Iodine induced thyrotoxicosis in apparently normal thyroid glands

Ståle Skare and Harald M. M. Frey

Abstract. Two male patients aged 36 and 52 years with thyrotoxicosis revealed a serum T₃ of 2.8 and 6.5 nmol/l and a serum T₄ of 166 and 238 nmol/l, respectively. Both had been exposed to iodine (2–10 mg daily) for 2–12 months before thyrotoxicosis was diagnosed. Urinary iodine excretion was high, 5000 and 10000 nmol/24 h (624–1250 μg). The uptake of ¹³¹I in the thyroid glands were low, none had goitre.

Their iodine intake was interrupted, urinary iodine excretion gradually decreased, and T₃ and T₄ in serum concomitantly normalized. They were clinically and biochemically euthyroid 9 and 11 weeks after withdrawal. After 14 and 22 weeks they had normal thyroid uptake of ¹³¹I, and thyroid scans showed glands of normal size and configuration, TRH-stimulation and a T₃-suppression tests became normal. ESR was not elevated in any of the cases, thyroid antibodies against thyroglobulin and follicular cell microsomes were absent and TSAb was undetectable during the thyrotoxic stage.

Thus no evidence of any pre-existing and/or pre-disposing pathological condition in the thyroid glands were found. The mechanism for the iodine-induced thyrotoxicosis in such cases remains obscure.

It has long been known that iodine intake in excess may induce thyrotoxicosis (Breuer 1900), but it was thought that this only occurred in glands carrying some underlying disease with autonomously functioning tissue, e.g. nodules or autoimmune thyroiditis (Connolly et al. 1970; Ermans & Camus 1972; Liewendahl & Turula 1972; Vagenakis et al. 1972; Stewart & Vidor 1976). Liewendahl & Gor-din (1974) published a case with thyrotoxicosis and goitre; both vanished after cessation of sea-kelp ingestion, and subsequently no abnormality was found in the thyroid. Savoie et al. (1975) reported ten patients where iodine had induced thyrotoxicosis in apparently normal thyroid glands. Seven of them were males. Sometimes a small goitre was present, and the thyrotoxicosis was occasionally followed by a transient hypothyroid phase.

We have had the opportunity of studying two male patients who we believe demonstrated this condition.

Patients and Methods

Case 1. T.T., born 1927. The family history was unremarkable, apart form the occurrence of goitre in an aunt. He had for some years been treated for a moderate hypertension with a thiazide diuretic. For about one year he had daily consumed one spoonful (approximately 10 mg iodine according to the producer) of dried, powdered sea-kelp ('Vitalia tarem'). He sought medical advice because of thyrotoxic symptoms, having a weight loss of 4 kg over the last 3 months. At the first examination he was agile with a regular pulse, rate 100/min, fine finger tremor and lid lag. The thyroid gland was not palpable. Laboratory findings: Serum T₃ 6.5 nmol/l, T₄ 238 nmol/l and TSH 0.2 μg/l. The relative uptake of ¹³¹I by the thyroid after 1, 24 and 48 h were 5, 2 and 2% of the dose given. High values of total iodine were found in serum
Serum T₃, T₄ and total iodine in serum and urine at intervals after iodine withdrawal for 2 patients with iodine-induced thyrotoxicosis.

**Table 1.**
Main clinical information concerning the 2 patients (T.T. and E.M.) at intervals after iodine withdrawal.

<table>
<thead>
<tr>
<th>Weeks after iodine withdrawal</th>
<th>Pulse rate beats/min</th>
<th>Body weight kg</th>
<th>Gland enlargement</th>
<th>Thyrotoxic signs</th>
<th>Thyrotoxic symptoms</th>
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<tbody>
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<td>7</td>
<td>72</td>
<td>76.0</td>
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<td>11</td>
<td>80</td>
<td>76.7</td>
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<td>14</td>
<td>60</td>
<td>78.4</td>
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<td>54</td>
<td>80.0</td>
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<td>E. M.</td>
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<td>74</td>
<td>57.5</td>
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and urine (Fig. 1). ESR 5 mm/h. Antibodies against thyroglobulin and follicular cell microsomes and TSAb were not detectable. Iodine was stopped and his condition gradually improved. He was euthyroid after 11 weeks (Table 1, Fig. 1). After 22 weeks, TSH values 0, 30 and 60 min after TRH injection were 0.4, 2.2 and 1.8 \( \mu \)g/l. The relative \( ^{131}I \) uptake by the thyroid were 4, 26 and 26\% after 1, 24 and 48 h. After suppression with 120 \( \mu g \) T\(_3\) daily for 7 days, the uptake values were 7, 11 and 10\%. A perchlorate discharge test was normal. The thyroid scan showed a normal gland. Shortly after becoming euthyroid, serum T\(_4\) dropped transiently to 70 nmol/l. His thyroid function has now been normal for 18 months.

**Case 2, E. M., born 1942, previously healthy.** In this case the family history revealed hypothyroidism in his mother. He had used dried sea-kelp ('Vitalia taremel') sporadically for some years, partly as an admixture to the bread dough, a practice which was stopped two weeks before the first consultation. Mild thyrotoxic symptoms had been present for about a year, weight loss 5 kg. At the first examination, he had fine finger tremor, regular pulse, rate 74/min and lid lag. The thyroid gland was not palpable. Laboratory findings: Serum T\(_3\) 2.8 nmol/l, T\(_4\) 166 nmol/l. TSH values 0, 30 and 60 min after TRH injection were 1.3, 0.9 and 0.7 \( \mu \)g/l. The relative uptake of \( ^{131}I \) by the thyroid 1, 24 and 48 h after the dose were 5, 4 and 4\%. High values of total iodine were found in serum and urine (Fig. 1). ESR 2 mm/h. Antibodies against thyroglobulin and follicular cell microsomes and TSAb were not detectable. His condition gradually improved after stopping iodine intake, and he was euthyroid 9 week later (Table 1, Fig. 1). After 14 weeks, the TSH values after TRH injection were 0.6, 2.8 and 2.2 \( \mu \)g/l. The thyroid uptake of \( ^{131}I \) was 6, 26 and 27\%, and 4, 6 and 6\% when repeated after suppression for 7 days with 120 \( \mu g \) T\(_3\) daily. A perchlorate discharge test was normal. The thyroid scan showed an even uptake in a normal sized gland. Shortly after being euthyroid, serum T\(_4\) dropped transiently to 72 nmol/l. After 4 weeks, it was in the mid-normal range. After he had been euthyroid for 6 weeks, he was experimentally exposed to 2 mg of iodine per day for 8 weeks. Daily urinary iodine excretion rose to 18000 nmol/l, which was higher than during the previous symptomatic episode. He did not develop clinical or biochemical evidence of thyrotoxicosis, the TRH stimulation test remaining normal. No relapse has occurred during 7 months of observation.

Serum concentrations of T\(_3\), T\(_4\) and TSH were measured by specific radioimmunoassay (Haug et al. 1977; Aakvaag et al. 1978; Torjesen et al. 1973). The normal range for T\(_3\) is 1.4–2.8 nmol/l for T\(_4\) 64–135 nmol/l and for TSH 0.2–1.2 \( \mu \)g/l. The TRH stimulation test was performed with 0.4 mg TRH (Torjesen et al. 1973). The relative uptake of \( ^{131}I \) was determined 1, 24 and 48 h after 1850 kBq (50 \( \mu \)Ci) \( ^{131}I \) orally. Technicon Autoanalyzer. Method File N-56 was used for measurements of total iodine. A passive haemagglutination technique was used for determination of thyroglobulin antibodies, and antibodies against follicular cell microsomes were determined by indirect immunofluorescence. TSAb was determined at the Royal Victoria Infirmary, Newcastle upon Tyne, England (Smith & Hall 1974). We define a normal response to T\(_3\) suppression as a > 50\% reduction in 24 h \( ^{131}I \) uptake, after the patient had been given 120 \( \mu g \) T\(_3\)/day for 7 days. The perchlorate discharge test is abnormal, if the activity of \( ^{131}I \) in the thyroid decreases more than 15\% during 40 min following 400 mg perchlorate, taken orally 1 h after a fasting oral load of \( ^{131}I \) (1850 kBq).

**Discussion**

Graves' disease was unlikely in these patients because of the rapid improvement that ensued when iodine was withdrawn, and the regaining of normal thyroid homeostasis shortly after the iodine excretion in the urine was normalized (Table 1, Fig. 1). In addition TSAb was undetectable. Toxic adenoma and toxic multinodular goitre were ruled out by palpation and the normal thyroid scans. Factitious thyrotoxicosis was excluded by history. Subacute granulomatous thyroiditis may have a toxic stage. Usually these patients have painful and swollen glands, fever and high ESR, but 'silent' cases have been reported (Papapetrou & Jackson 1975). Recently three groups have independently reported transient thyrotoxicosis and low iodine uptake by the gland in 9 patients with lymphocytic thyroiditis (Gluck et al. 1975; Asteris et al. 1977; Gorman et al. 1978). These cases were separated from 'silent' subacute thyroiditis only by histology. Some had a small goitre. The thyrotoxic episodes showed a tendency to relapse, and were sometimes followed by a transient hypothyroid phase.

Thyroid biopsy was not available in our patients because goitre was not present. Iodine-induced thyrotoxicosis can therefore not be separated with certainty from these types of thyroiditis in our cases. However, the history of iodine exposition verified by the high urinary iodine excretion and the gradual improvement after iodine withdrawal is strong evidence for iodine as the causative agent. The fact that no anatomical or functional defects were demonstrable in the glands after recovery constitutes no proof that they were disease-free.

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before the iodine intake started, but this assumption is very likely.

The pathogenesis of 'Iodine-Basedow' in previously normal glands is obscure. Increased proteolytic activity in the thyroid was demonstrated in rats exposed to high iodine intake for several weeks. (Sinadinović & Liewendahl 1976). An increased proteolytic activity would explain both the hypersecretion and the lack of goitre in our patients. In the experimental animals, thyrotoxicosis did not ensue. Excessive iodine intake may cause thyroid damage similar to thyroiditis in dogs (Belshaw & Becker 1973). In thyroid biopsies from 2 patients with iodine induced thyroiditis, no signs of any inflammatory process were demonstrated. Most follicles were covered with flattened endotheliform thyroid cells. Cells were rich in lysosomal acid phosphatase with apparent active proteolysis of thyroglobulin (Leger et al. 1977).

Okamura et al. (1978) recently described one patient who developed Hashimoto's thyroiditis after iodine consumption in excess. He had high titres of antibodies against follicular cell microsomes, and the diagnosis was confirmed by biopsy. Antibodies were undetectable before and after the episode. This patient was transiently hypothyroid and on no occasion thyrotoxic.

The negative result of the iodine provocation test in patient E.M. is somewhat surprising, and contrasts with the finding in one of the cases of Savoie et al. (1975), who became thyrotoxic 6 years after the first episode upon a second iodine exposure. This may indicate that the adaptability of the gland to an iodine load may vary with circumstances unknown at present. The positive family history with respect to thyroid disease in both patients may indicate a latent abnormality in their glands.

Acknowledgments

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References


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