Interactions of Vitamin A and Iodine Deficiencies: Effects on the Pituitary-Thyroid Axis

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Abstract: Vitamin A (VA) deficiency (VAD) and the iodine deficiency disorders (IDD) affect > 30% of the global population and these deficiencies often coexist in vulnerable groups. VAD has multiple effects on the pituitary-thyroid axis; VA status modulates thyroid gland metabolism, peripheral metabolism of thyroid hormone, and production of thyrotropin (TSH) by the pituitary. Findings from Africa children indicate that VAD in severely-IDD-affected children increases TSH stimulation and thyroid size, and reduces risk for hypothyroidism. In children with VAD, the higher TSH concentrations in the face of higher circulating total thyroxine suggest central resistance to normal TSH suppression by thyroid hormone. In IDD- and VAD-affected children receiving iodized salt, concurrent VA supplementation improves iodine efficacy. Recent VA and iodine depletion studies in rats indicate moderate VAD alone has no measurable effect on the pituitary-thyroid axis; however, concurrent iodine deficiency (ID) and VAD produce more severe primary hypothyroidism than ID alone. Repletion studies in VA- and iodine-deficient animals suggest: 1) primary hypothyroidism in animals with concurrent moderate VAD and ID does not reduce the efficacy of high doses of oral VA; 2) VAD does not reduce the efficacy of dietary iodine to correct pituitary-thyroid axis dysfunction due to iodine deficiency; and 3) given alone, without iodine repletion, high-dose VA supplementation in combined VAD and ID may reduce thyroid hyperstimulation and reduce risk for goiter.

Introduction

Vitamin A deficiency (VAD) and the iodine deficiency disorders (IDD) affect > 30% of the global population [1]. The most vulnerable groups are women of reproductive age and young children [2, 3]. These deficiencies often coexist in children in developing countries [4, 5]. In areas of endemic goiter, micronutrient status can be an important determinant of iodine and thyroid metabolism. Deficiencies of selenium [6, 7] and iron [8] can act in concert with iodine deficiency to impair thyroid metabolism and modify the response to prophylactic iodine [9, 10].

Effects on the thyroid gland and thyroid hormone metabolism

VAD has multiple effects on the pituitary-thyroid axis; vitamin A (VA) status modulates thyroid gland metabolism


[11,12], peripheral metabolism of thyroid hormone [13–18], and production of thyrotropin or thyroid-stimulating hormone (TSH) by the pituitary [19–22]. At the thyroid, VAD causes thyroid hyper trophy [11, 23] reduces thyroidal iodine uptake [24], impairs synthesis of thyroglobulin (Tg) and coupling of iodotyrosine residues to form thyroid hormone [12], and decreases intrathyroidal T₃ and T₄ [11, 12]. In the periphery, VAD increases total and free T₄, and T₁ [12, 13], reduces hepatic conversion of T₄ to T₃ [12, 25], and decreases T₃ uptake and binding [14, 15].

Ingenbleek [12] fed rats iodine-deficient (ID), vitamin A-deficient (VAD), or iodine- and vitamin A-deficient (ID + VAD) diets, and compared them to controls. Compared to controls, serum free and total T₄ were increased in the VAD group, reduced in the ID group, and intermediate in the VAD + ID group. TSH and T₄ concentrations were increased in the ID and the VAD + ID group. Overall, the data suggested ID + VAD produced greater impairments in thyroid metabolism than either ID or VAD alone [12]. Morley et al [16] gave pharmacologic doses of retinyl palmitate to rats and showed a decrease in thyroid gland size and serum TT₄ and TT₃, and an increase in thyroidal iodine uptake and hepatic conversion of T₄ to T₃.

The effect of VAD on thyroid metabolism may be mediated at least partly through shared transport proteins. Thyroid-binding globulin (TBG) carries the majority of T₄ and T₃ in plasma (ca. 70%), while transthyretin (TTR) binds 10–15% [26]. TTR is also the primary indirect carrier of vitamin A in the plasma through its interaction with retinol-binding protein (RBP) [27]. RBP is secreted from the hepatocyte as a complex with TTR, and binding of RBP to TTR prevents glomerular filtration and renal clearance of RBP, thereby enhancing vitamin A delivery [28]. Although VAD decreases hepatic release of RBP, release of TTR and serum TTR concentrations is similar during vitamin A depletion and repletion in rats [29, 30]. Animal studies have suggested that the binding capacity and affinity of TTR for thyroid hormone may be modified by interaction with RBP [27, 31–33].

**Effects on pituitary TSH production**

VAD may also affect thyroid metabolism through a central mechanism. Both the thyroid hormone-activated thyroid receptor and the retinoic acid-activated retinoid X receptor suppress transcription of the pituitary TSHβ gene by occupying half-sites on the promoter DNA of the gene [19–21]. Breen et al [22] found VAD in rats increased pituitary TSHβ mRNA levels 2-fold, and increased serum TT₄; both returned to normal after treatment with vitamin A. They concluded the increased TSHβ mRNA expression, despite high serum TT₄, implied VAD had made the pituitary thyrotrope relatively insensitive to feedback control by thyroid hormone. In pair-fed rats with VAD, Morley et al [13] also found an increase in hypothalamic thyrotropin-releasing hormone (TRH) and pituitary TSH despite high levels of circulating T₃ and T₄.

**Human studies**

Although VAD and IDD are common in many developing countries, there are few human data on a potential interaction in endemic regions. Several cross-sectional studies have investigated the relationship between VAD and thyroid function or goiter. In Senegalese adults, there was a strong negative correlation between increasing severity of goiter and serum retinol (SR), RBP, and TTR concentrations [34, 35]. In Ethiopian children, those with visible goiters (grade IB or II) had significantly lower SR and RBP than children without or with grade IA goiter [36]. In Ethiopian children with clinical signs of severe VAD, serum TSH was normal, and TT₃ (but not TT₄) was significantly correlated with SR and TTR [37]. A limitation of these studies is that it was not possible to clearly distinguish the effects of VAD from protein malnutrition [38]; protein malnutrition can decrease serum retinol, RBP, and TTR independent of vitamin A status.

A recent study investigated the effects of VAD on thyroid metabolism in an area of severe IDD, and compared the efficacy of iodized salt alone to iodized salt given with VA supplementation in a randomized, double-blind trial in children [5]. In a double-blind, randomized, 10-month trial, Moroccan children with IDD and VAD (n = 138) were given iodized salt and either VA (200000 IU) or placebo at 0 and 5 months. At 0, 5, and 10 months, measurements of VA status and thyroid function were performed. At baseline, increasing VAD severity was a predictor of greater thyroid volume and higher concentrations of TSH and thyroglobulin. In children with VAD, the odds ratio (OR) [95% CI] for goiter was 6.51 [2.94, 14.41]. VAD severity was also a strong predictor of higher concentrations of TT₄; the OR [95% CI] for hypothyroidism in VAD was 0.06 [0.03, 0.14]. The findings indicate that VAD in severely-IDD-affected children increases TSH stimulation and thyroid size, and reduces risk for hypothyroidism. In the children with VAD, the higher TSH concentrations in the face of higher circulating TT₄ suggest central resistance to normal TSH suppression by thyroid hormone. During the intervention, mean thyroglobulin, median TSH, and the goiter rate significantly decreased in the VA-treated group compared to placebo. This effect could be

due to decreased VA-mediated suppression of the pituitary TSHβ gene. In IDD- and VAD-affected children receiving iodized salt, concurrent VA supplementation improves iodine efficacy [5].

Recent animal studies

Biebinger et al [39] recently investigated the effects of concurrent vitamin A and iodine deficiencies on the thyroid-pituitary axis in rats. Weanling rats (n = 56) were fed diets deficient in vitamin A (VAD group), iodine (ID group), vitamin A and iodine (VAD + ID group), or sufficient in both vitamin A and iodine (control) for 30 days in a pair-fed design. Serum retinol (SR), thyroid hormones (FT₄, TT₃, FT₃, and TT₄), serum TSH, pituitary TSHβ mRNA expression levels, and thyroid weights were determined at the end of the depletion period. Compared to the control and ID groups, SR concentrations were ≈35% lower in the VAD and VAD + ID groups (p < 0.001), indicating moderate VA deficiency. Comparing the VAD and control groups, there were no significant differences in TSH, TSHβ mRNA, thyroid weight, or thyroid hormone levels. Compared to the control group, serum TSH, TSHβ mRNA, and thyroid weight were higher (p < 0.05), and FT₄ and TT₃ were lower (p < 0.001), in the VAD + ID and ID groups. Compared to the ID group, TSH, TSHβ mRNA, and thyroid weight were higher (p < 0.01) and FT₄ and TT₃ were lower (p < 0.001) in the VAD + ID group. There were no significant differences in TT₄ or FT₃ concentrations among groups. These data indicate moderate VAD alone has no measurable effect on the pituitary-thyroid axis. Concurrent ID and VAD produce more severe primary hypothyroidism than ID alone [39].

A follow-up study [40] investigated the effect of vitamin A supplementation and/or dietary iodine repletion, alone and in combination, on the thyroid-pituitary axis in rats with concurrent VAD and ID. Weanling rats (n = 96) were fed diets deficient in vitamin A and iodine or sufficient in both (control) for 30 days in a pair-fed design. Subsequently, deficient animals (VAD + ID) were repleted with iodine (IS), or vitamin A supplementation (VAS), or remained deficient. Serum TSH (p < 0.001) and thyroid weights (p < 0.05) were greater in VAD + ID compared to VAD + ID + VAS but not compared to VAD + ID after 30 days. Administration of VA did not result in a significant difference in TT₃ and FT₄ compared to VAD + ID. TT₃ concentrations were lower in VAD + ID at 30 days and VAD + ID, but the differences were not statistically significant. FT₃ concentrations were significantly lower in VAD + ID compared to control (p < 0.05). These findings suggest: 1) primary hypothyroidism in animals with concurrent moderate VAD and ID does not reduce the efficacy of high doses of oral VA; 2) VAD does not reduce the efficacy of dietary iodine to correct pituitary-thyroid axis dysfunction due to iodine deficiency; and 3) given alone, without iodine repletion, high-dose VA supplementation in combined VAD and ID may reduce thyroid hyperstimulation and reduce risk for goiter [40].

In conclusion, VAD has multiple effects on the pituitary-thyroid axis. VAD in severely-IDD-affected children increases TSH stimulation and thyroid size, and may reduce risk for hypothyroidism. In IDD and VAD-affected children receiving iodized salt, concurrent VA supplementation improves iodine efficacy. Recent VA and iodine depletion studies in rats indicate concurrent ID and VAD produce more severe primary hypothyroidism than ID alone. Repletion studies in VA- and iodine-deficient animals suggest VA supplementation, given alone without iodine repletion, may reduce thyroid hyperstimulation and reduce risk for goiter and, thereby, its sequelae.

References