0021-972X/97/$03.00/0
Journal of Clinical Endocrinology and Metabolism

1997 Germany
dl 3/2021
I reduced goiter but triggered reversible dysfunction in 10%
No discussion of Zn or Se levels, or root cause of initial goiter

Vol. 82, No. 12
Printed in U.S.A.

Randomized, Double Blind, Placebo-Controlled Trial of Low Dose Iodide in Endemic Goiter

GEORGE KAHALY, HANS PETER DIENES, JÜRGEN BEYER, AND GERHARD HOMMEL

Departments of Endocrinology/Metabolism, Pathology (H.P.D.), and Medical Statistics (G.H.), Gutenberg University Hospital, Mainz, Germany

ABSTRACT

Iodine (I) is essential for normal thyroid function, and the majority of subjects tolerate a wide range of dietary levels. However, a subset of individuals upon exposure to normal or elevated levels of I develop thyroid dysfunction and autoimmunity. In this double blind trial, we evaluated efficacy and tolerability of low dose I in adults with euthyroid, diffuse, endemic goiter. Sixty-two subjects were randomly assigned I (0.2 mg/day) or placebo for 12 months. After termination of therapy, both groups were followed for a further 6 months. Thyroid sonography and determinations of thyroid-related hormones, urinary I excretion per 24 h, and thyroid antibodies were carried out at baseline and at 3, 6, 9, 12, 15, and 18 months. Markedly elevated urinary I values were found during therapy in subjects receiving I (32 at baseline *vs.* 213 μg/24 h at 12 months; $P = 0.0001$) compared to placebo (34 and 33 μg/24 h, respectively; $P < 0.0001$ *vs.* I). I substantially reduced thyroid volume (29 *vs.* 18 mL at 12 months; −38%; $P = 0.0001$), and at 18 months, the therapeutic effect was sustained. In the placebo group, no significant changes were observed. High microsomal and thyroglobulin autoantibody titers were present in 3 of 31 (9.7%) subjects receiving I, and I-induced hypo- and hyperthyroidism developed in 2 and 1, respectively. Fine needle biopsy revealed marked lymphocytic infiltration in all 3 cases. After withdrawal of I, thyroid dysfunctions spontaneously remitted, and antibody titers as well as lymphocytic infiltration decreased markedly. Follow-up of these 3 subjects for an additional 2 yr showed normalization of antibody titers in 2. Thus, among subjects with endemic goiter, low dose I successfully normalized thyroid volume and body I supplementation; nevertheless, reversible I-induced thyroid dysfunctions and autoimmunity were observed in nearly 10% of the subjects. (*J Clin Endocrinol Metab* **82:** 4049–4053, 1997)

IODINE (I) deficiency is a worldwide major health problem, with some 1 billion people at risk (1, 2). Its consequences include goiter, irreversible mental retardation, and decreased survival among children (3). The recommended daily I intake is variable, depending on the age of the subjects. In the United States, the average I intake is 250 μg/day and may reach as much as 500 μg (4). In Europe, there is an inverse relationship between urinary I and thyroid volume in children, and goiter occurs as soon as the urinary I level is below a critical threshold of 10 μg/dL (5). Thus, I is essential for normal thyroid function, and fortunately, the majority of individuals tolerate a wide range of dietary levels. However, a subset of individuals upon exposure to normal or elevated levels of I develop thyroid dysfunction and autoimmunity (6).

Autoimmune thyroiditis is more prevalent in areas of adequate I intake than in areas of I deficiency (7–9). Studies of surgical pathology in areas of I deficiency have shown a dramatic rise in lymphocytic infiltration after I prophylaxis (10, 11) as well as increases in thyroid antibodies (12). A significant number of patients treated with the I-containing drug amiodarone develop thyroid dysfunction (13). Recently, a single oral dose of 0.8 g I administered to goitrous adults induced a TSH rise in 10 subjects and biochemical hyperthyroidism in 3 (14). I-induced thyrotoxicosis in Zimbabwe, a moderately I-deficient area, after the introduction of an I prophylaxis program with I salt (0.03 g I/kg) was reported (15), and introduction of I salt (148 parts/million I) in a severe I-deficient area of Zaire resulted in frequent hyperthyroidism in 29 of 191 (15%) goitrous individuals (16). On the other hand, I deficiency could be effectively treated for 9 months with single oral I doses of only 0.047 and 0.118 g (17); furthermore, a single oral I dose of 0.24 g corrected I deficiency in children for 6 months (18). Thus, there is an optimal range of daily I dosage, above and below in which the risk of various thyroid diseases increases. In this double blind, placebo-controlled trial, we evaluated the efficacy and tolerability of low dose I supplementation as well as its influence on various thyroid-related parameters in young adults with euthyroid, diffuse, endemic goiter.

Subjects and Methods

Consecutive subjects who attended the university endocrine outpatient clinic with clinical symptoms of untreated endemic goiter were recruited. Inclusion criteria were a diffuse goiter by palpation, a homogeneous pattern by ultrasound, euthyroidism, and negative personal as well as family history of autoimmune thyroid disease. A computer-generated randomization list (RAPROG program, HP 3000/70, Compiler library procedures RAND1) was used to assign each subject to receive either potassium I or placebo. Sixty-two subjects were recruited to give a 90% chance of finding a 30% difference between I and placebo at the 5% level. The code was broken when 62 subjects had completed the trial. Study protocol was approved by the ethics committee of the Gutenberg University Hospital, and informed consent to enter the trial was obtained from each subject. Thirty-one subjects [16 women and 15 men; mean age, 24 yr (range, 22–32 yr); mean weight, 70 kg (range, 52–90 kg); mean height, 175 cm (range, 163–190 cm)] were administered 0.2 mg I/day, and 31 (16 women and 15 men; mean age, 24 yr (range, 20–31 yr); mean weight, 70 kg (range, 53–88 kg); mean height, 173 cm (range, 163–192 cm)] each received placebo for 12 months. To observe the relapse

Received April 17, 1997. Revision received July 16, 1997. Accepted August 22, 1997.

Address all correspondence and requests for reprints to: Professor George J. Kahaly, University Hospital, Building 303, Mainz 55101, Germany.

rate, both groups were followed 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 the same. During the study, the randomization code was not available to the investigators. Thyroid ultrasound and measurements of thyroid-related hormones and antibodies, thyroglobulin, and 24-h urinary I excretion were performed at baseline and at 3, 6, 12, and 15 months. At 9 and 18 months, ultrasound was performed, and urinary I was determined.

Thyroid 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 interobserver 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 a goiter that should be treated (19).

TSH (baseline TSH, 0.3–4 mU/L; 30 min after iv administration of 200 μg TRH, 10 U/L; Antepan, Henning Berlin, Berlin, Germany), thyroglobulin (<9 ng/mL), and thyroid hormones (total T_4, 4–10 μg/dL; total T_3, 80–200 ng/mL; Boehringer Mannheim, Mannheim, Germany), thyroglobulin and thyroid microsomal (by enyzme-linked immunosorbent assay, <100 U/mL; Elias, Freiburg, Germany), as well as TSH receptor (<9 U/L, by RRA; Brahms, Berlin, Germany) autoantibodies were measured using commercially available kits. All samples were analyzed in duplicate in a single run. Three subjects were typed for human leukocyte antigen (HLA) classes I and II by a standard microlymphocytotoxicity technique.

Determination of urinary I excretion was performed by a modified ceric arsenious acid wet ash method. Urine was digested with chloric acid under mild conditions, and I was determined manually by its catalytic role in the reduction of ceric ammonium sulfate in the presence of arsenious acid (20).

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

Results

In contrast to placebo, markedly elevated urinary I values were found during as well as after low dose I supplementation (12 months *vs.* baseline, $P = 0.0001$; 12 months *vs.* placebo, $P < 0.0001$; Table 1). Administration of I (cumulative dose, 0.072 g) substantially reduced thyroid volume ($P = 0.0001$). At 12 months, the median reduction in goiter size was 38%, and the therapeutic effect was sustained at 18 months. Serum TSH and T_3 remained stable in both groups; in contrast, T_4 levels increased during I administration ($P =$

TABLE 1. Median (range) of thyroid-related parameters at baseline and at each visit during (12 months, therapy phase) as well as 15 and 18 months (follow-up) after starting placebo and low dose iodide (0.2 mg/day) supplementation therapy, respectively

	Therapy phase (months)					Follow-up (months)	
	0	3	6	9	12	15	18
Urinary iodine (μg/24 h)							
Iodide	32 2–80	128 18–205	175 25–356	205 35–410	213 43–445	83 39–211	65 27–113
Placebo	34 6–99	27 11–75	18 3–69	38 15–90	33 10–78	40 16–85	42 10–88
Thyroid vol (mL)							
Iodide	29 20–48	26 18–44	22 16–39	19.5 12–32	18 8–25	18 9–26	19 9–29
Placebo	26 20–43	24 21–43	27 19–45	28 19–47	25 18–41	24 20–42	27 19–45
Baseline TSH (mU/L)							
Iodide	0.98 0.5–3.3	1.06 0.4–3.5	1.00 0.0–4.3		0.89 0.0–9.7	0.98 0.3–5.0	
Placebo	1.11 0.5–4.7	1.23 0.8–3.8	1.47 0.5–3.3		1.09 0.4–2.1	1.33 0.4–3.3	
Stimulated TSH (mU/L)							
Iodide	8.16 3.3–19.6				7.86 0.0–57.9		
Placebo	9.45 4.1–31.9				9.5 4.6–21.8		
Total T_4 (μg/dL)							
Iodide	8.5 5.6–10.4	9.3 6.1–10.5	9.6 6.9–13.5		8.0 3.1–14.0	7.2 5.4–9.9	
Placebo	9.3 6.5–14.8	9.0 6.9–14.9	9.0 6.9–14.2		7.7 5.6–13.3	7.0 5–13	
Total T_3 (ng/mL)							
Iodide	129 94–187	149 87–178	153 119–206		117 78–283	113 88–169	
Placebo	133 96–193	156 111–189	143 105–192		118 85–179	113 74–178	
Thyroglobulin (ng/mL)							
Iodide	58 1–166	35 0–90			23 0–31	43 0–72	
Placebo	46 0–147	39 0–150			56 0–138	40 0–137	

All values are expressed as the median and range of the values recorded. Total T_4 (normal range), 4–10 μg/dL; total T_3, 80–200 ng/mL; baseline TSH, 0.3–4 mU/L; stimulated TSH, 30 min after TRH stimulation with 200 μg, iv: thyroglobulin, less than 9 ng/mL.

0.005). Thyroglobulin levels strongly declined during I therapy ($P < 0.001$) and increased again during the follow-up. In contrast to placebo, high thyroglobulin and thyroid microsomal autoantibody titers were present in 3 (2 women and 1 man) of 31 subjects (9.7%) receiving I; I-induced hypothyroidism developed in 2, and hyperthyroidism developed in 1, respectively (Table 2). These 3 subjects suffered from mild, nonspecific symptoms (*e.g.* tachycardia and weight loss in the patient with I-induced hyperthyroidism). Only propranolol (40 mg, 4 times daily) was administered. Thyroid dysfunctions spontaneously remitted, and antibody titers markedly decreased after withdrawal of I. Follow-up of these 3 patients for an additional 2 yr showed a decline in the antibody titers in 2 of 3 subjects to upper normal values (Fig. 1). In 2 of 3 cases, thyroid size remained small, with hypoechogenicity in sonography. Compared with antibody-negative patients, the 3 patients did not differ in baseline characteristics (*e.g.* age, thyroid volume, body weight, or levels of thyroid-related hormones). These 3 patients remained negative for TSH receptor antibodies, and HLA typing was negative for B8 and DR3/5 loci.

Thyroid cytology

At 12 months, fine needle aspiration biopsy was performed in the three antibody-positive cases. The cytological pattern was characterized by the predominance of lymphoid cells, chiefly consisting of lymphocytes. Follicular cells showing evidence of hyperactivity were primarily found in follicular formations. Colloid was scanty or entirely absent. Aggregates of filamentous nuclear debris were a consistent finding. Centroblasts intimately associated with macrophages and dendritic reticulum cells were also noted, and varyingly abundant plasma cells were commonly encountered. Oxyphilic follicular cells demonstrating abundant, grayish blue cytoplasm were also observed. In patient 2, the aspirate contained foci of mononuclear histiocytes. At 24 months, lymphoplasmatic infiltration markedly decreased in two of three subjects. In case 2, the aspirate revealed a persistent moderate lymphocytic infiltrate, the presence of small stromal fragments, and fibrocytes.

Discussion

This double blind study showed that supplementation with I 0.2 mg/day substantially reduced the size of euthyroid, diffuse, endemic goiters, but in contrast to placebo, reversible I-induced thyroid dysfunctions and autoimmunity were observed in nearly 10% of the cases. Thus, even low doses of I may significantly affect the immune system of subjects with chronic I deficiency, and it is possible that previous reports of thyroid dysfunction observed after dietary I supplementation (21, 22) were due to the effects of I on the immune system.

Epidemiological data support an enhancing effect of increasing I intake on thyroid autoimmunity (8, 9). For instance, the prevalence of lymphocytic infiltration in the nontumorous portion of thyroidectomy specimens rose from 8–31% in the 5 yr after introduction of I prophylaxis in Argentina (23), and an increase in thyroid antibodies was found 3 months after the acute administration of iodized oil to otherwise healthy people in Corfu, Greece, an area of endemic goiter (12). Of 30 additional patients treated with I (0.3 mg/day), 9 (30%) developed high thyroid antibody titers when tested 6 months after starting treatment. Induction of thyroid antibodies was dose dependent, as 12% of goitrous patients receiving only 0.15 mg I/day became antibody positive (24). In a double blind trial over a period of 6 months, we recently compared the effect of 0.5 mg I/day (cumulative dose, 0.09 g), and 0.125 mg levothyroxine/day in subjects with endemic goiter. Although both regimens were effective at reducing thyroid volume, partly reversible I-induced thyroid dysfunctions and autoimmunity were observed in 6 of 31 (19%) subjects (25). In concordance with the report by Koutras *et al.* (24), thyroid antibodies decreased markedly or disappeared after withdrawal of I. In an autopsy study, association between the presence of thyroid antibodies and lymphocytic infiltration of the gland was demonstrated (26),

TABLE 2. Course of thyroid-related hormones in the three subjects with iodide-induced thyroid dysfunction and autoimmunity at baseline and at each visit during (12 months) as well as 2 and 3 yr after starting low dose (0.2 mg/day) iodide supplementation therapy

	Therapy phase (months)					Follow-up (months)			
	0	3	6	9	12	15	18	24	36
Patient 1, male, 27 yr									
Basal TSH (mU/L)	1.02	0.4	0.0	0.0	0.0	0.33	1.44	1.23	1.47
Stimulated TSH	7.64				0.0	4.9			
Total T_4 (μg/dL)	6.7	9.7	13.5	14	14	9.5	7.8	6.5	6.2
Total T_3 (ng/mL)	143	178	206	296	283	154	125	135	121
Patient 2, female, 33 yr									
Basal TSH (mU/L)	1.38	3.07	4.29	5.50	9.71	4.56	3.41	1.87	1.91
Stimulated TSH	8.6				57.9	34.3			
Total T_4 (μg/dL)	8.6	8.4	7.8	4.0	3.1	6.7	7.3	7.7	7.1
Total T_3 (ng/mL)	112	147	145	95	78	116	129	126	140
Patient 3, female, 21 yr									
Basal TSH (mU/L)	1.12	0.92	0.98	4.48	6.6	5.04	2.39	1.5	1.3
Stimulated TSH	7.3				32.8	27.6			
Total T_4 (μg/dL)	8.5	9.3	9.2	6.1	4.2	7.1	7.2	7.8	8.3
Total T_3 (ng/mL)	143	135	126	108	101	115	116	129	167

Baseline TSH (normal range), 0.3–4 mU/L, stimulated TSH (30 min after iv administration of 0.2 g TRH), total T_4 (4–10 μg/dL), and total T_3 (80–200 ng/mL) are shown.

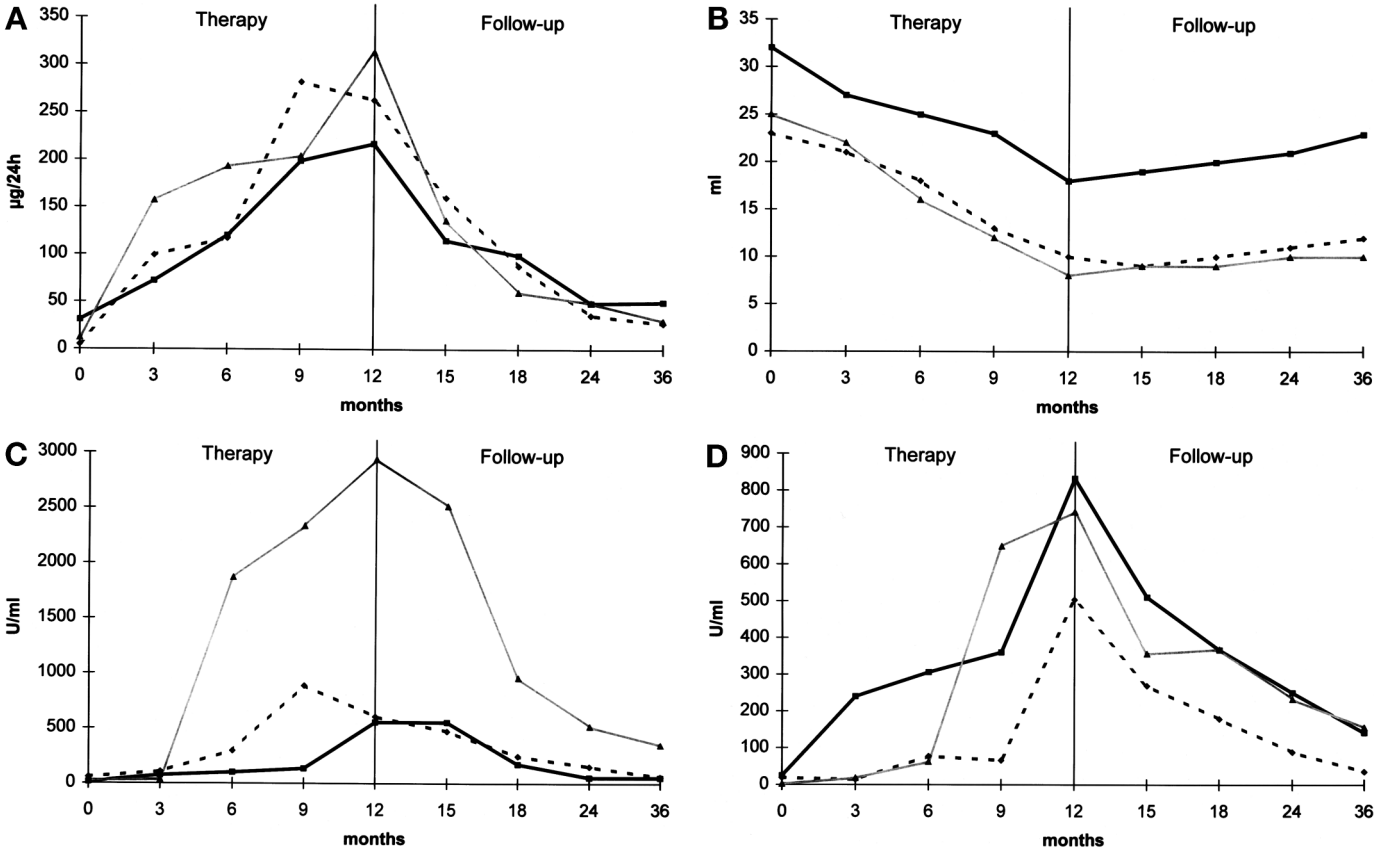

FIG. 1. Course of urinary iodine excretion per 24 h (a), thyroid volume (b), thyroglobulin (c), and thyroid microsomal (d) autoantibodies (normal range, <100 U/mL) in the three subjects (patient 1, *dashed line with circles*; patient 2, *black line with cubes*; patient 3, *gray line with triangles*) with iodide-induced thyroid dysfunctions and autoimmunity at baseline and at 3, 6, 9, 12, 15, 18, 24, and 36 months after starting low dose I supplementation therapy (0.2 mg/day for 12 months).

and histological features of 28 antibody-positive patients with I-induced hypothyroidism included diffuse lymphocytic infiltration and thyroid follicles of reduced size (27). Along with our cytological findings, stopping I intake led to normalization of thyroid function, decreased antibody titer, and disappearance of lymphocytic infiltration.

The clearest evidence for an effect of I has come from observations in experimental autoimmune thyroiditis (28). The main factors implicated in the stimulatory activity of I are the consequence of increased iodination of thyroglobulin (leading to specific increased immunogenicity) and/or nonspecific thyroid oxidative damage. Feeding of a high I diet to NOD (nonobese diabetic) mice with activated thyroid glands caused thyroid cell necrosis and autoimmunity, whereas antioxidants reduced lymphocytic infiltration in obese strain chickens (29). The response of murine T cell hybridoma to thyroglobulin is also directly related to its I content (30). In humans, I enhances *in vitro* IgG synthesis by peripheral blood lymphocytes (31). At plasma concentrations within the physiological range, I significantly increased both the number of cells synthesizing IgG and the amount of IgG released into the culture medium. Circulating thyroid antibodies are common in patients who develop hypothyroidism during amiodarone therapy (13), and this drug affects T cell function by increasing the number of both helper and cytotoxic T lymphocytes (32). *In vitro* studies have shown that I significantly inhibited interferon-α-induced expression of HLA class II antigens in thyroid cells, suggesting that I may influence antigen presentation (33). Furthermore, I together with interferon-γ increases the inducibility of the 72-kDa heat shock protein in cultured human thyroid epithelial cells (34).

In contrast to our findings, small quantities of I (1.5 and 4.5 mg/day) administered to normal subjects who resided in I-replete areas resulted in significant decreases in serum T_4, but not serum T_3, concentrations. Serum TSH increased, as did the TSH response to TRH. The smallest quantity of I that did not affect thyroid function was 0.5 mg/day (35). In other studies, however, this quantity of I enhanced the TSH response to TRH (36), and in a few patients it also increased the basal serum TSH concentration above normal (37). Thus, I supplementation as low as 0.2–0.5 mg/day above the normal diet in both I-sufficient and deficient areas might cause subtle changes in thyroid function.

There are a number of studies of endemic goiter in which various doses of I have been administered in various ways with no evidence of induction of thyroid autoimmunity (14–18). Furthermore, as thyroid autoantibodies transiently emerged in three subjects taking I, results should be cautiously interpreted. Although thyroid volume did not significantly change during the observation period (18 months) in the placebo group, there is no doubt that moderate I supplementation is necessary. As thyroid autoimmunity is

more prevalent in areas without endemic goiter, it seems that this is the price to be paid for the prevention of I deficiency disorders, whose devastating effects on the health of the people and on medical expenditures are well known (1–3).

References

1. **Dunn JT.** 1992 Iodine deficiency: the next target for elimination? N Engl J Med. 326:267–268.
2. **Dunn JT.** 1996 Seven deadly sins in confronting endemic iodine deficiency, and how to avoid them. J Clin Endocrinol Metab. 81:1332–1335.
3. **Delange FM, Ermans AM.** 1996 Iodine deficiency. In: Braverman LE, Utiger RD, eds. Werner and Ingbar's the thyroid, 7th ed. Philadelphia: Lippincott-Raven; 296–316.
4. **Pennington JA.** 1990 A review of iodine toxicity reports. J Am Diet Assoc. 90:1571–1581.
5. **Delange F, Benker G, Caron Ph, et al.** 1997 Thyroid volume and urinary iodine in European schoolchildren: standardization of values for assessment of iodine deficiency. Eur J Endocrinol. 136:180–187.
6. **Roti E, Vagenakis AG.** 1996 Effect of excess iodine; clinical aspects. In: Braverman LE, Utiger RD, eds. Werner and Ingbar's the thyroid, 7th ed. Philadelphia: Lippincott-Raven; 316–327.
7. **Konno N, Makita H, Yuri K, Iuzuka N, Kawasaki K.** 1994 Association between dietary iodine intake and prevalence of subclinical hypothyroidism in the coastal regions of Japan. J Clin Endocrinol Metab. 78:393–397.
8. **Weetman AP, McGregor AM.** 1994 Autoimmune thyroid disease: further developments in our understanding. Endocr Rev. 15:788–830.
9. **Dayan CM, Daniels GH.** 1996 Chronic autoimmune thyroiditis. N Engl J Med. 335:99–107.
10. **Weaver DK, Batsakis JG, Nishiyama RH.** 1969 Relationship of iodine to lymphocytic goiters. Arch Surg. 98:183–186.
11. **McConahey WM, Keating FR, Beahrs OH, Woolner LB.** 1962 On the increasing occurence of Hashimoto's thyroiditis. J Clin Endocrinol Metab. 22:542–544.
12. **Boukis MA, Koutras DA, Souvatzoglou A, et al.** 1983 Thyroid hormone and immunological studies in endemic goiter. J Clin Endocrinol Metab. 57:859–862.
13. **Martino E, Safran M, Aghini-Lombardi F, et al.** 1984 Environmental iodine intake and thyroid dysfunction during chronic amiodarone therapy. Ann Intern Med. 154:2722–2726.
14. **Elnagar B, Eltom M, Karlsson FA, et al.** 1995 The effects of different doses of oral iodized oil on goiter size, urinary iodine, and thyroid-related hormones. J Clin Endocrinol Metab. 80:891–897.
15. **Todd CH, Allain T, Gomo ZAR, et al.** 1995 Increase in thyrotoxicosis associated with iodine supplements in Zimbabwe. Lancet. 346:1563–1564.
16. **Bourdoux PP, Ermans AM, Mukalay wa Mukalay A, Filetti S, Vigneri R.** 1996 Iodine-induced thyrotoxicosis in Kivu, Zaire. Lancet. 347:552–553.
17. **Tonglet R, Bourdoux P, Tshilembi M, Ermans AM.** 1992 Effect of low oral doses of iodized oil in the control of iodine deficiency in Zaire. N Engl J Med. 326:236–241.
18. **Benmiloud M, Chauki ML, Gutekunst R, Teichert HM, Graham W, Dunn JT.** 1994 Oral iodized oil for correcting iodine deficiency: optimal dosing and outcome indicator selection. J Clin Endocrinol Metab. 79:20–24.
19. **Gutekunst R, Smolarek H, Hasenpusch U, et al.** 1986 Goiter epidemiology: thyroid volume, iodine excretion, thyroglobulin and thyrotropin in Germany and Sweden. Acta Endocrinol (Copenh). 112:494–501.
20. **Dunn JT, Crutchfield HE, Gutekunst R, Dunn AD.** 1993 Two simple methods for measuring iodine in urine. Thyroid. 3:119–123.
21. **Okamura K, Inoue K, Omae T.** 1978 A case of Hashimoto's thyroiditis with thyroid immunological abnormality manifested after habitual ingestion of seaweed. Acta Endocrinol (Copenh). 88:703–712.
22. **Adams DD, Kennedy TH, Stewart JC, et al.** 1975 Hyperthyroidism in Tasmania following iodide supplementation: measurements of thyroid stimulating antibodies and thyrotropin. J Clin Endocrinol Metab. 41:221–228.
23. **Harach HR, Williams ED.** 1995 Thyroid cancer and thyroiditis in the goitrous region of Salta, Argentina, before and after iodine prophylaxis. Clin Endocrinol (Oxf). 43:701–706.
24. **Koutras DA, Piperingos GD, Pallas D, et al.** 1990 Clinical, laboratory and immunologic effects of the treatment of endemic goiter with T_4, T_3 and KI. Thyroidology. 2:81–88.
25. **Kahaly G, Dienes HP, Hommel G.** Iodide induces thyroid autoimmunity in patients with endemic goiter. A randomised, double-blind, placebo-controlled trial. Clin Exp Immunol, In press.
26. **Yoshida H, Amino N, Yagawa K, et al.** 1978 Association of serum antithyroid antibodies with lymphocytic infiltration of the thyroid gland: studies of seventy autopsied cases. J Clin Endocrinol Metab. 46:859–862.
27. **Mizukami Y, Michigishi T, Nonomura A, et al.** 1993 Iodine-induced hypothyroidism: a clinical and histological study of 28 patients. J Clin Endocrinol Metab. 76:466–471.
28. **Sundick RS, Herdegen DM, Brown TR, Bagchi N.** 1987 The incorporation of dietary iodine into thyroglobulin increases its immunogenecity. Endocrinology. 120:2078–2084.
29. **Sundick RS, Bagchi N, Brown TR.** 1992 The role of iodine in thyroid autoimmunity: from chickens to humans: a review. Autoimmunity. 13:61–68.
30. **Champion B, Rayner DC, Byfield PGH, et al.** 1987 Critical role of iodination for T cell recognition of thyroglobulin in experimental murine thyroid autoimmunity. J Immunol. 139:3665–3670.
31. **Weetman AP, McGregor AM, Campbell H, et al.** 1983 Iodide enhances IgG synthesis by human peripheral blood lymphocytes *in vitro*. Acta Endocrinol (Copenh). 103:210–215.
32. **Rabinowe SL, Larsen PR, Antman EM, et al.** 1986 Amiodarone therapy and autoimmune thyroid disease. Increase in a new monoclonal antibody-defined T cell subset. Am J Med. 81:53–57.
33. **Davies TF, Young C, Platzer M.** 1989 The influence of antithyroid drugs and iodine on thyroid cell MHC class II antigen expression. Clin Endocrinol (Oxf). 31:125–135.
34. **Sztankay A, Trieb K, Lucciarini P, et al.** 1994 Interferon gamma and iodide increase the inducibility of the 72kD heat shock protein in cultured human thyroid epithelial cells. J Autoimmun. 7:219–230.
35. **Paul T, Meyers B, Witorsch RJ, et al.** 1988 The effects of small increases in dietary iodine on thyroid function in euthyroid subjects. Metabolism. 37:14–19.
36. **Gardner DF, Centor RM, Utiger RD.** 1988 Effects of low dose oral iodide supplementation on thyroid function in normal men. Clin Endocrinol (Oxf). 28:283–288.
37. **Chow CC, Phillips DIW, Lazarus JH, Parker AB.** 1991 Effect of low iodide supplementation on thyroid function in potentially susceptible subjects: are dietary iodide levels in Britain acceptable? Clin Endocrinol (Oxf). 34:413–416.