Iodine Induced Thyroid Disease

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ABSTRACT

Although iodine prevents goiter, enlarged thyroid glands continue to be detected in subjects, especially children, in spite of adequate iodine ingestion. Iodine may cause goiter in susceptible individuals by inhibiting the organic binding of iodine as is seen in adult asthmatics, neonates born of iodine ingesting mothers and in subjects residing along the littoral of Japan. Myxedema, especially in treated Graves’ disease and Hashimoto’s disease, may also be precipitated by iodine. On the other hand, iodine given to euthyroid subjects in areas of endemic goiter and to subjects with nontoxic nodular goiter may induce thyrotoxicosis by disclosing diffuse autonomously functioning thyroid tissue.

An indirect adverse effect of iodine upon the thyroid gland may be manifested by lymphocytic glandular infiltrates and chronic thyroiditis which were sparse or absent in thyroid glands removed from subjects living in iodine deficient areas before iodine prophylaxis and therapy. Not only has the incidence of thyroiditis increased, but the histologic and clinical distinctions between treated Graves’ disease and chronic thyroiditis have become indistinct. Experimentally, chronic thyroiditis has been produced in animals following large doses of iodine. Accumulated evidence supports the concept that iodine contributes to the genesis of chronic thyroiditis.

Effects of Iodine on Thyroid

The beneficial results of iodine prophylaxis in geographic areas of endemic goiter and endemic cretinism are amply documented.3,5,25 Since the introduction of iodine prophylaxis in 1924, however, investigators have warned of the possible detrimental effects of iodine upon the thyroid gland.15,17,18 The direct injurious effects of iodine upon thyroid gland manifest by goiter and thyrotoxicosis and the indirect evidence linking iodine with chronic lymphocytic thyroiditis will be reviewed.
Iodine may induce thyroid enlargement. A combined study of childhood goiter in Michigan, Texas, Georgia and Kentucky disclosed an overall prevalence of thyroid enlargement of 6.8 percent. Since the urinary excretion of iodine was 2 to 40 times higher than the level reflecting deficiency, the authors eliminated iodine lack as the cause of goiter in these children. Furthermore, 20 percent of the goiters were hard, suggesting a diagnosis of thyroiditis. Although multiple causes may be implicated in producing childhood goiter, iodine deficiency, at least in this study, was not one of them.

Wolfe has reviewed the goitrogenic effects of excessive iodine upon the thyroid gland and classified them as (1) an adult group, e.g. asthmatics taking potassium iodide, (2) iodine goiter of the newborn following placental transfer of iodine ingested by the mother, (3) endemic goiter found in Hokkaido, Japan, where seaweed ingestion provides inhabitants with up to 20,000 micrograms of iodine per day, and (4) hypothyroidism developing in Graves' disease treated with potassium iodide or Lugol's solution.

The goiters in these instances result from an inhibition, caused by high iodine levels, of organic binding of iodine. Normal individuals overcome the block to organification of iodine, even with sustained high iodine levels, in 24 to 36 hours. In susceptible subjects, the block to organification persists resulting in diminished hormone synthesis, enhanced iodine transport, increased thyroidal iodine and a persistent block to organification. The level of iodine required to block organification of iodine varies with the physiologic state of the thyroid gland but can result in a normal subject from a single dose of 750 micrograms of iodine.

Although inhibition of organic binding of iodine may explain one form of iodide induced myxedema, this mechanism can not be implicated in all instances. Patients with Graves' disease treated with radioactive iodine and subjects with Hashimoto's disease given even small doses of iodine are particularly susceptible to iodine-induced myxedema. In all subjects, the serum thyroid stimulating hormone (TSH) levels were elevated and the thyroid hormone levels (T4) decreased. With few exceptions, perchlorate administered to the patients failed to produce iodine discharge. Therefore, a demonstrable block to organic binding of iodine was absent, and the authors postulated a block in hormone synthesis beyond this step.

Besides causing goiter, iodine may also precipitate thyrotoxicosis (Jodbasedow phenomenon). Following the introduction of iodized salt in this country in the 1920's, an increased incidence of thyrotoxicosis was reported. Examples of iodine-induced thyrotoxicosis were rare and were associated with large doses of iodine given to subjects living in areas of severe iodine deficiency. In 1970, investigators in Tasmania reported a doubling of the incidence of thyrotoxicosis following the iodination of bread to achieve an average safe consumption of 80 to 250 micrograms per day. A compensatory increase in TSH production by the pituitary gland to keep thyroid hormone production at euthyroid levels in the iodine deficient state, followed by a sudden increase in available iodine with the production of excessive thyroid hormone, provided a logical, tidy explanation for Jodbasedow phenomenon.

An examination of adults with iodine thyrotoxicosis in Tasmania failed to confirm such a hypothesis. The thyrotoxicosis was sustained, and levels of thyroid stimulating hormone were normal. In the absence of long acting thyroid stimulator and exophthalmos, the authors did not feel Graves' disease could be implicated. Armed with this evidence and a
diffusely irregular thyroid scan, the investigators postulated that their cases of Jodbasedow in Tasmania resulted from autonomous thyroid tissue which, in the iodine deficient state, was supplied with only enough iodine to maintain an euthyroid subject. Even a small increment in iodine could precipitate thyrotoxicosis.

A similar mechanism of iodine-induced thyrotoxicosis was advanced after studying four of eight subjects with nontoxic nodular goiter, normal thyroid stimulating hormone levels and patchy radioactive thyroid scans who developed thyrotoxicosis after large doses of saturated solutions of potassium iodide.29 These patients differed from the Tasmanian group by their residence in a city unassociated with endemic iodine deficiency.

Direct evidence exists that iodine can produce goiter, myxedema and thyrotoxicosis, but evidence also indicates that iodine may indirectly contribute to thyroid disease. Changing patterns of thyroid disease manifested by an increased incidence of thyroiditis have been reported from numerous clinics.910,20 A survey of surgical thyroid disease at the University of Michigan Medical Center, Ann Arbor, demonstrated a significant change in the histologic appearance of thyroid glands following the introduction of iodine therapy (1922) and iodine prophylaxis (1924).31

Before the use of iodine (1915–1920) 96 percent of all glands were either colloid goiters or hyperplastic. Thyroiditis (Hashimoto’s disease and lymphocytic thyroiditis)14 and nodular colloid goiters with dense diffuse lymphocytic infiltrates and nodules were absent, and even sparse lymphocytic infiltrates were rarely encountered in preiodine goiters. A statistically significant increase in both chronic thyroiditis and nodular colloid goiter with lymphocytes occurred in the thyroid glands examined from three quinquennia (1925 to 1930, 1942 to 1947 and 1958 to 1963) after iodine prophylaxis and therapy (table I).

When the clinical records of all subjects with significant lymphocytic infiltrates in the thyroid gland were examined, several conclusions became evident to the present authors. The thyroid glands removed from thyrotoxic patients who had been treated with strong iodine solutions before operation could not, in many instances, be distinguished from the lymphocytic goiters (thyroiditis and nodular colloid goiter with lymphocytes) from euthyroid patients. During the last five years of the survey (1958 to 1963), this differentiation became more difficult than in previous quinquennia (table II).32 The appearance of glands from thyrotoxic patients containing lymphocytic infiltrates from 1925 to 1930 undoubtedly resulted from their treatment with strong iodine solutions since the lymphocytic infiltrates were absent in our material before the use of Lugol’s solution.

**Thyroiditis and Graves’ Disease**

The blurring of the distinction between thyroiditis and Graves’ disease has...
also been reported by others. A recent article reported 24 cases of clinical Graves' disease in nine subjects with histologic thyroiditis alone, five patients with predominant thyroiditis and 10 patients in whom the gland resembled our nodular colloid goiter with lymphocytes. Immunologically, disturbed cell mediated immunity and antithyroglobulin antibodies occur in both conditions, further evidence that these diseases may be closely related. However, before the trumpet of autoimmunity is sounded, one must account for the absence of thyroiditis or lymphocytic infiltrates in thyroid glands in our pre-iodine goiters.

If our observations are valid, studies from other areas of endemic goiter before iodine use should yield similar results. A report of over 1900 pre-iodine goiters from Rochester, MN, a region of endemic goiter, disclosed only three glands with significant inflammatory infiltrates. All were composed of leukocytes. An absence or low incidence of chronic lymphocytic thyroiditis before prophylactic iodine was also reported from Switzerland, the Andes Mountains and the mountainous reaches of northern Thailand. A detailed examination of goiter in the Himalayan Mountains, a region of severe iodine deficiency, disclosed neither thyroiditis nor lymphocytic glandular infiltrates. Natives from all of these regions shared two features — severe iodine deficiency in their diets and a paucity of lymphocytic infiltrates in their glands.

Scant intraglandular lymphocytic infiltrates are not confined to exogenous iodine deficiency. Dyshormonogenic goiters occur when intraglandular enzymatic deficiencies result in defective hormone biosynthesis in the presence of abundant exogenous iodine. Intraglandular failure to utilize available iodine properly results in nodules of colloid-poor acini lined by hyperplastic epithelium. As in severe exogenous iodine deficiency, lymphocytes are absent or sparse in these glands.

Following iodine prophylaxis and therapy in areas of endemic goiter, others have recorded a change in the morphology of the thyroid gland. Broders, reporting from the Mayo Clinic in 1936, commented on the increased lymphocytes in the thyroid gland after preoperative iodine therapy. The morphologic change from pre-iodine goiters was so impressive that he suggested iodine as a cause of chronic thyroiditis.

Numerous surveys since the control of endemic iodine deficient goiters have confirmed the increasing prevalence of thyroiditis. Although investigators have warned that patient selection alone may account for the increased incidence of thyroiditis, others feel the increase to be a real one. Even if selection were a major factor in the increasing incidence of thyroiditis, it would not explain the morphologic change in our own and others' material following iodine use.

The association of iodine and thyroidal lymphocytic infiltrates is supported not only by circumstantial but also by experimental evidence. McCarrison produced thyroiditis in rats fed flour, meat residue, olive oil and potassium iodide. Follis reported diffuse lymphocytic infiltrates in the thyroid glands of iodine deficient hamsters prepared with propylthiouracil treated with excessive iodine. An infiltrate of lymphocytes depended upon the dose of iodine and the presence of a hyperplastic gland.

This work lends experimental support to our observations of lymphocytic infiltrates in treated thyrotoxicosis and the histologic difficulties in separating it from chronic lymphocytic thyroiditis. To date, the most successful experimental production of thyroiditis has occurred in dogs treated by a subcutaneous injection of large doses of iodine and smaller doses.
of crude dog thyroglobulin without Freund's adjuvant. These experiments resulted in progressive, sustained thyroiditis histologically identical to Hashimoto's disease in man.

The siren song of autoimmunity has obscured the importance of iodine in the production of lymphocytic infiltrates in the thyroid gland. Our own experience, the reports of others from iodine-poor localities before and after iodine therapy and prophylaxis as well as experimental data suggest that iodine is necessary to produce lymphocytic goiters and chronic thyroiditis. Iodine may be toxic to a genetically susceptible gland. What seems more likely, however, is that a surfeit of iodine may permit the intraglandular production of enough intermediate metabolite, thyroid hormone, or thyroglobulin to unmask an autoimmune state manifested by chronic diffuse thyroiditis and its variants.

References


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