations in goitrous and non-goitrous children [85].

Supplementation trials

After two months of selenium supplementation in 52 school children deficient in selenium and iodine, mean serum T_4 and reverse T_3 fell significantly, whereas T_3 and TSH remained stable [86]. The authors suggested that deiodinase I could account for the changes seen in thyroid hormones concentrations. In cretins, two months of selenium supplementation exacerbated thyroid failure as evidenced by decreased serum T_4 and T_3 and increased TSH [87, 88]. The authors concluded that selenium deficiency may protect from some of the adverse effects of iodine deficiency, and therefore that iodine deficiency should be corrected before supplementing with selenium. However, low-dose selenium administration did not show any effect on thyroid hormone synthesis in subjects with mild iodine deficiency and sufficient selenium [89]. Because of the multiplicity of roles of selenoproteins in thyroid hormone metabolism and elsewhere, selenium may have both beneficial and adverse effects during iodine deficiency [2].

In a supplementation trial with oral iodized oil in western Côte d'Ivoire, the response to oral iodized oil among goitrous, selenium-deficient children was impaired by increasing severity of selenium deficiency [73]. These results suggest that more severe selenium deficiency may partially blunt the thyroid response to iodine supplementation.

Vitamin A

Vitamin A (retinol) in the body comes from two sources, pre-formed vitamin A in animal foods and from β-carotene and other provitamin A carotenoids in plant sources [90]. Besides its essential function in vision, retinol plays an important role in activating nuclear receptors in virtually all cell types via acidic forms of retinol, such as retinoic acid [90].

Animal studies

Vitamin A deficiency (VAD) causes thyroid hypertrophy in animals [91–93]. Histologic changes in the thyroid in VAD include keratinization and squamous metaplasia, increased entrance of follicular cells into the colloidal lumen, and increased lysosomal activity [91, 94]. These two latter changes may reflect abnormal thyroglobulin (Tg) synthesis [95]. A characteristic of VAD is impaired glycoprotein synthesis [96]. Tg is an iodinated glycoprotein produced in the thyroid follicular epithelium that serves a substrate for thyroid hormone synthesis and storage. Impairment of N-glycosylation pathways required for synthesis of Tg cause abnormal maturation and produce structural defects, including increased production of monomeric species of Tg [95]. Reduced coupling reactions increase the mono- and diiodothyronine (MIT and DIT) fractions and decrease intrathyroidal T_3 and T_4 [95]. Oba and Kimura [93] reported an increase in the inorganic iodine/hormone iodine ratio and decreased T_3 and T_4 in thyroids from rats with VAD. In addition, iodine uptake by the thyroid is decreased by VAD [94].

VAD has multiple effects on thyroid hormone metabolism. Several early studies [92, 93, 97] reported lower thyroid hormone levels in VAD animals. However, the majority of studies have found increased total and/or free T_4 and T_3 in VAD [95, 98–100]. In rats with VAD there is decreased turnover of T_4 due to reduced hepatic conversion of T_4 to T_3 [95, 101], decreased [I^{125}]-T_3 uptake by liver and kidney [102], and decreased T_3 binding to nuclear proteins compared to controls [103]. Compared to pair-fed rats, VAD increased serum total and free T_3 and T_4 by 60–100%, and serum TSH by 29%, suggesting failure of normal TSH suppression by T_4 [98]. The plasma TSH response to TRH was normal despite the high T_4 levels, and hypothalamic thyroid-releasing hormone (TRH) and pituitary TSH content were increased [98]. Subsequent studies in animals with VAD reported normal or reduced serum TSH levels, normal plasma TSH response to TRH, and increased serum T_3 [100, 104].

Ingenbleek [95] fed rats either iodine-deficient (ID), vitamin A-deficient (VAD), or iodine- and vitamin-A deficient (ID+VAD) diets, and compared them to controls. Both VAD and VAD+ID groups showed significant growth retardation compared to the ID group and control. There was no increase in thyroid weight in the VAD group, but an increase in both the ID and VAD+ID group. Serum free and total T_4 were increased in the VAD group, reduced in the ID group, and intermediate in the VAD+ID group. Free and total T_3 (TT_3) were increased in all 3 groups compared to control. TSH was increased in the ID and the VAD+ID group. In the rat thyroids, VAD+ID reduced radioiodine incorporation into Tg, increased the MIT+DIT/T_3+T_4 ratio, and, overall, produced greater impairments in Tg synthesis compared to either ID or VAD alone [95]. These data indicate concurrent vitamin A and iodine deficiency produces greater impairment of thyroid metabolism than either deficiency alone [95].

Morley *et al* [105] gave pharmacologic doses of retinyl palmitate to rats and showed a decrease in thyroid gland size and serum total T_4 (TT_4) and TT_3, and an increase in thyroidal iodine uptake and hepatic conversion of T_4 to T_3. Vitamin A did not alter basal TSH or its response to TRH. Other studies giving large doses of retinol or retinoic acid to rats have reported decreased pituitary TSH content [91] and decreased serum TT_3 and TT_4 [106].

Overall, the data indicate VAD produces multiple abnormalities in thyroid function:

- In the thyroid, VAD decreases thyroidal iodine uptake and iodine incorporation into Tg, impairs Tg synthesis, and increases thyroid size.
- In the periphery, VAD increases free and total thyroid hormone, reduces T_4 to T_3 conversion, and reduces peripheral uptake and nuclear binding of T_3.
- Centrally, VAD interferes with normal TSH suppression by T_4, and increases hypothalamic TRH and pituitary TSH content.

Mechanisms

The available data suggest VAD produces these adverse effects through:

- impairing glycosylation and maturation of Tg (discussed above)
- modifying thyroid hormone transport
- blunting feedback inhibition of pituitary TSH secretion by thyroid hormone

The effect of VAD on thyroid metabolism may be mediated at least partly through shared transport proteins. Thyroxine-binding globulin (TBG) carries the majority of T_4 and T_3 in plasma (~70%), while transthyretin (TTR) binds only 10–15% of circulating thyroid hormone [107]. However, because the affinity of TTR for T_4 is lower and the T_4·TTR dissociation rate is fivefold greater than that of T_4·TBG, TBG and TTR contribute equally to supply thy-

roid hormone to peripheral tissues [107]. TTR is also the primary indirect carrier of vitamin A (all-trans-retinol) in the plasma through its interaction with retinol-binding protein (RBP), the vitamin A transport protein [108]. ApoRPB is synthesized in the liver and is secreted bound to retinol as holoRBP. HoloRBP is secreted from the hepatocyte as a complex with TTR [109]. Each molecule of TTR contains two T_4-binding sites and binds to a maximum of two holoRBP molecules [109]. Retinol·RBP·TTR interactions are mutually enhancing, in that: a) compared to holoRBP, apoRBP has a lower affinity for TTR, and the TTR·apoRBP complex does not form at physiological concentrations [110]; b) the affinity of retinol to the RBP·TTR complex is higher than to apoRPB alone [110]; c) the binding of holoRBP to TTR prevents glomerular filtration and renal clearance of holoRBP, thereby enhancing vitamin A delivery [111]; and d) cellular vitamin A uptake may be greater from the holoRBP·TTR complex compared to holoRBP [112].

The effect of VAD on thyroid-binding proteins has been investigated by several authors. Although VAD decreases hepatic release of RBP, release of TTR is similar during vitamin A depletion and repletion in rats [113]. Serum TTR concentration is therefore unchanged by VAD [113, 114], although liver TTR may be increased [113] or unchanged [114]. Whether the binding capacity and affinity of TTR for thyroid hormone is changed by complexing with holoRBP is uncertain. Raz and Goodman [108] reported RBP had no effect on TTR affinity for T_4, while other authors have reported a decrease in the affinity of TTR for T_4 when not bound to RBP [115–117]. In rats, VAD produces a shift in the T_4 and T_3 distribution on thyroid-binding proteins, with a decrease in hormone binding to TTR and albumin, and an increase in binding to TBG [93, 99, 115]. Decreased TTR affinity for thyroid hormone may contribute to increased free T_4 and T_3 in VAD [115]. Of the three thyroid-binding proteins, only TBG is a glycoprotein. VAD impairs synthesis and decreases blood levels of other plasma glycoproteins, such as alpha1-macroglobulin [118]. Thus, TBG production may theoretically be impaired by VAD.

VAD may also affect thyroid metabolism through a central mechanism. Both the thyroid hormone-activated thyroid receptor and the 9-cis-retinoic acid-activated retinoid X receptor suppress transcription of the pituitary TSHβ gene by occupying half-sites on the promoter DNA of the gene [119]. Thus, vitamin A, after it enters the cell and is oxidized to retinoic acid, can modulate TSH production by RXR-mediated expression of TSHβ mRNA [120, 121]. Breen *et al* [122] reported VAD in rats increased pituitary TSHβ mRNA levels twofold, and increased serum TT_4; both returned to normal after treatment with retinoic acid. The authors concluded that the increased TSHβ mRNA, despite high serum TT_4, implied VAD had made the pituitary thyrotrope relatively insensitive to feedback control by thyroid hormone. In rats with VAD, Morley *et al* [98] had previously reported an increase in hypothalamic TRH and pituitary TSH in the face of high levels of circulating T_3 and T_4, implying central resistance to thyroid hormone. In euthyroid and hypothyroid rats, pharmacologic doses of retinoic acid reduced basal TSH secretion and TSH response to TRH [123]. Evidence of a similar effect in humans was suggested by the development of hypothyroidism after treatment with a synthetic retinoid that specifically binds to the retinoid X receptor in patients with T-cell lymphoma [124]. The physiological significance of the inhibitory action of vitamin A on TSH secretion remains unclear [119].

Human studies

Several cross-sectional studies have investigated the relationship between VAD and thyroid function or goiter. In vitamin A-sufficient Senegalese adults (mean serum retinol ± SD 43.2 ± 4.9 μg/dL), there was a strong negative correlation between increasing severity of goiter and serum retinol, RBP, and TTR concentrations [125, 126]. In mildly vitamin A-deficient Ethiopian children, those with visible goiters (grade IB or II) had significantly lower serum retinol and RBP than children without or with grade IA goiter [26]. In these children, serum TSH was normal, and there was a negative association between TBG and the triad of retinol, RBP, and TTR. In Ethiopian children with clinical signs of severe VAD, serum TSH was normal, and TT_3 (but not TT_4) was significantly correlated with retinol, TTR, and albumin [28]. However, in these studies it was not possible to distinguish the effects of VAD from protein malnutrition, which also can reduce serum retinol and RBP [127]. Among adequately nourished 7–14 year-old children in the 1987 National Nutrition Survey Philippines, the prevalence of goiter was 1.8% in children without VAD and 5.3% in those with VAD [27]. In severely iodine-deficient Senegalese adults, those who were hypothyroid had lower serum retinol and RBP, but similar TTR, compared to those who were euthyroid [128]. In mildly iodine-deficient Italian children, those with subclinical hypothyroidism had lower serum RBP, but similar serum retinol and TTR compared to euthyroid children [129]. In a small clinical trial of vitamin A repletion in patients with gastrointestinal disorders and VAD, two to eight weeks of treatment increased serum retinol, RBP, TT_4, TT_3, and free T_3, and had no effect on free T_4, TSH, or TTR [130]. Further research is needed to clarify the potential impact of vitamin A status on thyroid metabolism in IDD.

Zinc

Zinc is the most abundant intracellular trace element and is involved in a multitude of diverse catalytic, structural, and regulatory functions [131]. Zinc is a constituent of many enzymes, including oxidoreductases, transferases, hydrolases, lyases, isomerases, and ligases [132]. Therefore, zinc participates in protein, nucleic acid, carbohydrate, and lipid metabolism as well as in the control of gene transcription and other fundamental biological processes.

Evidence from rat studies

Several studies investigated the influence of zinc deficiency on thyroid metabolism in rats and found no effect [133–136], whereas other studies found reduced serum T_3 concentrations in zinc-deficient rats compared to pair-fed controls [137, 138]. Concurrent zinc and iodine deficiency in rats did not produce further impairment of thyroid hormone status compared to iodine deficiency alone [139, 140]. The impact of zinc deficiency on hepatic 5'-deiodinase I activity is also equivocal: decreased [138], unchanged [141], and increased 5'-deiodinase activity [136] has been reported. Similar to what is seen in iron deficiency, zinc-deficient rats showed blunted thermoregulation [142]. In guinea pigs, thyroid gland weights of zinc-deficient animals were significantly decreased and glands looked paler than compared to *ad libitum* controls [143]. The thyroids in the zinc-deficient animals exhibited atrophic changes and follicle degeneration. These histopathological changes may have been the result of increased susceptibility to oxidative damage, structural changes, and alterations in specific receptor sites and transport systems due to zinc deficiency [131].

Another potential link between zinc and thyroid metabolism is based on the hypothesis that T_3 receptors, like other nuclear receptors, include nuclear zinc-binding proteins [133]. Miyamato *et al* [144] showed that the removal of zinc from bacterially expressed T_3 receptors impaired their ability to bind DNA. Although results from *in vitro* experiments have not been consistent probably due to interfering substances within the assay, this finding agrees with the generally accepted model for zinc-nuclear receptor interactions [133].

Evidence from human studies

In a study of zinc-deficient males in Egypt, no evidence of hypothyroidism was found [145]. Moreover, normal zinc concentrations in patients with hyperthyroidism [146] and hypothyroidism [147] have been reported. Wada and King [148] showed that marginal zinc deficiency in humans was associated with a reduction in basal metabolic rate. In addition, there was a trend toward decreased thyroid hormone concentration when a low-zinc diet was fed for 54 days, although only free T_4 was significantly decreased at the midpoint of the low-zinc feeding period [148]. Although no significant difference in thyroid function was found in male subjects with low serum zinc levels compared to subjects with high serum zinc levels, serum T_4 concentration increased in the low zinc group following zinc administration [149]. A decrease in the T_3 concentration and the free T_3 index were observed in alcoholic cirrhotic patients with low serum zinc levels [130]. However, zinc supplementation did not normalize T_3 levels. In a cross-sectional study in Turkey, plasma zinc concentration in goitrous male adults was significantly lower than in the control group [150]. A limitation to these studies is the fact that plasma zinc level may be a poor indicator of zinc status, as it is influenced by stress, infection, food intake, and hormonal state [131].

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