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Effect of low dose iodide supplementation on thyroid function in potentially susceptible subjects: are dietary iodide levels in Britain acceptable?†

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Summary

OBJECTIVE The aim of the study was to evaluate the risk of exposure to an increase in dietary iodide intake amongst potentially susceptible population groups in Britain.

DESIGN A randomized controlled trial was performed in healthy women and in women with underlying thyroid abnormalities due to subclinical Hashimoto's thyroiditis (diagnosed on the basis of antithyroid antibodies) or previous iodide deficiency of supplementation with 500 μg/day iodide (giving a total intake of approximately 750 μg/day) for 28 days versus placebo.

PATIENTS Two hundred and twenty-five women aged 25–54, randomly selected from a general practice in Cardiff, were screened for thyroid microsomal antibody. Antibody positive women ($n=20$), and antibody negative controls ($n=30$) were recruited into the trial comparing iodide and placebo. In addition, groups of patients aged 60–75 randomly selected from the Cardiff practice ($n=29$), an iodide sufficient area, and a practice in Dowlais ($n=35$), a previously iodide deficient area, were also enrolled into the trial.

MEASUREMENTS Changes in free thyroxine and thyrotrophin levels were measured after 14 and 28 days of iodide supplementation.

RESULTS All the iodide supplemented groups responded in the same way with a small fall in free thyroxine and rise in thyrotrophin levels (combined fall in free thyroxine 14 days after the start of supplementation −1·22 (95% confidence interval −0·59 to −1·84) pmol/l and at 28 days −0·86 (−0·30 to −1·43) pmol/l and rise in thyrotrophin at 14 days 0·55 (0·19 to 0·92) mU/l and at 28 days 0·59 (0·12 to 1·07) mU/l). In two of the iodide supplemented subjects thyrotrophin levels rose above the laboratory reference range and in a further three subjects initially elevated thyrotrophin values increased further. In contrast, no changes in thyroid function were observed in the placebo treated controls and none developed biochemical hypothyroidism.

CONCLUSIONS Dietary iodide intakes of 750 μg/day or more may adversely affect thyroid function, especially in individuals with borderline hypothyroidism.

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There has been a threefold increase in the amount of iodide in the British diet over the past 30 years. Current average intakes are estimated at 255 μg/day, a figure substantially higher than the 1952 value of 80 μg/day and in excess of the recommended daily allowance of 150 μg/day (Wenlock *et al.*, 1982; DHSS, 1969). Much of the increase is as a result of the contamination of milk and dairy produce arising from the addition of iodide to cattle feed and the use of iodophor disinfectants in dairying. The iodide content of milk and dairy produce is also very variable and high concentrations may occur during the winter months when cattle are largely dependent on artificial feed. Iodide intakes from milk alone could exceed 400 μg/day (Wenlock, 1987). Ingestion of iodide contaminated milk or exposure to other adventitious sources of iodide may therefore lead to relatively high dietary intakes in a proportion of the population.

Little is known about the effects of prolonged high dietary iodide intakes on thyroid function. Individuals with underlying thyroid abnormalities appear, however, to be particularly susceptible. The most common forms of abnormality are Hashimoto's thyroiditis which may predispose to hypothyroidism (Braverman *et al.*, 1971), and the presence of nodules or other autoregulation defects in previously iodide deficient individuals which increase the susceptibility to hyperthyroidism (Fradkin & Wolff, 1983). Both conditions occur more frequently in women and tend to remain undiagnosed.

To evaluate the risk of exposure to high iodide intakes in potentially susceptible groups in Britain, we have carried out a placebo controlled trial of the effect of administering a daily supplement of 500 μg iodide for 28 days. The popula-

tions studied were randomly selected samples of normal women and women with subclinical Hashimoto's thyroiditis (diagnosed on the basis of thyroid microsomal antibody) or who were previously resident in an iodide deficient area.

Subjects and methods

Between March and June 1989 a random sample of 446 women aged 25–54, selected from the list of a general practice in Cardiff, were contacted by post and asked to attend for 'thyroid screening'. Non-responders were contacted by a further letter, telephone call or visit. Blood samples were collected for the measurement of thyroid microsomal antibody (thyroid peroxidase antibody) and thyroid function, and random urine samples for the measurement of iodide excretion. Individuals with current or previous thyroid disease (hypo or hyper-thyroidism), a history of iodide exposure, or with serious intercurrent disease were excluded from the study. Groups of women with microsomal antibody and controls, randomly selected from the antibody negative women, were recruited into a randomized controlled trial comparing the effect of 500 μg iodide (as potassium iodide capsules) versus placebo for 28 days. Thyroid function was measured in the subjects after 14 and 28 days of supplementation. Compliance was checked by tablet counts and the measurement of urinary iodide excretion. Non-compliant subjects were included in the analysis.

In addition, random samples of women aged 60–75 were chosen from (i) a practice in Dowlais near Merthyr Tydfil—an area of South Wales known previously to have been affected by mild iodide deficiency (Kelly & Sneddon, 1960) and (ii) from the same practice in Cardiff from which the younger women were selected. These groups were enrolled into the randomized controlled trial comparing iodide and placebo and assessed in the same way at 14 and 28 days. The study was approved by the South and Mid-Glamorgan ethical committees and each subject gave informed consent.

Serum free thyroxine (FT4) and thyrotrophin (TSH) were measured with the Amerlex and Amerlite assays respectively (Amersham International PLC, Chalfont, Bucks, UK). Our laboratory reference ranges were 8–26 pmol/l for FT4 and up to 5 mU/l for TSH. Urinary iodide was measured by the method of Benotti *et al.* (1965). The between assay coefficient of variation was 3·0% at a mean of 50·7 μg/l. Microsomal antibody was assayed with an enzyme linked immunoassay (Schardt *et al.*, 1982). Reference ranges for the antibody assays were based on the mean ± 2 SD values obtained in serum samples from 81 adult subjects with no evidence of thyroid disease. Mean within-subject differences in free thyroxine and thyrotrophin levels were calculated for each treatment group after 14 and 28 days supplementation with iodide or placebo. Significance tests and 95% confidence intervals were based on the *t*-distribution.

Results

Of the 446 women aged 25–54 selected from the Cardiff general practice, 50 were excluded according to the criteria and 171 declined to attend leaving 225 women who were screened for microsomal antibody. Twenty of the 31 antibody positive women and 30 of 48 antibody negative controls agreed to take part in the trial of iodide supplementation versus placebo. In the Dowlais practice, of the 142 subjects aged 60–75 selected there were 48 exclusions, 59 non-responders and 35 enrolled among whom the median length of residence in this previously iodide deficient area had been 66 years. Response rates for the group aged 60–75 in

Table 1 Basal urinary iodide excretion and iodide excretion following 14 and 28 days of supplementation with 500 μg iodide (as KI) or placebo in groups of women aged 25–54 with microsomal antibody ($n=20$), without antibody ($n=30$) and in women aged 60–75 in an area with previous mild iodide deficiency ($n=35$) and in a non-iodide deficient area ($n=29$). The results are expressed as geometric mean excretions (μg/l) with 95% confidence intervals

	Iodide supplemented			Control		
	0	14 days	28 days	0	14 days	28 days
Age 25–54						
Antibody positive	49 (29–83)	197 (134–288)	221 (141–344)	48 (30–78)	42 (29–61)	41 (16–106)
Antibody negative	62 (37–103)	198 (109–360)	373 (219–635)	61 (40–92)	68 (49–93)	62 (47–81)
Age 60–75						
Previously iodide deficient	55 (36–82)	492 (318–762)	402 (250–644)	68 (47–100)	65 (46–93)	82 (56–120)
Previously non-iodide deficient	52 (29–95)	292 (206–414)	256 (187–350)	57 (38–86)	48 (27–85)	40 (24–68)

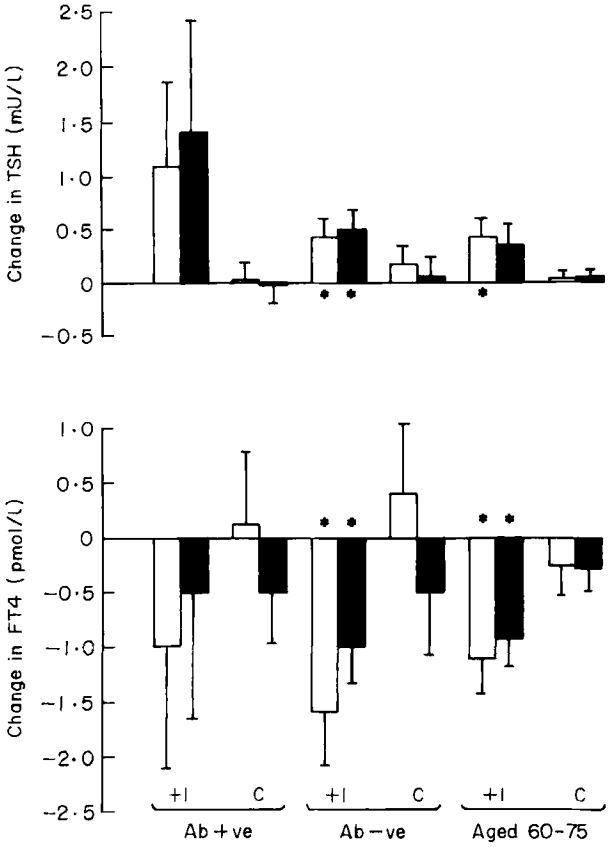

Fig. 1 Mean (±SE mean) within-subject changes in free thyroxine (FT4) and thyrotrophin (TSH) levels among the microsomal antibody positive ($n=20$) and antibody negative ($n=30$) women and women aged 60–75 years ($n=64$) after □, 14 days and ■, 28 days supplementation with I, 500 μg iodide or C, placebo. * Significantly ($P<0·05$) different from zero.

Cardiff were similar, where of 112 selected there were 35 exclusions, 48 non-responders and 29 subjects enrolled.

For each group, mean urinary iodide excretion was calculated rather than the iodide/creatinine ratio because of unexpectedly large variations in creatinine levels. Basal geometric mean urinary iodide excretion (Table 1) was similar in all the groups ranging from 48 μg/l in the antibody positive control group to 68 μg/l in the previously iodide deficient controls. Iodide excretion rose markedly in the iodide supplemented groups though the rise in the elderly subjects, especially those from the iodide-deficient area, was significantly greater than that observed in the younger women. In contrast, iodide excretion in the control groups varied little over the study period.

The effect of iodide on thyroid function in the groups is shown in Fig. 1 (the results for the elderly populations in Cardiff and Dowlais have been combined as the changes were similar). No patients became clinically or biochemically hyperthyroid. All iodide supplemented groups showed similar small decreases in FT4 and compensatory rises in TSH which were statistically significant in the antibody negative and elderly groups (Fig. 1). The overall fall in FT4 14 days after the start of supplementation was −1·22 (95% confidence interval −0·59 to −1·84) pmol/l and at 28 days −0·86 (−0·30 to −1·43) pmol/l and rise in TSH at 14 days 0·55 (0·19 to 0·92) mU/l and at 28 days 0·59 (0·12 to 1·07) mU/l. TSH levels rose above the laboratory reference range (≤5·0 mU/l) in two of the iodide supplemented elderly subjects (from 3·7 and 5·0 to 7·2 and 8·2 mU/l respectively at 28 days). In a further elderly subject in Cardiff TSH increased from 7·3 to 11·1 mU/l, and in two women in the antibody positive group from 12·4 to 24·6 and from 5·3 to 6·8 mU/l. In contrast, there were no significant changes in thyroid function in the placebo treated controls and none developed biochemical evidence of hypothyroidism.

Discussion

The dose of iodide administered in the present study when added to the usual iodide intake of around 250 μg/day would provide a total intake in the supplemented groups of approximately 750 μg/day, a level within the reported range of dietary intakes in Britain (Wenlock *et al.*, 1982). The urinary excretion data in Table 1 show that significant increases in iodide excretion were observed in each supplemented group while levels in the control groups were unchanged. Calculation of the mean urinary iodide concentration in groups of subjects, as used in Table 1, is a validated alternative to the iodide/creatinine ratio (Bourdoux *et al.*, 1985). The apparently greater response of iodide excretion following supplementation in some groups is more likely to reflect differences in compliance than differences in the kinetics of absorption and excretion. Assuming an average urinary output of 1·5 l/day the mean unsupplemented daily iodide excretion in the women was of the order of 72–102 μg/day, values which are within the range of estimates of daily iodide excretion obtained in seven English towns in 1985 (Nelson *et al.*, 1988). The current values, however, suggest that intakes in this population are towards the lower end of the distribution of iodide intake in Britain. This could be explained in part by the unusually mild winter preceding the study and the consequent early turning out of cattle to pasture resulting in low iodide levels in dairy produce.

Administration of the 500 μg supplement for as short a period as 14–28 days had a measurable effect on thyroid function that was similar in both normal individuals and subjects with underlying thyroid susceptibility (Fig. 1). The

changes were small in comparison with the normal reference ranges for FT4 (8–26 pmol/l) and TSH ($\leqslant$ 5 mU/l) and would therefore not be of clinical significance for the majority of the population. Nevertheless, a small shift in the mean of a population tends to result in greater changes among individuals lying at the extreme of that distribution. That this phenomenon may be occurring in the present survey is supported by the findings that two iodide supplemented individuals became biochemically hypothyroid with raised thyrotrophin levels, and in three others initially elevated thyrotrophin values increased further.

Previous studies have shown that pharmacological doses of iodide of between 10 and 1000 mg per day can cause hypothyroidism in normal individuals (Wolff, 1969). More recently, the administration of 500 μg of iodide to normal volunteers in the United States was shown to affect the TSH response to thyrotrophin releasing hormone although there was no effect on the baseline FT4 or TSH levels (Gardner *et al.*, 1988). Patients with Hashimoto's thyroiditis are reported to be more likely to develop hypothyroidism than normal individuals when exposed to relatively high doses of iodide (Braverman *et al.*, 1971) but there is no information on their susceptibility to smaller doses. By contrast, hyperthyroidism is likely to occur among previously iodide deficient individuals exposed to small increases in dietary iodide intake, a phenomenon that has been extensively documented following iodization programmes in endemic goitre areas (Fradkin & Wolff, 1983). The data presented in this British study, however, show that both the thyroiditis and previously iodide deficient groups appear to respond in the same way to low dose supplementation as do individuals with healthy thyroid glands. It is possible, though, that the failure to precipitate hyperthyroidism among the previously iodide deficient women was due to the relatively small size of the study as hyperthyroidism following iodide exposure may be an infrequent occurrence.

In conclusion, the results of this study underline the need for monitoring of iodide intakes in Britain. They also indicate that dietary intakes of 750 μg/day or more are not advisable as they may adversely affect thyroid function, especially in individuals with borderline hypothyroidism.

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