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# Facts about Iodine and Autoimmune Thyroiditis

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Since the 2006 publication by Tang, *et al.*,<sup>1</sup> reporting a positive association between iodization of salt in China and autoimmune thyroiditis (AIT), I have received a lot of calls and e-mails questioning the use of iodine in patients with autoimmune thyroiditis. Iodophobes were elated with this publication, which vindicated their iodophobic viewpoint. However, a year later in 2007, the same authors, using the same data<sup>2</sup> retracted their original statement and concluded that: “Chronic iodine excess does not apparently increase the risk of autoimmune thyroiditis.”

I will present some facts about iodine and autoimmune thyroiditis.

In 1912, pathologist H. Hashimoto published in a German medical journal,<sup>3</sup> his histological findings in four thyroid glands removed at surgery: numerous lymphoid follicles; extensive connective tissue formation; diffuse round cell infiltration; and significant changes of the acinar epithelium. He called this pathology of the thyroid “struma lymphomatosa”, but it became popular under the name “Hashimoto thyroiditis”. At the time of Hashimoto’s publication, autoimmune thyroiditis 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.<sup>4</sup>

In several communities worldwide, an increased incidence of AIT was reported following implementation of iodization of sodium chloride.<sup>5</sup> In areas of the US where this relationship has been studied, mainly in the Great Lakes Region, a similar trend was reported. In 1966 and 1968, Weaver, *et al.*,<sup>6,7</sup> from Ann Arbor, Michigan reported: “The salient histopathological feature of the thyroid glands, removed at operation in a five-year period before iodine prophylaxis (1915-1920), was the *paucity* of lymphocytes in their parenchyma and, more impor-

tantly, the *absence* of thyroiditis of any form ... It should be emphasized that the thyroid glands prior to the use of iodized salt were devoid of lymphocytes, and nodular colloid goiters with dense lymphocytic infiltrates were found after the introduction of iodized salt in 1924.”

Furszyfer, *et al.*,<sup>8</sup> 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. They found the incidence to be higher in women 40 years and older versus 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; 1955-1967 — the average annual incidence of Hashimoto’s per 100,000 population were 2.1, 17.9, and 54.1 for women 39 years and less. For women 40 years and older, the average annual incidence over the same three periods were 16.4, 27.4, and 94.1.

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.*,<sup>6,7</sup> 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.<sup>4</sup> This suggests that inadequate iodide intake aggravated by goitrogens, not excess iodide, was the cause of this condition. To be discussed later, AIT cannot be induced by inorganic iodide in laboratory animals unless combined with goitrogens, therefore inducing iodine deficiency.

The pathophysiology of AIT is poorly understood. Experimentally induced autoimmune thyroiditis in laboratory animals by acutely administered iodide required the use of antithyroid drugs, essentially goitrogens, to produce these effects.<sup>9-12</sup> These goitrogens induced thyroid hyperplasia and iodide deficiency. Antioxidants either reduced or prevented the acute iodide-induced thyroiditis in chicks<sup>13</sup> and mice.<sup>14</sup> Bagchi, *et al.*,<sup>13</sup> and Many, *et al.*,<sup>14</sup> proposed that the thyroid injury induced by the combined use of iodide and goitrogens occurs through the generation of reactive oxygen species.

We have previously proposed a mechanism for the oxi-

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ductive damage caused by low levels of iodide combined with antithyroid drugs:<sup>2</sup> 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<sub>2</sub>O<sub>2</sub>. The excess H<sub>2</sub>O<sub>2</sub> 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.<sup>11</sup> This H<sub>2</sub>O<sub>2</sub> production is above normal due to a deficient feedback system, caused by high cytosolic calcium due to magnesium deficiency and low levels of iodinated lipids which requires for their synthesis iodide levels two orders of magnitude greater than the RDA for iodine.<sup>4</sup> Once the low iodide supply is depleted, TPO in the presence of H<sub>2</sub>O<sub>2</sub> 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, resulting in the lymphocytic infiltration and in the clinical manifestations of Hashimoto's thyroiditis. Eventually, the oxidative damage to the TPO results in deficient H<sub>2</sub>O<sub>2</sub> 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*,<sup>15</sup> gave compelling evidence that iodide at 10<sup>-5</sup> molar confers protection to TPO against oxidative damage. To achieve peripheral levels of 10<sup>-5</sup> 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<sub>2</sub>O<sub>2</sub>.
- KI at 10<sup>-5</sup> 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. Further, AIT patients with hypothyroidism have significantly lower iodine levels in the thyroid gland than AIT patients with normal thyroid function. For the US population, Oker-

lund<sup>16</sup> reported a mean value of around 10 mg iodine/thyroid, with a range of 4-19 mg. In 56 patients suffering from autoimmune thyroiditis, but with normal thyroid function, a mean value of 4.8 mg/thyroid was reported. In 13 patients with autoimmune thyroiditis and hypothyroidism, the mean value was 2.3 mg/thyroid.

Based on the above facts, it is obvious that iodine deficiency, not excess, is the cause of AIT.

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