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Iodide induces thyroid autoimmunity in patients with endemic goitre: a randomised, double-blind, placebo-controlled trial

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Abstract

Objective: Iodine is essential for normal thyroid function and the majority of individuals tolerate a wide range of dietary levels. However, a subset of individuals, on exposure to iodine, develop thyroid dysfunction. In this double-blind trial, we evaluated the efficacy and tolerability of low-dose iodine compared with those of levo-thyroxine (T_4) in patients with endemic goitre.

Methods: Sixty-two patients were assigned randomly to groups to receive iodine (0.5 mg/day) or T_4 (0.125 mg/day) for 6 months. Subsequently, both groups were subject to placebo for another 6 months. Thyroid sonography, determination of thyroid-related hormones and antibodies, and urinary excretion of iodine were carried out at baseline and at 1, 6 and 12 months.

Results: At 6 months, markedly increased urinary values of iodine were found in patients receiving iodine (36 μg/24 h at baseline, 415 μg/24 h at 6 months) compared with those receiving T_4 (47 μg/24 h at baseline, 165 μg/24 h at 6 months; $P < 0.0001$ compared with iodine group). T_4 administration engendered a greater ($P < 0.01$) decrease in thyroid volume (from 32 ml to 17 ml, $P < 0.0001$) than did intake of iodine (33 ml to 21 ml, $P < 0.005$). High microsomal and thyroglobulin autoantibody titres were present in six of 31 patients (19%) receiving iodine, and iodine-induced hypo- and hyperthyroidism developed in four and two of them, respectively. Fine-needle biopsy revealed marked lymphocyte infiltration in all six. After withdrawal of iodine, thyroid dysfunction remitted spontaneously and antibody titres and lymphocyte infiltration decreased markedly. Follow-up of these six patients for an additional 3 years showed normalisation of antibody titres in four of them.

Conclusion: Although nearly comparable results were obtained with both treatment regimens regarding thyroid size, partly reversible iodine-induced thyroid dysfunction and autoimmunity were observed among patients with endemic goitre.

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Introduction

Iodine deficiency remains the single most important world-wide public health problem related to the thyroid gland. The consequences are goitre, hypothyroidism, and abnormal development (1). For the thyroid, the raw material is iodine, and the most important means for meeting changing conditions is modulation by thyroid-stimulating hormone (TSH) (2). The best indications of iodine deficiency are urinary concentration of iodine, thyroid size, serum thyroglobulin, and TSH concentrations. In Europe, there is an inverse relationship between urinary iodine and thyroid volume in children (3). Thus iodine is essential for normal thyroid function and, fortunately, the majority of individuals tolerate a wide range of dietary levels. People without evidence of underlying thyroid disease usually remain euthyroid despite ingesting large amounts of iodine, as a result of the acute inhibitory effects of excess intrathyroidal iodine on the organification of iodine and on subsequent hormone synthesis. This autoregulation involves a decrease in the capacity of the thyroid iodine trap, perhaps corresponding to a decrease in the thyroid sodium/I symporter, which has recently been cloned. However, a subset of individuals, upon exposure to iodine, may develop thyroid dysfunction and autoimmunity (4, 5).

Outbreaks of iodine-induced hyperthyroidism have been reported in the past when iodine prophylaxis was introduced to treat populations with endemic goitre (6, 7). Introduction of iodine salt or oral iodine oil in endemic areas resulted in an increased incidence of self-limited hyperthyroidism (8, 9). Recently, Bourdoux *et al.* (10) reported that, after 2 years of prophylaxis with iodine salt (up to 148 p.p.m.) in Zaire, resulting in urinary excretion of 0.2–0.5 mg iodine daily, 14% of 190 patients had undetectable serum TSH values. Severe thyrotoxicosis also occurred in Zimbabwe after introduction of iodine salt (30–90 p.p.m.) (11). In contrast, administration of oral iodine oil in Senegal

did not induce hyperthyroidism (12). Furthermore, iodine deficiency was treated effectively for 9 months with only a single oral dose of 47 or 118 mg (13) and, elsewhere, a single oral dose of 240 mg iodine corrected iodine deficiency in children for 6 months (14).

Autoimmune thyroiditis is more prevalent in iodine-replete areas compared with areas of iodine deficiency (5, 15). Studies of surgical pathology in areas of iodine deficiency have shown a dramatic increase in lymphocyte infiltration after iodine prophylaxis (16, 17), and clinical reports have described an increased production of thyroid antibodies in association with iodine intake (18, 19). Thus there is an optimal range of daily dosage of iodine, above and below which the risk of various thyroid diseases increases. In the present double-blind trial, we evaluated the efficacy and tolerability of low-dose iodine to reduce the size of the thyroid gland, and compared it with the effects of T_4, in patients with endemic goitre.

Patients and methods

Consecutive patients who attended the endocrine outpatient clinic with clinical symptoms of untreated endemic goitre were recruited. Inclusion criteria were a diffuse goitre by palpation, a homogeneous pattern by ultrasound, euthyroidism, and negative personal and family history of autoimmune disease. The study protocol was approved by the Ethics Committee of the University Hospital and written informed consent to their inclusion in the trial was obtained from each participant. A computer-generated randomisation list (RAPROG program, HP 3000/70, Compiler library procedures RAND1) was used to assign each patient to receive either iodine or T_4. Sixty-two patients were recruited, to give a 90% chance of finding a 30% difference between iodine and T_4 at the 5% level. Thirty-one patients (19 women and 12 men, median age 26 years, range 21–47 years, median weight 75 kg, range 47–105 kg) were administered 0.125 mg/day T_4, and 31 (18 women and 13 men, median age 27 years, range 19–50 years, median weight 73 kg, range 48–102 kg) each received 0.5 mg/day potassium iodide for 6 months. To observe the relapse rate, both groups received placebo for another 6 months. Trial tablets were prepared in identical numbered packages by staff not further involved in the study (Merck, Darmstadt, Germany). All trial tablets looked and tasted the same. During the study, the randomisation code was not available to the investigators.

Thyroid ultrasound and measurement of thyroid-related hormones and autoantibodies, thyroglobulin, and 24-h urinary excretion of iodine were performed at baseline and at 1, 6 and 12 months. At 3 and 9 months, ultrasound was performed and urinary iodine was determined. Sonography (Sonoline SL linear scanner with a high resolution, 7.5-MHz transducer, Siemens, Erlangen, Germany) was performed by one experienced investigator (G K), to keep inter-observer variance low. The length, width and thickness of both thyroid lobes were measured. The volume was estimated by multiplication of thickness, width, length and a corrective factor (0.479). A thyroid volume exceeding 20 ml in women and 25 ml in men was considered to represent a goitre that should be treated (20). TSH (normal range 0.3–4 mU/l, 30 min after i.v. administration of 0.2 g thyrotrophin-releasing hormone (TRH), Antepan, Henning, Berlin, Germany), thyroglobulin (normal range <9 ng/ml), and thyroid hormones (total T_4, normal range 4–10 μg/dl; total triiodothyronine (T_3), normal range 80–200 ng/ml; Boehringer Mannheim, Mannheim, Germany), and autoantibodies to thyroglobulin and thyroid microsomes (normal range by enzyme-linked immunosorbent assay <100 U/ml, Elias, Freiburg, Germany) and TSH receptor (normal range <9 U/l, by radio receptor assay (RRA), Brahms, Berlin, Germany) were measured using commercially available kits. All samples were analysed in duplicate in a single run. Six patients were typed for human leucocyte antigen (HLA) classes by a standard microlymphocytotoxicity technique. Determination of urinary excretion of iodine was performed by a modified ceric arsenous acid wet ash method: urine was digested with chloric acid under mild conditions and iodine was determined manually by its catalytic role in the reduction of ceric ammonium sulphate in the presence of arsenous acid (21).

All values are expressed as the median and range. Statistical analysis was with χ^2 and Mann–Whitney tests. Wilcoxon matched-pairs, signed-rank test was used to compare pre-treatment findings with results at review within each group.

Results

Compared with intake of a cumulative dose of 90 mg iodine (6 months compared with baseline, $P < 0.005$; Table 1), administration of T_4 (cumulative dose 23 mg) engendered a greater decrease in thyroid volume (6 months compared with baseline, $P < 0.0001$): the median reduction in goitre size was 36% and 47% in the iodine and T_4 groups, respectively ($P < 0.01$). At 12 months, the therapeutic effect was sustained in the iodine group (6% change), but thyroid volume increased again in the T_4 group (by 22%; 12 months compared with 6 months, $P < 0.001$); this difference between the groups wa significant ($P < 0.01$). During treatment, thyroglobulin concentrations declined strongly, slightly more in response to T_4; during the placebo phase, they increased again in the T_4 group only ($P < 0.001$). Whereas serum TSH remained stable in the iodine group, it was suppressed during T_4 treatment ($P < 0.0005$). Markedly increased urinary iodine values were found during iodine treatment (6 months compared with baseline, $P < 0.0001$; 6-month value compared with that in the T_4 group, $P < 0.001$).

In contrast to the T_4 group, high titres of thyroglobulin and thyroid microsomal autoantibodies were present in six (five women) of 31 patients (19%) receiving iodine (Fig. 1); iodine-induced hypothyroidism developed in four of them and hyperthyroidism in two (Table 2). The latter two patients suffered from mild symptoms, and only propranolol was administered. Thyroid dysfunction remitted spontaneously and antibody titres decreased markedly after withdrawal of iodine. Follow-up of these six patients for an additional 3 years showed a decline in the antibody titres to normal values in four of them. In four patients, thyroid size remained small, with hypoechogenecity on sonography. Compared with antibody-negative patients, these six patients with positive titres did not differ in baseline characteristics (e.g. thyroid size or concentrations of thyroid-related hormones). They remained negative for TSH receptor antibodies, and HLA typing revealed no mutual or common antigens (Table 3).

Thyroid cytology

At 6 months, fine-needle aspiration biopsy was performed in the six patients with positive antibody titres. Smears were dominated by lymphoid cells in large numbers. There was a mixed population of lymphocytes, immunoblasts and plasma cells, and germinal centre cells including centroblasts and reticular cells were prominent. The follicular epithelial cells appeared to be degenerate or hyperplastic. Aggregates of filamentous

Table 1 Median and range of thyroid-related parameters at baseline, and at each visit over a period of 6 months (treatment phase), and 9 and 12 months (placebo phase) after the start of low-dose potassium iodide (0.5 mg/day) supplementation or levo-thyroxine (LT_4) treatment (0.125 mg/day).

	Treatment phase				Placebo phase	
Months:	0	1	3	6	9	12
Thyroid volume (ml)						
KI	33 20–59	29 18–57	24 15–49	21 12–38	21 11–39	23 9–44
LT_4	32 20–58	23 15–44	21 13–36	17 12–31	20 15–40	24 18–46
Urinary iodine (μg/24 h)						
KI	36 13–69	201 125–343	324 189–500	415 278–660	251 143–418	147 97–237
LT_4	47 28–77	90 69–139	145 88–174	165 95–212	78 53–136	56 39–91
Total T_4 (μg/dl) (normal range 4–10)						
KI	7 5.1–9.6	7 4.9–9.6		7.5 2.6–15.8		7.5 5.7–10
LT_4	8 5.3–9.2	10 7.2–11		9 7.1–10.8		8.5 6.0–9.7
Total T_3 (ng/ml) (normal range 80–200)						
KI	134 89–186	130 86–158		112 71–276		131 92–171
LT_4	122 102–178	129 99–169		126 89–158		119 87–154
Thyroglobulin (ng/ml) (normal values <9)						
KI	37 12–65	32 10–59		22 6–41		25 9–47
LT_4	45 32–92	28 17–62		19 4–38		34 13–78
Baseline TSH (mU/l) (normal range 0.3–4)						
KI	1.4 0.5–3.2	1.3 0–3.1		0.9 0.0–7.5		1.1 0.0–9.6
LT_4	1.2 0.5–3.4	0.1 0–0.3		0.1 0–0.2		1.5 0.4–3.2
Stimulated TSH (mU/l)†						
KI	7.8 4.9–17.2			8.6 0.0–51		
LT_4	9.2 5.8–18.7			0.2 0.1–0.4		

† Stimulated TSH, 30 min after TRH stimulation with 0.2 g i.v.

nuclear debris were a consistent finding (Fig. 2). Oxyphilic follicular cells demonstrating abundant, greyish blue cytoplasm were observed. The nuclei were hyperchromatic and pronounced anisonucleosis was commonly noted. Colloid was scant or absent. In patient 2, the aspirate contained foci of mononuclear histiocytes and single multinucleated giant cells. At 12 months, repeated biopsy (Fig. 3) showed a marked decrease in lymphoplasmatic infiltration in four of the patients. However, in patients 1 and 2, the aspirate revealed a persistent moderate lymphocyte infiltrate, the presence of stromal fragments and fibrocytes. At 48 months, baseline TSH had increased again in patient 1. Cytology revealed cohesive clusters of oxyphilic follicular cells, surrounded by a few scattered lymphocytes and fibroblasts.

Discussion

This double-blind study has shown that 0.5 mg/day iodine and 0.125 mg/day T_4 were effective in reducing thyroid size. However, T_4 produced a greater decrease in thyroid volume and a variation in thyroid size after the end of treatment at 6 months. Furthermore, partly reversible iodine-induced thyroid dysfunction and autoimmunity were observed in nearly 20% of young adults, particularly women, with euthyroid, diffuse, endemic goitre. HLA-typing failed to reveal a genetic similarity, specifically a common MHC allele, in the patients with iodine-induced thyroid autoimmunity. These results are in agreement with those of another double-blind trial in which low-dose iodine (0·2 mg/day for 1 year) successfully normalised thyroid size and body iodine content; nevertheless, reversible iodine-induced thyroid dysfunction was also noted in 10% of the patients (22).

In a study by Jonckheer *et al.* (23), administration of iodine at 1 mg/week for 6 weeks, followed by administration of 2 mg/week for another 6 weeks, did not affect thyroid function. In the United States, 0.5 mg/day was the smallest quantity of iodine, in excess of that consumed with the diet, that did not affect thyroid function (24). Other studies have suggested that administration of 0.5 mg iodine daily induced a small but significant increment in basal and TRH-stimulated serum TSH concentrations (25, 26). Ingestion of iodine at 1.5 mg/day for 15 days by euthyroid patients invariably resulted in a significant decrease in serum free T_4 concentrations, with a significant compensatory increase in basal and stimulated TSH (26). Thus supplements of iodine as low as 0.2–0.5 mg/day above the normal diet in both iodine-replete and iodine-deficient areas might cause subtle changes in thyroid function.

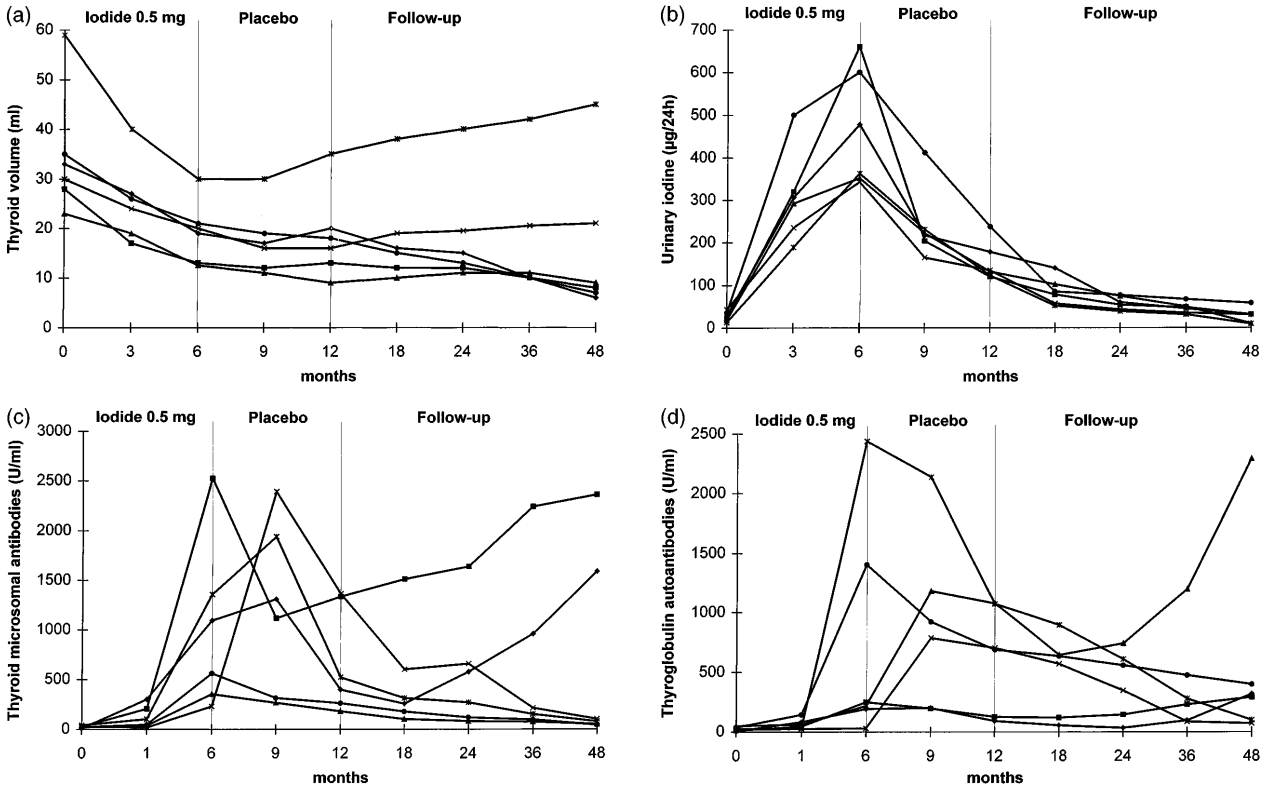

Figure 1 Changes in (a) thyroid volume, (b) urinary excretion of iodine per 24 h, (c) thyroid microsomal autoantibodies and (d) thyroglobulin autoantibodies (normal range <100 U/ml), in the six patients with iodide-induced thyroid dysfunction and autoimmunity, at baseline and at 1, 3, 6, 9, 12, 18, 24, 36 and 48 months after the start of low-dose potassium iodide supplementation (0.5 mg per day for 6 months).

Table 2 Basal TSH (normal range 0.3–4 mU/l), stimulated TSH (30 min after i.v. administration of 0.2 g TRH), total T_4 (normal range 4–10 μg/dl) and total T_3 (normal range 80–200 ng/ml) in the six patients with iodine-induced thyroid dysfunction and autoimmunity at baseline and at each visit over a period of 6 months, and 1, 2, 3 and 4 years after the start of low-dose (0.5 mg/day) potassium iodide supplementation.

	Treatment			Follow-up					
Months:	0	1	6	9	12	18	24	36	48
Patient 1 (woman aged 47 years)									
Basal TSH (mU/l)	0.81	2.7	7.25	6.08	2.17	2.28	3.12	3.81	5.19
Stimulated TSH (mU/l)	4.9	11.2	51	24.5	15.4				
Total T_4 (μg/dl)	7.9	5.3	2.6	5.8	6.2	9.0	9.9	8.6	6.7
Total T_3 (ng/ml)	136	129	71	118	139	148	166	159	151
Patient 2 (woman aged 19 years)									
Basal TSH (mU/l)	1.86	2.9	6.44	5.26	4.81	2.9	2.8	2.72	2.21
Stimulated TSH (mU/l)	7.3	17.6	32.8	27.5	19.7				
Total T_4 (μg/dl)	8.7	7.3	2.9	4.3	5.7	6.9	7.7	8.3	5.9
Total T_3 (ng/ml)	152	127	86	105	129	112	139	168	143
Patient 3 (woman aged 33 years)									
Basal TSH (mU/l)	1.17	1.54	0.3	2.17	9.26	5.1	2.77	1.68	1.13
Stimulated TSH (mU/l)	8.6	12.2	0.3	34.3	59.7				
Total T_4 (μg/dl)	9.6	5.5	11.7	10.4	9.5	8.1	7.8	8.3	6.6
Total T_3 (ng/ml)	186	92	196	141	155	120	134	113	96
Patient 4 (woman aged 42 years)									
Basal TSH (mU/l)	1.24	0.81	2.3	8.6	7.2	3.3	1.93	1.6	0.9
Stimulated TSH (mU/l)	8.4	9.5	22.1	43.1	36.1				
Total T_4 (μg/dl)	6.9	9.0	7.0	5.3	6.4	8.8	8.1	8.7	7.6
Total T_3 (ng/ml)	127	141	105	97	111	154	137	161	144
Patient 5 (woman aged 47 years)									
Basal TSH (mU/l)	0.45	0.0	0.0	0.0	0.0	0.41	0.92	1.09	2.02
Stimulated TSH (mU/l)	5.5	0.1	0.0	0.1	0.3				
Total T_4 (μg/dl)	7.1	9.6	12.7	9.8	9.1	8.9	6.6	6.9	5.7
Total T_3 (ng/ml)	117	155	263	187	171	139	154	153	128
Patient 6 (man aged 32 years)									
Basal TSH (mU/l)	1.16	1.96	0.0	0.0	0.0	4.77	3.75	2.28	1.85
Stimulated TSH (mU/l)	7.6	9.9	0.0	0.0	0.4				
Total T_4 (μg/dl)	6.4	8.7	15.8	11.3	10	8	8.1	8.9	9.5
Total T_3 (ng/ml)	123	149	276	196	169	121	126	152	114

In our patients, T_4 treatment led to an earlier and greater decrease in thyroid size, in addition to complete suppression of serum TSH, but a variation in volume was observed again after withdrawal of T_4. In comparison, successful treatment outcome was sustained in the iodine group. Thus enhancement of iodine concentration in the thyroid cells seems to be crucial for involution of the characteristic hyperplastic picture with abundant parenchyma and rare colloid, and may be at least as relevant as TSH modulation for the pathophysiology of goitre (2). Furthermore, the importance of pre-existing thyroid hyperplasia for the development of thyroid autoimmunity after iodine supplementation can be demonstrated in two ways: a) lymphocytes need to enter the thyroid from the circulation in order that any of the pathogenic events

Table 3 HLA typing in the six patients with iodine-induced thyroid autoimmunity.

	Patient					
Locus	1	2	3	4	5	6
A	2, 24	1, 28	2, 29	1, 3	2, 25	3, 30
B	8, 44	8, 60	55, 58	7, 8	7, 44	13, 44
Cw	2, 7	3, 7	1	7	5, 7	5, 6
DR	1, 3	13, 15	8, 11	1, 13	4, 15	7, 15
DQ	2, 5	6	4, 7	5, 6	6, 7	2, 6
DR (51–53)	52	51, 52	52	52	51, 53	51, 53

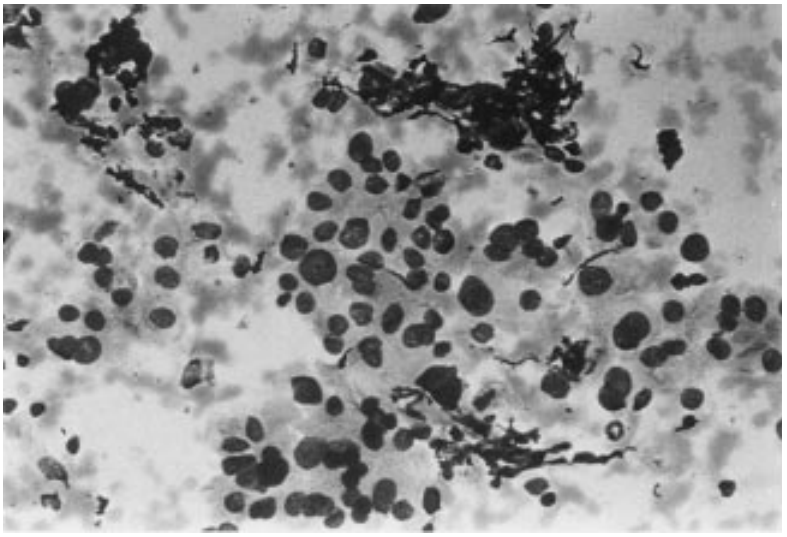

Figure 2 Fine-needle aspiration biopsy of the thyroid gland in a female patient with endemic goitre who developed iodide-induced hypothyroidism and thyroid autoimmunity, 6 months after starting low-dose potassium iodide supplementation with 0.5 mg/day. The aspirate smears were air dried and stained with May–Grünwald–Giemsa. Oxyphilic cells are surrounded by filamentous nuclear debris, indicating inflammatory tissue destruction. Original magnification × 500.

may ensue, and thyroidal cell proliferation may expand the lymphocyte infiltrate; b) the thyroid adapts to an insufficient supply of iodine through an increase in the capacity of the iodine trap, both by TSH-independent augmentation of membrane iodine trapping and by TSH stimulation of the iodine pump. This leads to an accumulation within the gland of a larger percentage of the ingested exogenous iodine (2, 5).

Epidemiological data support an enhancing effect of increasing iodine intake on thyroid autoimmunity, and sudden changes in iodine intake may be more important for the development of thyroiditis and thyroid autoantibodies than prolonged exposure to a high but constant intake of iodine (5, 15). This would explain the adverse effects of iodine prophylaxis in iodine-deficient patients in Argentina, where the prevalence of lymphocyte infiltration in thyroidectomy specimens increased from 8 to 31% in the 5 years after introduction of prophylactic iodine (27). A striking increase in thyroid antibodies was also reported after the use of amiodarone was initiated in Portugal, an area of low iodine intake (28), whereas no such effect was observed in the iodine-sufficient United Kingdom (29). Furthermore, an increase in thyroid antibodies was found 3 months after administration of iodine oil to patients with goitre in Greece (19). Among 30 additional cases treated with iodine (0.3 mg/day), nine (30%) developed high antibody titres. Induction of thyroid antibodies was dose dependent, as 12% of patients with goitre who received only 0.15 mg/day iodine became antibody positive (30). In agreement with our results, thyroid antibodies decreased markedly or disappeared after withdrawal of iodine. In a histological study, association between the presence of thyroid antibodies and lymphocyte infiltration of the gland was demonstrated (31), and histological features of 28 antibody-positive patients with iodine-induced hypothyroidism included diffuse lymphocyte infiltration with follicles of reduced size containing sparse colloid (32). Along with our cytological findings, cessation of intake of iodine led to normalisation of thyroid function, decreased antibody titre, and disappearance of lymphocyte infiltration.

In experimental thyroiditis, the main factors implicated in the stimulatory activity of iodine are increased iodination of thyroglobulin, a non-specific thyroid oxidative damage, or both (33). High-iodine diet caused thyroid cell necrosis and autoimmunity, whereas antioxidants reduced lymphocyte infiltration in obese strain chickens (34). Uptake and metabolism of iodine is crucial to the development of thyroiditis, as administration of perchlorate and mononitrotyrosine (to inhibit iodine transport and promote thyroidal iodine loss respectively) *in ovo* virtually prevents thyroiditis in these birds, thus implying a role for physiological concentrations of iodine (33). Response of murine T cell hybridomas to thyroglobulin is also directly related to its iodine content (35, 36).

Iodine also acts directly on the immune system. *In vitro*, it significantly induced expression of MHC class II antigens in FRTL-5 cells (37). Furthermore, together with gamma-interferon, iodine increases the inducibility of the 72-kDa heat shock protein in cultured human thyroid cells (38). Studies with the BB/W rat have shown that dietary iodine supplementation exacerbates thyroiditis (39). A reduction of thyroidal infiltration in response to T_4 treatment was observed, but the protective effect was lost when the rats were additionally treated with iodine, illustrating its key role in this disease (40). In humans, iodine enhances *in vitro* IgG synthesis by peripheral blood lymphocytes (41). In physiological plasma concentrations, iodine significantly increased both the number of cells synthesising IgG and the amount of IgG released into the culture medium.

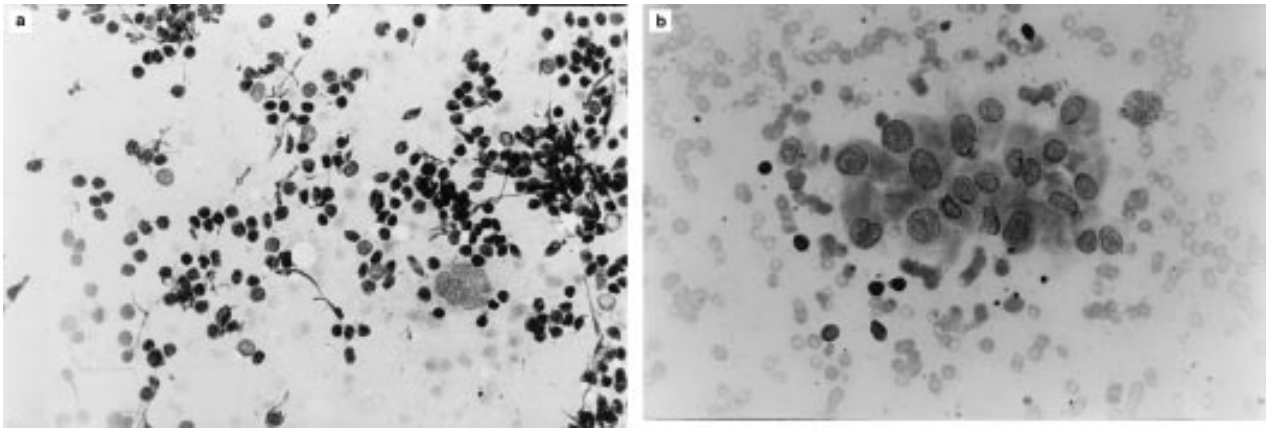

Figure 3 Fine-needle aspiration biopsies of the thyroid gland in patient 1, who developed iodide-induced thyroid autoimmunity (May–Grünwald–Giemsa stain; original magnification×500). (a) Light micrograph 6 months after the start of low-dose potassium iodide supplementation (0.5 mg/day). The aspirate smear contains scant colloid and abundant cells, predominantly lymphoblasts and a few thyroid follicles. Most of the lymphoid cells are mature lymphocytes and plasmocytes; nonetheless, centrofollicular lymphoid cells are also observed. The lymphocytes appear to have artefacts produced by extension, such as a rope-like prolongation or tail. (b) Light micrograph at 12 months. Monolayer of oncocytes with abundant, fine granular cytoplasm and large, hyperchromatic and pleomorphic nucleus. In the background, there are a few lymphocytes.

Finally, the iodine-containing drug, amiodarone, affects T cell function by increasing the number of both helper and cytotoxic T lymphocytes (42), and induces destructive thyroiditis, resulting in thyrotoxicosis, as suggested by clinical, histological, and *in vitro* studies (43–45).

In this trial, comparison between T_4 and iodine was limited to the fixed doses of each that were chosen. Although the doses were considered to be reasonable, it may be that different doses of either agent could have induced more or less change in various thyroid-related parameters. These considerations indicate that the conclusions we have drawn are limited to our particular experimental conditions. Furthermore, this study was conducted in patients who were iodine-deficient at the outset. The question as to whether the same dose of iodine would have similar effects in members of a population who are already receiving adequate dietary amounts of iodine warrants investigation in further trials.

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