

Autoimmune Thyroiditis and Iodine Therapy

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ABSTRACT

The incidence of Hashimoto's thyroiditis, also referred to as goitrous autoimmune thyroiditis, is estimated to be equivalent to that of Grave's disease. Although first discovered one hundred years ago, the pathophysiology of this disease has not yet been completely defined. Patients present with varying degrees of symptoms and may present euthyroid. Studies have found associations between genetic predisposition, environmental factors and co-occurrence of other autoimmune disorders within patients with autoimmune thyroiditis. This has further impeded advances to clearly define the mechanisms associated with autoimmune thyroiditis as there are a number of potential confounding factors which are not shared by all patients. Concern has been raised suggesting that iodination of salt led to the emergence or increase in prevalence of autoimmune thyroiditis. In regions where chronic excess consumption of iodine occurs, studies have not found an association between iodine intake and prevalence of this disorder. Furthermore, autoimmune thyroiditis patients with low thyroid levels of iodine are at risk of developing hypothyroidism. Therefore iodine therapy is indicated in patients with autoimmune thyroiditis to preserve normal function of the thyroid, unless the patient has goiter. Patients receiving iodine therapy must be monitored closely to ensure the condition does not exacerbate.

Keywords: Autoimmune thyroiditis; Hashimoto's thyroiditis; Iodine therapy; Hypothyroidism

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In 1912, pathologist H. Hashimoto published in a German medical journal his histological findings from four thyroid glands out of 5000 removed during surgery, which consisted of: numerous lymphoid follicles; extensive connective tissue formation; diffuse round cell infiltration; and significant changes of the acinar epithelium.¹ He called this pathology of the thyroid “struma lymphomatosa”, but it became popularly known as “Hashimoto thyroiditis”. At the time of Hashimoto’s publication, autoimmune thyroiditis (AIT) was not observed in the US population until the iodization of salt. Hashimoto’s thyroiditis is now classified as goitrous AIT because the gland is enlarged, in distinction to atrophic AIT where atrophy and fibrosis are predominant. Both conditions are chronic, progressing over time to hypothyroidism in a significant percentage of patients.² An ultrasound of the thyroid may be helpful to differentiate between the two. Other forms of AIT include: chronic AIT, silent thyroiditis and postpartum thyroiditis (usually associated with selenium insufficiency), cytokine-induced thyroiditis (as seen in cancer patients on cytokine chemotherapy), and viral-induced thyroiditis.

In several communities worldwide, increased incidence of AIT was reported following implementation of iodization of sodium chloride.³ In areas of the US where this relationship has been studied, mainly in the Great Lakes Region, a similar trend was reported. Weaver *et al.* reported that thyroid glands excised prior to efforts to prevent iodine deficiency were void of lymphocytes in the parenchyma and also noted an absence of thyroiditis during this period.^{4,5} After the introduction of iodized salt in 1924, thyroid glands with nodular colloid goiters with dense lymphocytic infiltrates were isolated.^{4,5}

Furszyfer *et al.* from the Mayo Clinic, studied the average annual incidence of Hashimoto’s thyroiditis among women of Olmsted County, Minnesota, during three consecutive periods covering 33 years of observation from 1935 to 1967.⁶ They found the incidence to be higher in women of 40 years and older than in women 39 years and younger. However, in both groups, there was a progressive increase in the incidence of Hashimoto’s thyroiditis over time. During the three periods evaluated — 1935–1944, 1945–1954, and 1955–1967 — the

average annual incidence of Hashimoto’s per 100,000 population were 2.1, 17.9, and 54.1, respectively, for women up to 39 years old. For women who were 40 years and older, the average annual incidence over the same three periods were 16.4, 27.4, and 94.1, respectively.⁶

It is important to point out that the Mayo Clinic study started 10–15 years after implementation of iodization of salt in the area. Therefore, even during the first decade of observation, the prevalence of AIT was already significant. Again, it must be emphasized that prior to the implementation of iodized salt, as observed by Weaver *et al.*^{4,5} this pathology of the thyroid gland was not reported in the US, even though Lugol solution and potassium iodide were used extensively in medical practice at that time in daily amounts two orders of magnitude greater than the average intake of iodide from table salt.² This suggests that inadequate iodide intake aggravated by goitrogens, not excess iodide, was the cause of this condition.

It is estimated that that the incidence of Hashimoto’s thyroiditis is approximately equal to that of Grave’s disease (0.3–1.5 cases per 1,000 population per year) and occurs with a frequency that is 15–20% greater in women than men.^{7–9} Although most prevalent between the ages of 30 to 50 years, thyroiditis may be seen in any age group including children.

AIT may go undiagnosed, although patients may have TG and TPO antibodies they are often asymptomatic.^{7–9} A Japanese study found that 3% of children between the ages of 6 and 18 had thyroiditis with biopsies revealing focal rather than diffuse thyroiditis.¹⁰ In a population study, Turnbridge *et al.* found that 1.9–2.7% of women had present or past thyrotoxicosis, 1.9% had overt hypothyroidism, 7.5% had elevated TSH levels, 10.3% had test results positive for TPO (microsomal antigen) Ab measured by hemagglutination assay (MCHA), and about 15.0% had goiter.⁹ Familial predisposition has also been reported. Children of parents who had a history of thyroid disease had a 24% prevalence of thyroid “abnormalities”¹¹ including a prevalence of 6.9% abnormal thyroids, and 9.3% with positive TG Ab measured by anti-thyroglobulin hemagglutination antibodies (TGHA) and 7.8% positive microplate colorimetric hybridization

assay (MCHA) assays. A study found that 8% adults in Finland had positive TGHA results, and 26% had positive MCHA results with 30% of these people having elevated TSH. Two to five percent were believed to have asymptomatic thyroiditis as they presented with positive antibody titers with elevated TSH but did not present with symptoms.⁷ These findings are consistent with the presence of focal collections of lymphocytes on histologic examination of the thyroid glands, which are often associated with elevated levels of TSH, representing one end of a spectrum of thyroid damage.¹² The rate of women becoming hypothyroid with both positive antibody test results and raised TSH levels is 5% per year.⁷ It is a reasonable approximation that the women have a greater than 10% prevalence of positive antibody tests and 2% prevalence of clinical disease while men have a prevalence one tenth of this.¹³

The pathophysiology of AIT is poorly understood. The immune response in Hashimoto's thyroiditis is characteristically destructive, while in Grave's disease the response is stimulatory. The difference in response may be due to characteristics of the immune response. Environmental factors that may be associated with AIT include high iodine intake, selenium deficiency, pollutants, infectious disease and certain medications¹⁴ Prolonged exposure to iodine increases iodination of thyroglobulin, which, in turn, increases its antigenicity initiating the autoimmune response.¹³ Selenium is a mineral and is found in selenoproteins with antioxidant properties. A deficiency in selenium can lead to decreased activity of selenoproteins which can lead to increases in reactive oxygen species, promoting inflammation and disease.¹³ Smoke, polychlorinated biphenyls, solvents, heavy metals and other environmental pollutants have also been implicated in the autoimmune process and inflammation.¹³ Many autoimmune diseases have shared etiology and co-occur within patients.¹⁵ Hashimoto's thyroiditis has been associated with autoimmune disorders such as type 1 diabetes, celiac disease, type 2 and type 3 polyglandular autoimmune disorders (APS) and lymphocytic hypophysitis.¹⁵⁻¹⁸ Type 2 APS is defined by the occurrence of Addison's disease with thyroid autoimmune disease and/or Type 1 diabetes mellitus.¹⁹ Type 3 APS is thyroid autoimmune diseases associated with other autoimmune diseases

(excluding Addison's disease and/or hypoparathyroidism).¹⁹ These associations indicate shared etiology and increased susceptibility of patients to autoimmune diseases. Similar to celiac disease, gluten sensitivity has also been associated with AIT.^{13, 20, 21}

Recent studies looking at the incidence of parvovirus B19 infections in Hashimoto's thyroiditis demonstrated approximately 80% of the patients to have positive antibodies compared with 12% in the controls. Just as the mononucleosis virus can insert itself into human taste buds, so too has parvovirus B19 DNA been found in thyroid cells in humans. However, Hashimoto's thyroiditis was not induced in mice given the virus.²²⁻²⁹ Further studies are required to investigate this association.

Many Hashimoto's thyroiditis patients do not have an increase in RAIU or release of hormone from the thyroid with TSH injection suggesting partial destruction of the thyroid by the autoimmune response.³⁰ Further, in these patients, the thyroid does not organify properly.³¹ This has been demonstrated in patients with Hashimoto's thyroiditis, where 400 mg potassium perchlorate 1 hour after giving a tracer iodide releases 20-60% of the glandular radioactivity. Additionally, a fraction of iodinated compounds in blood are not soluble in butanol, but rather an abnormal peptide-linked iodinated component, likely serum albumin iodinated in the thyroid gland as part of the hyperplastic response. A similar iodoprotein is also found in thyroid carcinoma, Graves' disease, and one form of goitrous cretinism.¹³

Iodide is actively transported from blood to thyrocytes via the sodium iodide symporter (NIS). In patients with autoimmune thyroid disease, antibodies against NIS have been reported which inhibits iodide transport and may modulate thyroid function.³² However, it is important to note that less than 10% of Hashimoto's thyroiditis patients have the presence of anti-NIS antibodies and clinical relevance is still unknown.^{33, 34} Animal studies have suggested that even a mild iodine deficiency offers partial protection against autoimmune thyroiditis;^{35, 36} however, this remains controversial as iodine intake is important for both thyroid hormone synthesis as well as induction and modulation of thyroid autoimmunity. In regions where

consumption of foods high in iodine (e.g. seaweed consumption in Japan), an excessive amount of dietary iodine ($\geq 1000 \mu\text{g/day}$) can cause transient hypothyroidism in patients with autoimmune thyroiditis.³⁷ Reduction in iodine intake can reverse the hypothyroidism.³⁸ In patients with a pre-disposition to autoimmune disorders, iodine excess can accelerate or exacerbate autoimmune thyroiditis and iodine deficiency can attenuate the disorder.³⁹ Animal studies suggest that excess iodine stimulates thymus development and affects immune cell function.⁴⁰ Furthermore, dysregulated thymic function plays a role in autoimmune thyroiditis.⁴¹

AIT experimentally induced in laboratory animals by acutely administered iodide could not induce thyroiditis, as the use of anti-thyroid drugs, essentially goitrogens, was needed to produce these effects.^{42–45} These goitrogens induced thyroid hyperplasia and iodide deficiency. Antioxidants either reduced or prevented the acute iodide-induced thyroiditis in chicks⁴⁶ and mice.⁴⁷ Bagchi *et al.*⁴⁶ and Many *et al.*⁴⁷ proposed that the thyroid injury induced by the combined use of iodide and goitrogens occurs through the generation of reactive oxygen species.

Abraham had previously proposed a mechanism for the oxidative damage caused by low levels of iodide combined with anti-thyroid drugs.² Inadequate iodide supply to the thyroid gland, aggravated by goitrogens, activates the thyroid peroxidase (TPO) system through elevated TSH, low levels of iodinated lipids, and high cytosolic free calcium, resulting in excess production of H_2O_2 . The excess H_2O_2 production is evidenced by the fact that antioxidants used in Bagchi's experiments did not interfere with the oxidation and organification of iodide and therefore neutralized only the excess oxidant.⁴⁴ This H_2O_2 production is higher than normal due to a deficient feedback system caused by high cytosolic calcium due to magnesium deficiency and low levels of iodinated lipids, which require iodide levels two orders of magnitude greater than the RDA of iodine for their synthesis.² Once the low iodide supply is depleted, TPO in the presence of H_2O_2 and organic substrate reverts to its peroxidase function, which is the primary function of haloperoxidases, causing oxidative damage to molecules nearest to the site of action: TPO and the substrate thyroglobulin (Tg). Oxidized TPO

and Tg elicit an autoimmune reaction with production of antibodies against these altered proteins, with subsequent damage to the apical membrane of the thyroid cells, therefore resulting in the lymphocytic infiltration and clinical manifestations of Hashimoto's thyroiditis. Eventually, the oxidative damage to TPO results in deficient H_2O_2 production. Hypothyroidism occurs in AIT when oxidation and organification of iodide in the thyroid gland become deficient enough to affect synthesis of thyroid hormones.

In vitro studies with purified fractions of calf thyroid glands by De Groot *et al.*⁴⁸ provided compelling evidence that iodide at 10^{-5} molar confers protection to TPO against oxidative damage. To achieve peripheral levels of 10^{-5} molar iodide, a human adult needs a daily amount of 50–100 mg. DeGroot's findings can be summarized as follows:

- TPO is inactivated by H_2O_2 .
- Potassium iodide (KI) at 10^{-5} molar protects TPO from oxidative damage.
- Potassium bromide and potassium fluoride do not share this protective effect of KI.
- The protective effect of KI is not due to the covalent binding of iodine to TPO but due to the presence of KI itself in the incubation media.

The concentrations of iodine measured in the thyroid of patients with AIT are the lowest observed. Furthermore, AIT patients with hypothyroidism have significantly lower iodine levels in the thyroid gland than AIT patients with normal thyroid function. A study on the US population carried out by Okerlund⁴⁹ reported a mean value of around 10 mg of iodine/thyroid in healthy study patients, with a range of 4–19 mg. In 56 patients suffering from AIT, but with normal thyroid function, a mean value of 4.8 mg/thyroid was reported. In 13 patients with AIT and hypothyroidism, the mean value was 2.3 mg/thyroid. These results suggest iodine is important for normal function of the thyroid in patients with AIT and that iodine excess is not a cause of AIT. These results are consistent with other studies where no associations between chronic excess iodine intake and increased risk of AIT.⁵⁰

Patients with AIT are often euthyroid but may develop hypothyroidism. Theories surrounding

the pathogenesis of disease indicate an abnormal immune response which allows development of autoantibodies against thyroid antigens and some body tissues. As there is a risk for AIT patients to develop hypothyroidism it is advised that patients with autoimmune thyroiditis maintain adequate intake of iodine to support normal thyroid function.

In the presence of a large thyroid gland or goiter, alternative therapies such as thyroid hormone replacement may be indicated.

DISCLOSURE OF INTERESTS

Dr. Flechas has nothing to disclose.

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