

Effect of small doses of iodine on thyroid function in patients with Hashimoto's thyroiditis residing in an area of mild iodine deficiency

W Reinhardt, M Luster¹, K H Rudorff², C Heckmann², S Petrasch, S Lederbogen, R Haase, B Saller, C Reiners¹, D Reinwein and K Mann

Department of Medicine, Division of Endocrinology, University of Essen, Essen, Germany, ¹Department of Nuclear Medicine, University of Wuerzburg, Wuerzburg, Germany and ²Endocrine Outpatient Clinic, Wuppertal Hospital, Wuppertal, Germany

(Correspondence should be addressed to W Reinhardt, Department of Medicine, University Clinic, Hufelandstr. 55, D-45122 Essen, Germany)

Abstract

Objective: Several studies have suggested that iodine may influence thyroid hormone status, and perhaps antibody production, in patients with autoimmune thyroid disease. To date, studies have been carried out using large amounts of iodine. Therefore, we evaluated the effect of small doses of iodine on thyroid function and thyroid antibody levels in euthyroid patients with Hashimoto's thyroiditis who were living in an area of mild dietary iodine deficiency.

Methods: Forty patients who tested positive for anti-thyroid (TPO) antibodies or with a moderate to severe hypoechogenic pattern on ultrasound received 250 µg potassium iodide daily for 4 months (range 2–13 months). An additional 43 patients positive for TPO antibodies or with hypoechogenicity on ultrasound served as a control group. All patients were TBII negative.

Results: Seven patients in the iodine-treated group developed subclinical hypothyroidism and one patient became hypothyroid. Three of the seven who were subclinically hypothyroid became euthyroid again when iodine treatment was stopped. One patient developed hyperthyroidism with a concomitant increase in TBII titre to 17 U/l, but after iodine withdrawal this patient became euthyroid again. Only one patient in the control group developed subclinical hypothyroidism during the same time period. All nine patients who developed thyroid dysfunction had reduced echogenicity on ultrasound. Four of the eight patients who developed subclinical hypothyroidism had TSH concentrations greater than 3 mU/l. In 32 patients in the iodine-treated group and 42 in the control group, no significant changes in thyroid function, antibody titres or thyroid volume were observed.

Conclusions: Small amounts of supplementary iodine (250 µg) cause slight but significant changes in thyroid hormone function in predisposed individuals.

European Journal of Endocrinology 139 23–28

Introduction

It has been suggested that iodine supplementation is associated with a greater incidence of autoimmune thyroid diseases. Hashimoto's thyroiditis is relatively uncommon in areas with low dietary iodine (1), whereas an increasing prevalence of the disorder was associated with increased iodine intake in some areas of North America (2). Boukis *et al.*, in Greece, observed a significant increase in the titres of anti-thyroid antibodies of patients after iodine supplementation (3). In a population of Argentinian patients, an increased lymphoid infiltration in the thyroid was observed after iodine prophylaxis was begun (4). Laurberg *et al.* (5) found a high incidence of autoimmune hyperthyroidism (Graves' disease) in areas with a high iodine intake, and of multinodular toxic goitre in an area with low iodine intake. In addition, patients with underlying

Hashimoto's thyroiditis are known to be prone to develop hypothyroidism after iodine administration (6).

In Japan (an area with a high dietary iodine intake), patients with autoimmune thyroiditis became euthyroid again after reduction of dietary iodine intake (7, 8). However, until now the influence of iodine on thyroid function in patients with Hashimoto's thyroiditis has been examined using doses of up to 150 mg iodine per day. Most studies have been carried out in areas with adequate iodine intake, such as the USA or Great Britain (6–10). One study in France (an area of mild iodine deficiency) evaluated thyroid function in patients with Hashimoto's thyroiditis after the daily administration of 500 µg iodine for 1–9 months (11).

We wanted to evaluate the effect of relatively low doses of iodine (250 µg) on thyroid function in patients with underlying Hashimoto's thyroiditis who were residing in an area of mild iodine deficiency.

Patients and methods

Patients

Patients were enrolled in three different thyroid centres in Germany (Essen, Wuerzburg, Wuppertal), from areas of mild iodine deficiency (mean daily iodine excretion 70 µg/g creatinine).

Indices of thyroid function (thyroid-stimulating hormone (TSH) and free thyroxine (fT₄)) and thyroid antibodies (TPO-Ab, TBII) were determined at the beginning and at the end of the study. Iodine excretion (spot urine) was measured before and after iodine treatment. All study participants were euthyroid (TSH and fT₄ concentrations within normal limits) and were negative for TBII antibodies before the beginning of the study. None received specific thyroid medication or iodinated contrast media within 3 months before enrolment. Previous episodes of hyper- or hypothyroidism were an exclusion criterion. A total of 83 patients with autoimmune thyroiditis entered the study.

Forty patients (three men, 37 women; mean age 40.5 years) received 250 µg/day potassium iodide for a mean period of 4 months (range 2–13 months). Among these 40 patients, six had positive TPO antibody titres, four showed a mild to marked hypoechogenic pattern on ultrasound and 30 patients fulfilled both these criteria. Forty-three euthyroid patients (two men, 41 women; mean age 42 years) with increased TPO antibody titres ($n=40$) and reduced echogenicity on ultrasound ($n=41$) served as a control group. Characteristics of the treatment group and the controls are summarized in Table 1.

Patients were re-examined 4 months after the administration of iodine had begun; iodine treatment was then stopped and patients were followed at 4-month intervals. A subgroup of 12 patients received iodine for up to 13 months. In patients who developed thyroid dysfunction (TSH >4 mU/l or <0.1 mU/l), thyroid hormone parameters were reevaluated within 5 days to confirm the results; then iodine treatment was stopped.

Table 1 Baseline characteristics of 83 patients with autoimmune thyroiditis, at entry to the study. Values are number or median (range).

	Iodine group ($n=40$)	Control group ($n=43$)
Sex (F/M)	37/3	41/2
Mean age (years)	40.5	42
Low echogenicity (mild, moderate, marked)	34	40
Thyroid volume (ml)	17 (7–117)	15 (9–34)
Women (No. >18 ml)	15	11
Men (No. >25 ml)	2	0
TSH 3–4 mU/l (No.)	7	8
TSH (mU/l) Median	1.5 (0.5–3.8)	1.6 (0.3–3.9)
TPO-Ab (U/ml)	729 (3–6104)	483 (23–7216)

Biochemical measurements

fT₄ was measured by a competitive immunoluminescence assay (automatic chemiluminescence system (ACS); Ciba-Corning Co., Freiwald, Germany) (normal values 10–25 pmol/l; interassay coefficient of variation (CV) 4.1%). TSH was determined by a two-site luminescence immunoassay (ACS TSH; Ciba-Corning Co.) (normal values 0.3–4.0 mU/l; interassay CV 5.1%).

Antibodies to TPO were measured by a luminescence enzyme immunoassay (Biermann Co., Bad Nauheim, Germany). Titres >100 U/ml were considered positive. Antibodies to the TSH receptor were determined using a radioreceptor assay (Brahms Co., Berlin, Germany) (normal values <10 U/l).

Urinary iodine excretion was measured in a spot urine sample by a modified cer/arsenite method (12) (interassay CV 7.2%) and expressed as the ratio of iodine excretion to that of creatinine (µg iodine/g creatinine).

All biochemical determinations were made in duplicate.

Thyroid ultrasound

Real-time ultrasound was performed in all the study participants by the same investigator, using a 7.5 MHz transducer (Toshiba Co.) before and at the end of the study. Echogenicity was graded, using the categories proposed by Marcocci *et al.* (13), as mildly, moderately and markedly reduced.

Statistical analysis

Changes in urinary iodine excretion in patients before and after iodine treatment were calculated by paired *t*-test. χ^2 analysis was used to compare patients who developed thyroid dysfunction in the iodine group and in the control group.

Results

As expected, iodine excretion increased in patients receiving 250 µg iodine daily, from a baseline mean of 72 ± 38 µg/g creatinine to 268 ± 173 µg/g creatinine (mean \pm s.d.; $P < 0.001$, paired *t*-test).

In 32 patients in the iodine-treated group and 42 patients in the control group, no major changes in thyroid hormone parameters were observed. Major changes in thyroid function did occur in nine of the 83 patients with autoimmune thyroiditis. Eight of them were in the iodine-treated group, and one was in the control group ($P < 0.05$, χ^2 analysis). In seven of the nine, only mild biochemical changes were observed, leading to subclinical hypothyroidism (TSH >4 mU/l, fT₄ within normal limits), whereas the remaining two patients respectively developed overt hyper- or hypothyroidism.

Table 2 Changes in thyroid function in seven individual patients before and after daily administration of 250 µg iodine and in one patient in the control group, all of whom developed (subclinical) hypothyroidism.

Patient No.	Sex	Age (years)	TSH (mU/l)		fT ₄ (pmol/l)		TPO-Ab (U/ml)		Thyroid volume (ml)	Hypoechoogenicity on ultrasound
			Before	After	Before	After	Before	After		
Iodine group										
1	F	40	2.5	43.3	10	7	163	1060	7	Marked
2	F	48	3.8	5.0	11	13	362	280	11	Mild
3	M	50	3.5	4.9	14	14	10	10	27	Marked
4	F	42	2.4	4.8	14	13	2094	1843	15	Marked
5	F	35	3.2	4.7	15	13	2718	2736	10	Mild
6	F	45	2.1	4.1	15	13	3	17	11	Marked
7	F	43	2.4	4.1	11	12	752	852	13	Marked
Control group										
8	F	31	3.3	5.2	12	13	173	214	9	Moderate

Seven of the 40 patients in the iodine-treated group developed hypothyroidism (one overt, six subclinical: TSH >4.0 mU/l; fT₄ within normal limits) after 4 months of iodine supplementation, but only one of the 43 control subjects became subclinically hypothyroid (Table 2).

Thyroid dysfunction was detected at the regular check-up 4 months after iodine treatment. Iodine was then stopped. Follow-up of the patients after iodine withdrawal is summarized in Table 3. Patient No. 1 was evaluated after 2 months because she developed clinical symptoms of hypothyroidism; she then received thyroxine (T₄) treatment. Patient No. 3 also developed hypothyroidism on follow-up and was given T₄. Patient No. 2 remained subclinically hypothyroid. In three patients (Nos 4, 5 and 7), TSH values returned to the normal range after iodine was withdrawn. Patient 6 also received T₄ treatment, because she complained of weight gain and mild clinical symptoms of hypothyroidism.

A 23-year-old female with coexisting myasthenia gravis (taking the birth control pill) and a mild hypoechoic pattern on ultrasound showed overt hyperthyroidism (fT₄ 30 pmol/l; (normal range 10–25 pmol/l); TSH suppressed) with a concomitant increase in TBII titres to 17 U/l, 3 months after iodine administration. With the exception of TPO-Ab titres, these parameters returned to normal values after iodine was withdrawn (Table 4).

Among patients with initial TSH values of at least 3 mU/l (*n* = 7 in the iodine-treated group), four exhibited an increase in TSH, one had a decrease and in two the TSH value remained unchanged. Among the eight patients in the control group with a basal TSH value of at least 3 mU/l, one exhibited an increase in TSH, in four there was a decrease and in three the TSH remained unchanged.

Fifty percent of the patients (four of eight) who became hypothyroid after iodine supplementation had a

Table 3 Thyroid hormone parameters (in seven patients treated with 250 µg iodine, and in one patient from the control group) after iodine withdrawal.

Patient No.	Months after iodine withdrawal					
	0		4		8	
	TSH (mU/l)	fT ₄ (pmol/l)	TSH (mU/l)	fT ₄ (pmol/l)	TSH (mU/l)	fT ₄ (pmol/l)
Iodine group						
1	43.3	7				
2	5.0	13	5.2	13	4.9	14
3	4.9	14	18	8		
4	4.8	13	3.8	14	3.0	14
5	4.7	13	4.0	14	3.8	14
6	4.1	13				
7	4.1	12	3.5	13	3.0	14
Control group						
8	5.2	13	–	–	5.6	12

–, not done.

Table 4 Thyroid hormone parameters in a 23-year-old woman who developed hyperthyroidism after the administration of 250 µg iodine for 3 months, at which time iodine treatment was stopped. Normal values or ranges are shown in parentheses.

Parameter	Time (months)			
	0	3	5	10
fT ₄ (pmol/l) (10–25)	15	30	12	13
T ₃ (nmol/l) (1.23–3.08)	2.55	5.14	2.51	2.37
TSH (mU/l) (0.3–4)	1.2	<0.1	0.1	2.4
TBII (U/l) (<10)	5	17	13	5
TPO-Ab (U/ml) (<100)	2795	2765	>3000	1677

baseline serum TSH value of at least 3 mU/l, (4/8), whereas none of those with an initial TSH <2 mU/l became hypothyroid. All patients with significant changes towards hyper- or hypothyroidism displayed low echogenicity on ultrasound (mild to marked). Two patients (Nos 3 and 6) with negative TPO-Ab titres, but with low echogenicity, developed (subclinical) hypothyroidism.

There was no significant change in TPO-Ab levels or thyroid volume during the study period. Median thyroid volume in the iodine-treated group was 17 ml at the beginning and 16 ml at the end of the study; corresponding values in the control group were 16 and 15 ml. Neither TPO-Ab titres nor thyroid volume was of prognostic value in terms of predicting thyroid dysfunction.

Discussion

We observed slight but significant alterations in thyroid hormone parameters in patients with autoimmune thyroiditis receiving even small amounts of iodine for a mean period of 4 months. Twenty percent of patients in the iodine-supplemented group developed (subclinical) hypothyroidism and one patient became hyperthyroid, but in only 2% of the control group were significant changes observed within 1 year. Three of seven patients who developed subclinical hypothyroidism became euthyroid again after iodine was withdrawn, and one patient remained subclinically hypothyroid.

In general, the progression to hypothyroidism in patients with underlying autoimmune thyroid disease is very slow, with a progression rate of 2.1% per year in females who are positive for thyroid antibodies (14). In the presence of additional increased TSH concentrations (greater than 6 mU/l), the progression rate increases to 4.3% per year. After 20 years, 55% of patients are hypothyroid (14). Thus basal TSH seems to be a good predictor: the risk of becoming hypothyroid was significantly increased in patients with TSH values greater than 2 mU/l. In Switzerland, Engler *et al.*,

obtained similar results (15); during a mean observation period of more than 5 years, the cumulative risk of developing hypothyroidism was 21% when basal TSH was 6 mU/l, and it increased to 59% with a basal TSH of 20 mU/l. In our study, we evaluated only patients with basal TSH concentrations less than 4 mU/l, and only seven patients in the treatment group and eight patients in the control group had TSH values between 3 and 4 mU/l. We demonstrated that patients who developed (subclinical) hypothyroidism had TSH values greater than 3 mU/l at baseline (four of eight patients), whereas none of the patients with TSH values less than 2 mU/l developed (subclinical) hypothyroidism. The magnitude of the antibody titres was not influenced by thyroid function.

We included patients with a diffuse hypoechogenic pattern on ultrasound, because it may be assumed that patients without increased thyroid antibody titres may have autoimmune thyroid disease, as a result of antibody production in the thyroid itself (16). Gutekunst *et al.* (17) showed that patients without detectable antibodies, but with a diffuse hypoechogenic pattern on ultrasound, had cytological features of lymphocytic thyroiditis. Marcocci *et al.* (13) also found diffuse low thyroid echogenicity in about 20% of patients with autoimmune thyroiditis and reported a significant association of hypothyroidism and reduced thyroid echogenicity. We also were able to confirm such an association, because all patients in our iodine-treated group who developed thyroid dysfunction had mild to marked reduced echogenicity, whereas none of those with a normal echogenic pattern developed thyroid dysfunction. Moreover, two patients with low echogenicity but normal TPO antibody titres became hypothyroid (one subclinical, one manifest).

To date, studies have evaluated thyroid function after the administration of moderate and high doses of iodine (up to 150 mg/day) in areas with an adequate iodine supply, but results have been equivocal. Chow *et al.* (9) evaluated thyroid function after the administration of 500 µg iodine for 1 month compared with placebo and found a small decrease in fT₄ and an increase in TSH by 2 weeks after iodine treatment. Paul *et al.* (10) administered 1500 µg/day for 3 months to seven patients with underlying Hashimoto's thyroiditis and observed only a small and insignificant increase in TSH. It has also been reported (6) that the administration of large amounts of iodine resulted in hypothyroidism in 60% of a study population.

Many patients with Hashimoto's thyroiditis exhibit an abnormal response to an iodide perchlorate excretion, suggesting an intrathyroid organification defect of iodine (18). Our present data suggest that the administration of even small amounts of iodine may lead to inadequate iodine organification and a consequent defect in hormone synthesis in predisposed individuals.

In a French study, thyroid function was evaluated for a period of 1–9 months after the administration of

500 µg iodine to 14 patients with high anti-microsomal antibody titres who were residing in a mildly iodine deficient area. In six of the patients there was a significant increase in T₄ concentrations and in six others there was a significant decrease in T₄ and concomitant increase in TSH concentrations (11). In our study, one patient who had coexisting myasthenia gravis developed hyperthyroidism, with a concomitant development of positive TBII titres, and the patient became euthyroid again after iodine supplementation was withdrawn. The mechanism of iodine-induced increases in TBII is unknown. Wilson *et al.* (19) were able to demonstrate an increase in TBII in patients with Graves' disease who received large amounts of iodine before surgery. They administered 120 mg iodine daily for a period of 10 days and found an increase in TSH receptor antibody levels and an increase in B-cell activity, indicated by increased immunoglobulin production from mitogen-stimulated peripheral blood lymphocytes. They speculated that iodine affects the immune system directly. Our group was unable to confirm this finding after short-term administration of high amounts of iodine to patients with Graves' disease, before surgery (20). In contrast to the patients in the study by Wilson *et al.* (19), our patients received methimazole in addition to iodine, and we did not observe an increase in their TBII titres. One possible explanation could be that, in the present study, our patients might have had Graves' disease as the underlying pathology, rather than Hashimoto's thyroiditis: Roti *et al.* (21) demonstrated a susceptibility to develop hyperthyroidism in patients with a previous episode of Graves' disease who received large amounts of iodine. In that study, two patients developed subclinical hypothyroidism, but two patients became hyperthyroid after receiving iodine treatment for 3 months. After iodine was withdrawn, our patients remained euthyroid and TBII negative.

To summarize: we observed slight but significant changes in thyroid hormone function after the administration of 250 µg iodine to euthyroid patients with underlying autoimmune thyroiditis. These changes were generally mild, leading to subclinical hypothyroidism in six of 40 patients and to hypothyroidism in one patient. Patients with reduced echogenicity on ultrasound and patients with TSH concentrations greater than 3 mU/l who were receiving iodine seemed to be at greater risk of developing thyroid dysfunction. Thyroid volume and anti-TPO-Ab titres were of minor prognostic importance. Thus iodine may change the natural course of autoimmune thyroiditis, resulting in a more rapid progression towards hypothyroidism.

References

- Headington JT & Tantajumroon T. Surgical thyroid disease in northern Thailand. A study in geographic pathology. *Archives of Surgery* 1967 **95** 157–161.
- Furszyfer J, Kurland LT, McConahey WM & Woolner LB. Epidemiologic aspects of Hashimoto's thyroiditis and Graves' disease in Rochester, Minnesota 1935–1967, with special reference to temporal trends. *Metabolism* 1972 **21** 197–204.
- Boukris MA, Koutras DA, Souvatzoglou A, Evangelopoulou A, Vrontakis M & Mouloupoulos SD. Thyroid hormone and immunological studies in endemic goiter. *Journal of Clinical Endocrinology and Metabolism* 1983 **57** 859–862.
- Harach H, Escalante DA, Onativia JL, Day ES & Williams ED. Thyroid carcinoma and thyroiditis in an endemic goiter region before and after iodine prophylaxis. *Acta Endocrinologica* 1985 **108** 55–60.
- Laurberg P, Pedersen KM, Vestergaard H & Sigurdsson G. High incidence of multinodular toxic goiter in the elderly population in a low iodine intake area vs. high incidence of Graves' disease in the young in a high iodine intake area: comparative surveys of the thyrotoxicosis epidemiology in East-Jutland, Denmark, and Iceland. *Journal of Internal Medicine* 1991 **229** 415–420.
- Braverman LE, Ingbar SH, Vagenakis AG, Adams L & Maloof F. Enhanced susceptibility to iodine myxedema in patients with Hashimoto's disease. *Journal of Clinical Endocrinology and Metabolism* 1971 **32** 515–521.
- Konno N, Yuri K & Miura K. Screening for thyroid diseases in an iodine sufficient area with sensitive thyrotropin assays and serum thyroid autoantibody and urinary iodine determination. *Clinical Endocrinology* 1993 **38** 273–281.
- Tajiri J, Higashi K, Morita M, Umeda T & Sato T. Studies of hypothyroidism in patients with high iodine intake. *Journal of Clinical Endocrinology and Metabolism* 1986 **6** 412–417.
- Chow CC, Phillips DIW, Lazarus JH & Parkes AB. Effect of low dose iodide supplementation on thyroid function in potentially susceptible subjects. Are dietary iodide levels in Britain acceptable? *Clinical Endocrinology* 1991 **34** 413–416.
- Paul T, Reinhardt W, Meyers B, Ingbar SH & Braverman LE. Small increases in iodine intake do not induce hypothyroidism in euthyroid patients with Hashimoto's disease. *Clinical Research* 1987 **35** 400A.
- Fragu P, Schlumberger M & Tubiana M. Thyroid iodine content and serum thyroid hormone levels in autoimmune thyroiditis: effect of iodide supplementation. *Journal of Nuclear Medicine* 1985 **26** 133–139.
- Wawschinek O, Eber O, Petek W, Wakonig P & Gürakar A. Bestimmung der Harnjodausscheidung mittels einer modifizierten Cer-Arsenitmethode. *Berichte der Österreichischen Gesellschaft für Klinische Chemie* 1985 **8** 13–15.
- Marocci C, Vitti P, Cetani F, Catalano R & Pinchera A. Thyroid ultrasonography helps to identify patients with lymphocytic thyroiditis who are prone to develop hypothyroidism. *Journal of Clinical Endocrinology and Metabolism* 1991 **72** 209–213.
- Vanderpump MPJ, Turnbridge WMG, French JM, Appleton D, Bates D, Clark F, Grimley Evans J, Hasan DM, Rodgers H, Turnbridge F & Young ET. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. *Clinical Endocrinology* 1995 **43** 55–68.
- Engler H, Staub JJ, Kunz M, Althaus B, Ryff A, Viollier E & Girard J. Ist eine isolierte TSH-Erhöhung behandlungsbedürftig? *Schweizerische Medizinische Wochenschrift* 1992 **122** 66–69.
- Baker JR Jr, Saunders NB, Wartofsky L, Yueh-Chu LT & Burman KD. Seronegative Hashimoto thyroiditis with thyroid autoantibody production localized to the thyroid. *Annals of Internal Medicine* 1988 **108** 26–30.
- Gutekunst R, Hafermann W, Mansky T & Scriba PC. Ultrasonography related to clinical and laboratory finding in lymphocytic thyroiditis. *Acta Endocrinologica* 1989 **121** 129–135.
- Braverman LE, Woeber KA & Ingbar SH. Induction of myxedema by iodide in patients after radioiodine or surgical treatment of diffuse toxic goiter. *New England Journal of Medicine* 1969 **281** 816–821.
- Wilson R, McKillop JH & Thompson JA. The effect of pre-operative potassium iodide therapy on antibody production. *Acta Endocrinologica* 1990 **123** 531–534.

- 20 Reinhardt W, Olbricht T, Jockenhövel F, Cissewski K, Lederbogen S, Krause U & Reinwein D. Schilddrüsenantikörper vor und nach Plummerung bei Patienten mit Morbus Basedow. In *Therapie der Hyperthyreose*, pp 347–351. Eds D Reinwein & B Weinheimer. Berlin, New York: W. de Gruyter Verlag, 1994.
- 21 Roti E, Minelli R, Bianconi L, Salvi M, Gavaruzzi G & Braverman LE. Effects of chronic iodine administration on thyroid status in

euthyroid subjects previously treated with antithyroid drugs for Graves' hyperthyroidism. *Journal of Clinical Endocrinology and Metabolism* 1993 **78** 928–932.

Received 3 July 1997
Accepted 23 December 1997