

The Role of Iodine Deficiency and Subsequent Repletion in Autoimmune Thyroid Disease and Thyroid Cancer

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ABSTRACT

Iodine is an essential trace mineral that is necessary for thyroid hormone production. With the prevalence of iodine deficiency worldwide, universal salt iodization programs were successfully implemented to reduce the incidence of iodine deficiency disorders; however, unexpected increases in the prevalence of thyroid autoimmunity occurred, and iodine excess was implicated as the causative factor. Despite these observations, epidemiological studies are inconsistent, and the etiology of autoimmune thyroid disease remains undefined. A review of observational and *in vitro* studies revealed that iodine alone is not responsible for thyroid autoimmunity. Experimental models used to explain iodine excess as the culprit in thyroid autoimmunity fail to induce thyroid autoantibodies unless iodine is in the presence of excess inflammatory cytokines (interferon [IFN]- γ) and hydrogen peroxide (H_2O_2). Within iodine-deficient populations, regulatory mechanisms to limit oxidative stress and excess iodine are lost. Thyroid-stimulating hormone persistently activates the sodium-iodide symporter, while iodine concentrations fail to achieve levels high enough to produce iodolactones, which are responsible for modulating NADPH oxidase and H_2O_2 production. Subsequently, the thyroid becomes susceptible to oxidative stress as iodine is reintroduced. Oxidation of thyroid peroxidase and thyroglobulin initiate the release of inflammatory cytokines (IFN- γ) and lymphocytic infiltration, which induce autoantibody production and thyroid autoimmunity. Population studies revealed that iodine administration even below the recommended dietary allowance alters thyroid autoimmunity. Despite increases in thyroid antibodies, these changes are found to be transient. Interestingly, reports of iodine in combination with other nutrients and standardized botanical extracts have been used successfully to restore thyroid function. On the basis of our review of the literature, it is apparent that a loss of regulatory mechanisms due to preexisting iodine deficiency followed by iodine repletion, as opposed to iodine excess, is a causal factor in the development of thyroid autoimmunity.

Keywords: Hashimoto's; Thyroid autoimmunity; Iodine excess; Iodolactones; Thyroid cancer

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INTRODUCTION

Iodine is essential for thyroid function. The thyroid actively concentrates iodine 20–50 times that of serum levels to ensure adequate production of the thyroid hormones, thyroxine (T4), and triiodothyronine (T3).^{1,2} Daily iodine requirements are met solely through dietary intake. Due to iodine redistribution during glacier recession, iodine deficiency has become a global phenomenon that affects approximately 30% of the world's population.³ Iodine deficiency disorders (IDDs), which include goiter and cognitive impairment, continue to impact populations worldwide. In an effort to eradicate IDDs, universal salt iodization (USI) programs have been implemented since the 1990s and cover an estimated 71% of the world's population.³ The dosage used is based on the recommendation of the World Health Organization (WHO) of 150 µg/day of iodine for adults to prevent and eradicate IDDs⁴ (Box 1).

Shortly after the implementation of USI programs, researchers in epidemiological studies reported unexpected changes in the incidence of autoimmune thyroid disease.^{5–7} In several studies done in the United States, researchers reported an increase in Hashimoto's thyroiditis in both iodine-deficient and iodine-replete areas.⁸ Despite these reports, researchers in other observational studies failed to find a correlation between iodine and the development of thyroid autoimmunity, with no association between thyroid antibodies and iodine intake.^{8–10} Although extensively researched, the association between excess iodine and thyroid autoimmunity remains controversial.¹¹

IODINE METABOLISM AND REGULATORY MECHANISMS

Iodine is crucial in the formation of thyroid hormone. The sodium-iodide symporter (NIS) transports iodide (I⁻) into the thyrocyte to be organified to iodine (I₂) and bound to thyroglobulin (TG) by thyroid peroxidase (TPO) and hydrogen peroxide (H₂O₂) (Figure 1). The iodine–thyroglobulin complexes then combine to form thyroid hormones. The nicotinamide adenine dinucleotide

Box 1: World Health Organization recommendations for iodine intake by age or population group.⁴

- Children 0–5 years: 90 µg/day
- Children 6–12 years: 120 µg/day
- Individuals >12 years: 150 µg/day
- Pregnancy: 250 µg/day
- Lactation: 250 µg/day

phosphate (NADPH) oxidase system is upregulated by intracellular calcium to generate H₂O₂, a reactive oxygen species (ROS). To prevent excess H₂O₂, iodolactones negatively inhibit NADPH oxidase, and glutathione peroxidase degrades H₂O₂.^{12–14} (Figure 1). In iodine deficiency, the loss of negative feedback on H₂O₂ production has been implicated in thyroid dysfunction and as a possible mechanism in the generation of autoantibodies.

Studies suggest that when iodine intake is above 1.5 mg daily, TPO synthesizes iodolactones.¹⁶ TPO facilitates the iodination of arachidonic acid and other polyunsaturated fatty acids to produce iodolactones.¹⁷ Research shows that measurable concentrations of δ-iodolactone are found in the thyroid tissue, prevent excess iodide uptake and the generation of H₂O₂ by NADPH oxidase, and regulate thyroid function.¹⁸ Furthermore, specific iodolactones are able to inhibit signal transduction pathways to regulate cellular proliferation, modulate goiter formation, and normalize thyroid size.^{14,17–20} However, in iodine deficiency, iodolactones are obsolete, and the thyroid gland is susceptible to oxidative damage and loss of cell-cycle control.

LOSS OF AUTOREGULATION DURING IODINE DEFICIENCY

In chronic iodine deficiency, compensatory mechanisms fail to maintain iodine concentration, and the thyroid is susceptible to damage. As iodine concentrations decrease, the pituitary gland secretes thyroid-stimulating hormone (TSH) to induce NIS expression.¹⁸ TSH remains high, and the NIS fails

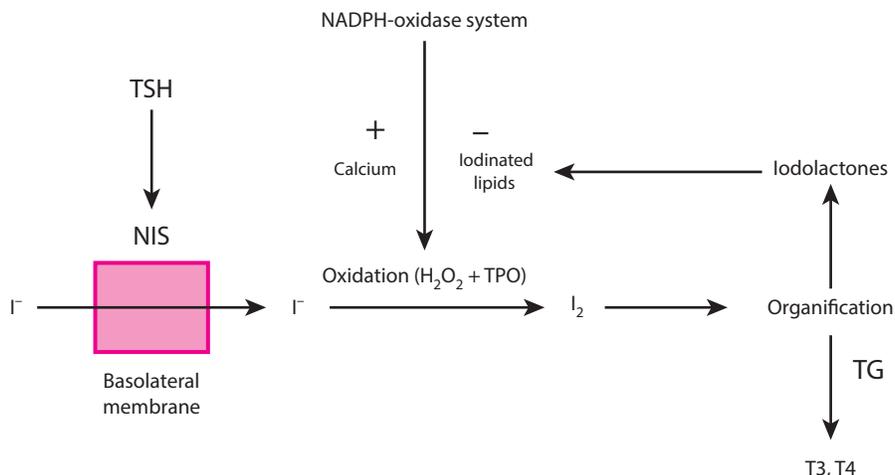


Figure 1: The import of iodide (I^-) by the sodium-iodide symporter (NIS) into the thyrocyte and the subsequent organification of I^- to form iodine (I_2).¹⁵ I_2 is then bound to thyroglobulin (TG) to form thyroid hormones, thyroxine (T4), and triiodothyronine (T3). The organification process is catalyzed by thyroid peroxidase (TPO) and hydrogen peroxide (H_2O_2), produced by the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system. Iodinated lipids provide negative feedback on NADPH oxidase to reduce H_2O_2 and oxidative damage to the thyrocyte. DIT, diiodotyrosyl; GPx, glutathione peroxidase; MIT, monoiodotyrosyl; TSH, thyroid-stimulating hormone.

to shut down, predisposing the gland to excess iodine during supplementation, a phenomenon found in individuals with preexisting autoimmune thyroiditis (AIT).⁴ In addition, thyroid activity remains high, leading to hyperplasia and goiter.¹² Researchers in cross-sectional studies reported that patients with nodular goiters often have an increase in thyroid antibodies, which is more common in iodine deficiency.^{4,21} These observations suggest that immune stimulation to thyroid proteins occurs during iodine deficiency and may be a causative factor in the development of thyroid autoimmunity.

THYROID AUTOIMMUNITY

Autoimmunity occurs when the immune system fails to differentiate between foreign antigens and self, producing autoantibodies. Thyroid autoimmunity is the most common autoimmune disease, affecting 1.5% of the population.⁵ Autoimmune thyroid diseases includes Graves' disease and chronic AIT, of which Hashimoto's thyroiditis is the most prevalent. Hashimoto's thyroiditis is characterized by an inflammatory state within the thyroid gland following T- and B-cell infiltration and antibody

destruction.⁵ Ultrasonographic signs of inflammation and serum concentrations of antibodies to TG, TPO, or both are features used to detect disease and may be present years before clinical symptoms emerge.⁷

HASHIMOTO'S DISEASE

The etiology of AIT is poorly understood. Several underlying mechanisms in its development have been proposed, such as alterations in free radical production,²² increased antigen presentation by the thyroid,²³ and complex gene-environment interactions that alter thyroid function and inflammatory processes. It is shown that patients with Hashimoto's thyroiditis have increased antigen presentation by thyrocytes, represented by increased expression of intercellular adhesion molecule 1 (ICAM-1) in the thyroid tissue.²⁴ ICAM-1 binds ligands to antigen-presenting cells to initiate T- and B-cell activation. An increase in ICAM-1 is seen with inflammatory cytokines (interleukin 1, tumor necrosis factor α , interferon [IFN]- γ), hormones, cellular stress (H_2O_2), and other environmental factors.^{23,25} In the presence of oxidative damage,

thyroid cells release chemotactic factors that recruit antigen-presenting cells and lymphocytic infiltration.^{22,26}

In iodine deficiency, the thyroid is susceptible to oxidative damage. As TSH stimulates NIS and TPO activity, low levels of iodinated lipids with high cytosolic free calcium allow for excess H₂O₂ to be produced.¹⁶ Iodine alone fails to initiate immune activation; rather, experimental studies show that iodine in the presence of inflammatory cytokines augments immune function. In an *in vitro* study, researchers observed increased ICAM-1 mRNA expression in the presence of potassium iodide only when low-dose IFN- γ was added.^{23,27} In the presence of excess H₂O₂, oxidative damage to TPO and TG cells leads to antigen presentation and lymphocytic infiltration, which facilitates the production of anti-TPO and anti-TG antibodies.^{16,28} This mechanism may account for the prevalence of AIT upon iodine supplementation through USI programs.²⁹ In this scenario, iodine deficiency causes thyroid dysfunction in predisposed individuals, which leads to oxidative damage, inflammation, and immune stimulation upon supplementation.

The lowest concentrations of iodine are found in individuals with thyroid autoimmunity. In 13 patients with overt symptoms of hypothyroidism and AIT, an average of 2.3 mg of iodine was found in the thyroid, as compared with 10 mg in healthy subjects.¹⁶ On the basis of data derived from the National Health and Nutrition Examination Survey, although iodine intake in the United States continues to decrease, the prevalence of AIT continues to increase.^{21,30,31} This correlation suggests that iodine deficiency may be a causative factor in patients with AIT.

In contrast, previously published epidemiological and clinical data associate excess iodine as a causative factor in autoimmune thyroid disease in susceptible individuals.³² Although the mechanism remains unclear, AIT animal models show an aggravation of AIT lymphocytic infiltration and thyroid follicular damage in a dose-dependent manner with the administration of iodine.^{32,33} Animal models use mice that spontaneously develop AIT or combine a goitrogen with iodine deficiency to assess the effects of iodine supplementation on thyroid autoimmunity.^{33,34} Combined with observational studies

showing an increase in AIT incidence with USI programs, these data remain the foundational evidence that iodine excess causes AIT. Questions arise whether the preexisting thyroid dysfunction, which occurs as a result of spontaneous mononuclear cell infiltrates into the thyroid as designed by the model, or iodine deficiency is the true culprit in AIT in these models. Studies identify the failure of the NIS in the presence of iodine excess as the culprit; however, this occurs in individuals with goiters after long-standing iodine deficiency.³⁵ Although a slight distinction, a more accurate conclusion is thus that iodine deficiency plus the reintroduction of iodine is the cause to AIT.

THYROID CANCER

In population studies done in the United States, researchers reported more than a 50% reduction in iodine intake, yet a 6.6% annual increase in the incidence of thyroid cancer.^{36,37} Although a slight increase of thyroid cancer seems to be associated with low iodine intake, many epidemiological studies remain controversial.³⁸ The two most common subtypes of thyroid cancer are papillary and follicular carcinoma. Changes in the distribution of these subtypes have been linked to dietary iodine intake, as a shift toward less aggressive papillary carcinoma increases with optimal levels.³⁹

A number of mechanisms have been proposed that could account for the relationship between iodine and thyroid cancer. In animal studies, 54%–100% of animals fed iodine-deficient diets showed an increase in TSH and thyroid tumors, both follicular and papillary carcinomas.³⁶ It is possible that low iodine intake leads to chronic TSH secretion and thyroid hyperplasia, which increases thyrocyte susceptibility to mutagens, oxidative stress, and malignant transformation.⁴⁰ In addition, iodine deficiency increases H₂O₂-mediated ROS generation, which is known to damage DNA and result in mutations.^{36,38}

As previously outlined, low concentrations of iodinated lipids increase oxidative damage, while sufficient levels regulate cell proliferation and apoptosis.^{12–14,18} *In vitro* studies demonstrate that solutions of iodolactones effectively regulate cell proliferation and reduce malignancy in breast and

thyroid tissue.⁴¹ Thyroid carcinoma cells in the presence of δ -iodolactone show a dose-dependent decrease in cell proliferation and apoptosis.¹⁷ While more studies are needed to confirm the effects in humans, the therapeutic use of iodolactones has been proposed to induce goiter involution, normalize thyroid size, and reduce malignancy of certain types of cancer.^{18–20}

ENVIRONMENTAL FACTORS

The etiology of thyroid autoimmunity and thyroid cancer likely involves complex interactions between genetic, endogenous, and environmental factors. Environmental factors, such as exposure to radiation, heavy metals, chemical contaminants, halogens, infectious disease, drugs, and selenium deficiency, are also implicated in thyroid autoimmunity.^{5,7,21} Environmental interactions have been shown to influence oxidative stress, thyroid antigens, and antibody production and may also contribute to iodine deficiency. Chemicals such as bromine, choline, and polychlorinated biphenyls have been shown to competitively inhibit iodide uptake by the NIS and cause oxidative damage.^{11,21} These factors need to be taken into account when interpreting epidemiological data in association with autoimmunity and recommendations on iodine intake.

CONCLUSIONS

As outlined in the review, the presence of thyroid dysfunction due to iodine deficiency may explain

the prevalence of thyroid autoimmunity upon iodine repletion. In population studies of iodine repletion, even minimal increases of iodine below the recommended dietary allowance have been shown modulate thyroid autoimmunity, signifying that the culprit is likely not iodine excess, but rather persistent NIS stimulation, excess H_2O_2 , and oxidative damage to thyroid proteins that initiate immune activation.^{42,43} Reports of transient increases in thyroid antibodies with iodine supplementation suggest that, under medical supervision, continual iodine intake in combination with other nutrients important in thyroid hormone production may restore thyroid function.⁴³

There is no doubt that iodine is imperative to the production of thyroid hormones and plays an essential role in thyroid function. On the basis of the body of *in vitro* and observational evidence reviewed, supplemental iodine may be of benefit to patients with autoimmune thyroid disorders. Safety measures must be in place to rule out the presence of autonomous nodules or “hot” nodules before iodine supplementation, as iodine can induce a thyroid storm in these individuals. Although practitioners use the listed combination of natural health products with success, further medical standards for screening and monitoring are needed, along with research to identify safe iodine dosing, for those with preexisting thyroid dysfunction.

DISCLOSURE OF INTERESTS

The authors have no disclosures to report.

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