

CLINICAL STUDY

Minimal impact of excess iodate intake on thyroid hormones and selenium status in older New Zealanders

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Abstract

Objective: Iodine deficiency has re-emerged in New Zealand, while selenium status has improved. The aim of this study was to investigate the effects of excess iodine intake as iodate on thyroid and selenium status.

Methods: In a randomized controlled trial on older people (mean \pm s.d. 73 ± 4.8 years; $n=143$), two groups received > 50 mg iodine as iodate/day for 8 weeks because of supplement formulation error, either with 100 μ g selenium (Se+highI) or without selenium (highI). Four other groups received 80 μ g iodine as iodate/day with selenium (Se+lowI) or without selenium (lowI), selenium alone (Se+), or placebo. Thyroid hormones, selenium status, and median urinary iodine concentration (MUIC) were compared at weeks 0, 8, and 4 weeks post-supplementation.

Results: MUIC increased nine- and six-fold in Se+highI and highI groups, decreasing to baseline by week 12. Plasma selenium increased in selenium-supplemented groups ($P<0.001$). The level of increase in whole blood glutathione peroxidase (WBGpX) in the Se+highI group was smaller than Se+ ($P=0.020$) and Se+lowI ($P=0.007$) groups. The decrease in WBGpX in the highI group was greater than other non-selenium-supplemented groups, but differences were not significant. Ten of 43 participants exposed to excess iodate showed elevated TSH (hypothyroidism) at week 8. In all but two, TSH had returned to normal by week 12. In three participants, TSH decreased to <0.10 mIU/l (hyperthyroidism) at week 8, remaining low at week 12.

Conclusions: Excess iodate induced hypothyroidism in some participants and hyperthyroidism in others. Most abnormalities disappeared after 4 weeks. Excess iodate reduced WBGpX activity and resulted in smaller increases in WBGpX after selenium supplementation.

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Introduction

Healthy individuals can tolerate iodine intake of up to 1 mg/day, as the thyroid gland can regulate synthesis and release of thyroid hormones over a wide range of intake (1). However, such doses may cause hypothyroidism in individuals with damaged thyroid glands because of abnormal downregulation of iodine transport into the gland. Adverse effects may also occur in individuals with nodular goiter. In populations with chronic iodine deficiency, an increase in iodine intake may result in iodine-induced hyperthyroidism (thyrotoxicosis), the main complication of iodine prophylaxis in several countries, including New Zealand (2–6). Iodine-induced hypothyroidism may also occur (7).

Excess chronic iodine intake as iodide is associated with an increase in goiter and subclinical hypothyroidism because of inhibition of thyroid hormone synthesis (3, 8). Excess iodine can also trigger an immune response, resulting in autoimmune thyroiditis (1), inflammation of the thyroid, sensitivity reactions, or acute toxicity (3, 8). Such effects can occur in persons

with normal thyroid glands when exposed to high iodide intake from dietary supplements, including seaweed extracts, and iodine-containing drugs (8). Effects may reverse when iodine is withdrawn (3). The same high intake of iodine may cause hyperthyroidism in some people and hypothyroidism in others (9). Excess intake of iodine as iodate may have additional toxicological effects (10).

Iodine status in New Zealand has decreased over the past two decades because of reduction in use of iodophor cleaning agents in the dairy industry and iodized table salt, resulting in re-emergence of mild iodine deficiency (11–13). The elderly are particularly vulnerable because they consume fewer servings of dairy products (14). In contrast, selenium status is improving (13) due to higher selenium content of animal food resulting from supplementation and to the consumption of high-selenium imported foods. However, our selenium status is still insufficient for maximal activities of the selenoenzyme glutathione peroxidase (GPx) (15, 16). Both selenium and iodine are essential for optimal thyroid function (17, 18). Selenium is an essential

component of iodothyronine deiodinase enzymes that convert thyroxine (T_4) to the active hormone triiodothyronine (T_3). The GPxs are also implicated in protection against oxidative damage to the thyroid gland (18). Interaction between selenium and thyroid metabolism occurs particularly where there is severe deficiency of both iodine and selenium (19) and is also of interest in New Zealanders with marginal selenium status and mild iodine deficiency (15).

We have reported previously the results of a randomized controlled trial comparing the effects of 12-week supplementation with 100 $\mu\text{g/day}$ selenium with or without 80 $\mu\text{g/day}$ iodine or a placebo on selenium, iodine, and thyroid status in older New Zealanders (16). An error in iodine supplement formulation resulted in some participants in two further groups receiving supplements containing > 50 mg iodine as iodate/day for 8 weeks before the error was discovered and supplementation stopped. This paper reports the effects of 8 weeks of supplementation with excess iodate on selenium status and thyroid function of these two groups in comparison with the results at 8 weeks of the above four groups supplemented with selenium (100 $\mu\text{g/day}$), low iodine (80 $\mu\text{g/day}$), selenium plus low iodine, or placebo.

Experimental methods

Subjects and recruitment

A randomized controlled trial was carried out with 143 older male and female residents of Dunedin in the South Island of New Zealand from August to November 2005. Participants were aged (mean \pm s.d.) 73 ± 4.8 years, non-institutionalized, free from serious medical illness, not using medications for thyroid function or with any known thyroid problems, and not taking supplements containing selenium or iodine. Subjects were recruited via advertisements in newspapers and newsletters, on notice boards in retirement villages, supermarkets, hospitals, and leisure centers; by letters sent to participants in a previous study; and by visits and presentations to various senior citizen organizations. Potential participants were screened by telephone using a brief questionnaire that included questions on age, health, and inclusion criteria. All participants gave informed consent, and the Ethics Committee of the University of Otago, Dunedin, New Zealand, approved the protocol. The study was registered with the Australian New Zealand Clinical Trials Registry as ACTRN012605000368639.

Study design

Respondents who met inclusion criteria were mailed information sheets and consent forms and then after consent were randomized into treatment groups. Block

randomization with stratification by sex was used to assign participants into one of six treatment groups. The randomization schemes were generated by using the Randomization website (<http://www.randomization.com>). An error in the manufacture of some supplements resulted in very high levels of iodate (> 50 mg iodine) in tablets used for two groups. This error was not discovered until 8 weeks after commencement; supplementation was terminated immediately on discovery of the error. The six groups were as follows: 100 μg selenium (Se+; $n=25$), 100 μg selenium + 80 μg iodine as iodate (Se+lowI; $n=26$), 100 μg selenium + 50 mg iodine as iodate (Se+highI; $n=22$), 80 μg iodine (lowI; $n=25$), 50 mg iodine (highI; $n=21$), and placebo ($n=24$). The focus of this paper is on the results for the two groups receiving high iodate (Se+highI; high I). Results of the Se+, Se+lowI, lowI, and placebo groups at 0 and 12 week have been analyzed to determine the effects of 12-week supplementation with nutritional levels of selenium and iodine on selenium, iodine, and thyroid status and have been published previously (16). For this current study, the raw data at 8 weeks for these four groups have been analyzed for comparison here with the two groups receiving high iodate supplements, whose supplementation was terminated at 8 weeks. There were no statistically significant differences (ANOVA) in baseline measures of selenium, iodine, or thyroid hormone status among the six groups (Table 1).

Randomization, recruitment, and allocation to groups were all carried out by independent researchers. The participants, those administering the interventions and those assessing the outcomes of the intervention, were blinded to treatment assignment.

Participants completed a brief questionnaire on demographics, dietary habits, supplement and medication use, smoking habits, consumption of foods high in selenium or iodine, and self-reported health status. Fasting blood samples were collected at baseline week 8, 4-week post-supplementation (week 12), and casual morning urine samples at baseline and weeks 8 and 12. Thyroid hormone status (TSH, free T_3 (FT₃), free T_4 (FT₄)), selenium status (plasma selenium (PSe)), whole blood GPx activity (WBGPx), and median urinary iodine concentrations (MUIC) were determined at baseline and weeks 8 and 12.

Treatments

Tablets, identical in size, shape, and color, were produced by Alaron Products (Port Nelson, New Zealand) in July 2005. We had previously obtained supplements from this company without incident. Iodine tablets contained potassium iodate (KIO₃) and selenium tablets contained L-selenomethionine. Ten tablets were randomly selected from each group and analyzed for iodine and selenium content in September 2005 by Hill Laboratories Ltd (Hamilton, New Zealand)

Table 1 Baseline concentrations of measures of iodine and selenium status in older participants. Results expressed as mean (\pm s.d.) or median^a (IQR).

Group	n	PISe (μ mol/l)	WBGPx (U/g Hb)	MUIC ^a (μ g/l)	TSH (mIU/l)	FT ₄ (pmol/l)	FT ₃ (pmol/l)
All subjects	143	1.21 \pm 0.29	43.2 \pm 9.3	55 (68)	2.6 \pm 1.3	14.1 \pm 2.1	4.86 \pm 0.54
Se+	26	1.23 \pm 0.31	43.8 \pm 12.3	40 (60)	2.6 \pm 1.1	14.0 \pm 2.0	4.70 \pm 0.46
Se+ lowI	25	1.11 \pm 0.33	43.5 \pm 8.9	59 (66)	2.5 \pm 1.4	14.6 \pm 2.1	4.84 \pm 0.42
Se+ highI	22	1.22 \pm 0.21	43.6 \pm 6.0	87 (78)	2.7 \pm 1.1	14.0 \pm 2.8	4.91 \pm 0.50
Se-lowI	25	1.22 \pm 0.36	43.2 \pm 9.1	45 (43)	2.5 \pm 1.5	13.9 \pm 2.2	4.91 \pm 0.51
Se-highI	21	1.20 \pm 0.16	41.1 \pm 8.6	85 (84)	3.0 \pm 1.7	13.8 \pm 1.8	5.13 \pm 0.39
Placebo	24	1.23 \pm 0.29	43.6 \pm 9.1	53 (52)	2.5 \pm 1.1	14.3 \pm 2.9	4.73 \pm 0.78

PISe, plasma selenium; WBGPx, whole blood glutathione peroxidase; MUIC, median urinary iodine concentration; FT₄, free thyroxine, FT₃, free triiodothyronine. There were no significant differences in baseline measures of selenium, iodine, or thyroid hormones among the six groups (ANOVA; $P > 0.05$).

using inductively coupled plasma spectrometry with a detection limit of 0.01 μ g Se/tablet and 0.02 μ g I/tablet respectively. Selenium and iodine contents of the tablets are summarized in Table 2. Participants consumed one tablet daily for 8 weeks; they were encouraged to maintain their normal diets and to avoid supplements containing selenium or iodine for the study duration. Compliance was monitored via completion of a daily checklist and from the number of tablets returned at study conclusion.

Sample collection

Blood was collected in EDTA vacutainers (Becton Dickinson, Franklin Lakes, NJ, USA) for separation of whole blood and plasma and additive free vacutainers for serum. Samples were kept on ice and centrifuged within 3 h of collection. Aliquots of whole blood, plasma, and serum were stored at -80°C until analysis. Casual morning (between 0730 and 0930 h) urine samples were collected in clean plastic specimen containers and stored at -20°C until analysis.

Biochemical analyses

PISe concentration was determined in duplicate by graphite furnace Atomic Absorption Spectroscopy with Zeeman background correction (AA-800, Perkin-Elmer Corp., Norwalk, CT, USA) by a modification of the

Table 2 Iodine (median^a (1st quartile and 2nd quartile)) and selenium (mean \pm s.d.^a) content of tablets^b.

Treatment	Se content (μ g/tablet)	I content (μ g/tablet)
Se+	107 \pm 15	<0.01
Se+ low I	94 \pm 44	80 (71, 103)
Se+ high I	98 \pm 11	54 450 (53 825, 55 725)
LowI	<0.01	79 (76, 82)
HighI	0.17 \pm 0.19	54 850 (53 925, 55 625)
Placebo	<0.01	<0.01

^aTen tablets ($n=10$) were randomly selected from each group.

^bAnalyzed by R J Hill Laboratories Ltd (Hamilton, New Zealand) using inductively coupled plasma mass spectrometry.

method of Jacobson and Lockitch (20). Accuracy was assessed by analysis of certified reference materials (CRM) with each batch; seronorm reference serum (batch no. JL4409; Laboratories of Sero AS, Billingstad, Norway), with a certified selenium concentration of 0.92 (95% CI 0.84, 1.00) μ mol Se/l, gave a mean (\pm s.d.) concentration of 0.88 ± 0.04 μ mol/l (coefficient of variation (CV) 4.9%; $n=45$). Analysis of Utak Reference Plasma (batch no. 66 816, lot 7081, UTAK Laboratories, Inc., Valencia, CA, USA), with a certified selenium concentration of 1.52 (95% CI 1.14, 1.90) μ mol Se/l, gave a mean of 1.39 ± 0.09 μ mol/l (CV 6.2%; $n=45$).

GPx activity was measured in whole blood using RANSEL kits (#RS 505, 506 Randox Laboratories Ltd, Antrim, UK) and automated on a Cobas Fara auto-analyzer (Hoffman-La Roche). WBGPx was assayed as a measure of erythrocyte GPx activity, which has been shown previously by us to constitute 95% of whole blood activity with the use of this assay method (21). Because no RANSEL controls were available at the time, pooled samples of whole blood were analyzed with each batch and gave a mean activity of 45.5 ± 2.8 U/g Hb (CV 6.2%; $n=196$).

Urinary iodate concentration (UIC) was determined using the ammonium persulfate method recommended by the WHO/UNICEF/ICCIDD (22). Analysis of a CRM, Seronorm Trace Elements Urine (lot no. NO2525, Sero AS, Asker, Norway), with a certified iodine concentration of 141 μ g I/l (95% CI 132, 150), gave a mean of 13 ± 8 μ g I/l (CV 5.7%; $n=92$). Analysis of pooled aliquots of urine with each batch of samples gave a mean of 45 ± 10 μ g I/l (CV 4.4%; $n=43$). Urine samples with high iodate concentrations were diluted for analysis as required.

Southern Community Laboratories, Dunedin, New Zealand, performed analysis of serum TSH, FT₃, FT₄, and thyroglobulin antibody (TgAb) concentration. TSH was assayed using a two-site sandwich chemiluminescent immunoassay with a lower limit of detection of 0.004 mIU/l. Serum FT₄ and FT₃ were analyzed using a competitive chemiluminescent immunoassay with a lower limit of detection of 1.3 pmol FT₄/l and 0.3 pmol FT₃/l respectively. Analysis of CRM,

BIORAD Immunoassay Plus material (Irvine, CA, USA), with certified concentrations of 0.60 mIU TSH/l (95% CI 0.48, 0.72), 10.5 pmol FT₄/l (95% CI 8.4, 12.7), and 3.6 pmol FT₃/l (95% CI 2.9, 4.3), gave mean concentrations of 0.6 ± 0.03 mIU TSH/l (CV 4%), 9.3 ± 0.7 pmol FT₄/l (CV 8.5%), and 3.3 ± 0.14 pmol FT₃/l (CV 4.2%) respectively. Baseline TgAbs were measured using an Access 2 analyzer (Beckman Coulter, Inc., Fullerton, CA, USA) by immunoenzymatic assays with chemiluminescent detection. For clinical assessment, normal ranges for TSH, FT₃, and FT₄ concentrations given by Southern Community Laboratories were 0.3–5.0 mIU TSH/l, 2.8–6.8 pmol FT₃/l, and 10–23 pmol FT₄/l. For all analytical methods, all samples from each participant were analyzed in the same batch.

Statistical analysis

All statistical analyses were conducted using PASW Statistics 18 (SPSS, Inc., Chicago, IL, USA). Statistical significance was assessed at $P < 0.05$. Descriptive statistics (mean \pm s.d.) are presented for baseline characteristics. Positively skewed data were log transformed and described using median (interquartile range (I.Q.R.)). Differences among groups of normally distributed variables (baseline PISE, WBGPx, TSH, FT₃, and FT₄; changes in PISE and WBGPx) were tested using one-way ANOVA for continuous data, with Bonferroni *post hoc* tests for multiple comparisons. Differences between groups of skewed variables (UIC, changes in UIC) were tested using the Kruskal–Wallis test.

Results

Baseline MUIC of all participants was 54.5 μ g/l (I.Q.R. 67.5; $n=137$); 49% of participants had MUIC < 50 μ g/l and 82% had < 100 μ g/l, indicating mild to moderate iodine deficiency (Table 1). In participants who received high iodate supplements, and for whom MUIC values were available at 0, 8, and 12 weeks, MUIC in the Se+highI group ($n=21$) increased from 83 (79) to 7800 (9334) μ g/l at 8 weeks but returned to 62 (52) μ g/l by week 12, and in the highI group ($n=17$) from 86 (98) to 4969 (23983) μ g/l returning to 93 (131) μ g/l by week 12. MUIC in the Se+lowI group increased from 63 (66) to 93 (92) μ g/l at week 12 and in the lowI group from 45 (43) to 56 (57) μ g/l.

Changes in PISE concentration and WBGPx activity differed among the six groups ($P < 0.0001$; Figs 1 and 2 respectively). Mean (\pm s.d.) baseline PISE was 1.20 ± 0.29 μ mol/l ($n=142$) and increased by 0.89, 0.85, and 0.76 μ mol/l (72, 77, and 62%) in Se+, Se+lowI, and Se+highI groups at 8 weeks respectively ($P < 0.0001$; Fig. 1); these changes were not significantly different among these three groups but were all greater than those for groups not supplemented with selenium ($P < 0.0001$), for which there was no

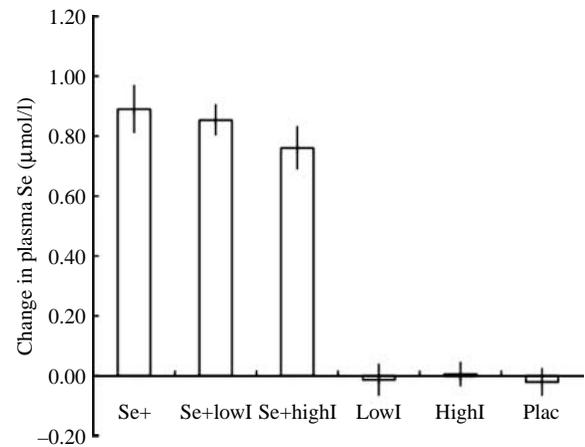


Figure 1 Change in plasma selenium (PISe) concentrations in participants during 8-week supplementation with 100 μ g selenium (Se+), selenium plus low (80 μ g) iodine (Se+lowI) or high (50 mg) iodine (Se+highI) intake, low (lowI) or high (highI) iodine intake, or a placebo (Plac). Changes in PISE concentration differed among the six groups (ANOVA, $P < 0.0001$). Changes in selenium-supplemented groups were all greater than changes in groups not supplemented with selenium ($P < 0.0001$). Values are mean \pm s.e.m.

change in PISE. WBGPx increased by 2.8, 3.1, and 1.0 U/g Hb (6.4, 7.1, and 2.3%) in the Se+, Se+lowI, and Se+highI groups, respectively, significantly greater than the non-selenium-supplemented groups ($P < 0.0001$; Fig. 2). These changes were significantly different among these three groups ($P = 0.05$). The increase in WBGPx in the Se+highI group (+1.0 U/g Hb) was smaller than the Se+ (+2.8 U/g Hb; $P = 0.020$) and the Se+lowI (+3.1 U/g Hb; $P = 0.007$) groups in spite of similar selenium intake (100 μ g), but the differences were not significant after adjustment for multiple comparisons (Bonferroni). The change in the Se+highI group was also not significantly different from the non-selenium-supplemented groups. A decrease in WBGPx (–1.10 U/g Hb; –2.6%) in the highI group was greater than that for the lowI (–0.38 U/g Hb; –0.9%) and the placebo (–0.27 U/g Hb; –0.6%) groups, but differences were not significant.

Clinical assessment of the 43 participants in the highI and Se+highI groups exposed to high iodate supplements showed that ten had elevated TSH at week 8 (i.e. above normal range of 0.3–5.0 mIU/l), indicating that they had developed an underactive thyroid (hypothyroidism; Table 3). In all but two, TSH had returned to normal range by week 12. The elevated TSH was accompanied by a decrease in FT₄ at week 8 to below the normal range (10–23 pmol/l) in four participants, but which returned to normal at 12 weeks. Thus, of the ten participants with elevated TSH, six had transient subclinical hypothyroidism and four developed transient clinical hypothyroidism. There was a small elevation in FT₃ within the normal range

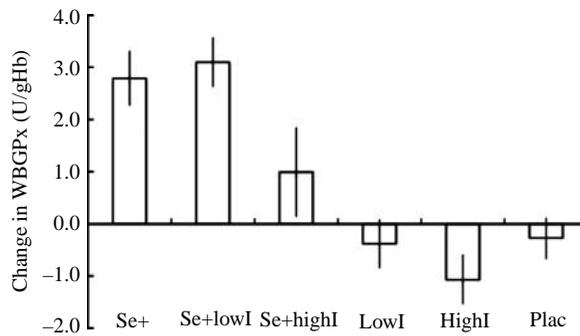


Figure 2 Change in whole blood glutathione peroxidase (WBGpX) activities in participants during 8-week supplementation with 100 µg selenium (Se+), selenium plus low (80 µg) iodine (Se+lowI) or high (50 mg) iodine (Se+highI) intake, low (lowI) or high (highI) iodine intake, or a placebo (Plac). Changes in WBGpX activity differed among the six groups (ANOVA, $P < 0.0001$). Values are mean \pm S.E.M.

(2.8–6.8 pmol/l) in two participants, but which had returned to baseline concentrations at 12 weeks (Table 3). Two participants (no. 46 and 81) developed evidence of hyperthyroidism, with TSH decreasing to < 0.10 mIU/ml at week 8 and remaining low at 12 weeks, and in a third participant (no. 97), an already low TSH at baseline further decreased at week 8 (Table 3), indicating an underlying thyroid problem exacerbated by excess iodate supplementation. The decrease in TSH was accompanied by a slightly elevated FT₃ in all participants and elevated FT₄ outside the normal range in two (participant no. 46 and 97). TgAbs were elevated in six of the 43 participants exposed to high iodate, two of whom developed hypothyroidism (no. 49 and 103), one developed hyperthyroidism (no. 46), and three were unaffected.

All participants exposed to excess iodate intake were asymptomatic. The thyroid hormone results were referred to an Endocrinologist who did not consider that further clinical evaluation was necessary at that time. Participants were referred to their general practitioners for further evaluation with respect to the potential toxicity of iodine as iodate.

Mean FT₃ and TSH concentrations differed among the six groups at 8 weeks (ANOVA, $P < 0.001$, $P = 0.014$ respectively) due entirely to higher mean TSH and FT₃ values for the highI group and Se+highI ($P < 0.10$) and a higher FT₃ value for the highI group ($P < 0.05$), the groups that included those participants who developed thyroid dysfunction as a result of high iodate intake (results not shown). Mean FT₄ concentrations did not change during the study period.

Discussion

Our results are of particular relevance in assessing potential adverse effects of a prolonged very high iodine intake, particularly in older people, and in evaluating the tolerable upper intake limit (UL) for iodine. Evidence of iodate-induced hypothyroidism in some participants and of hyperthyroidism in others was observed. Most of the abnormal thyroid hormone levels had returned to normal 4 weeks after cessation of high iodate supplementation. We have also shown a potential adverse effect of excess iodate intake on the selenoenzyme GPx.

Factors affecting the response to excess iodine include route of intake, bioavailability of iodine, duration of intake, and physiological status of the individual including age, sex, body size, previous iodine intake, thyroid health, and general health (8). For example,

Table 3 Individual serum TSH, FT₄, and FT₃ concentrations in those participants exposed to excess iodine intake who developed hypothyroidism or hyperthyroidism.

Subject	Sex (M/F)	Treatment	TSH (mIU/l)			FT ₄ (pmol/l)			FT ₃ (pmol/l)		
			Week 0	Week 8	Week 12	Week 0	Week 8	Week 12	Week 0	Week 8	Week 12
Hypothyroidism											
1	M	HighI	2.2	6.9	1.8	12.6	10.8	12.8	5.2	4.8	4.6
49	F	HighI	6.3	23.1	8.0	12.4	9.2	13.1	5.0	4.9	5.2
106	M	HighI	5.7	9.6	4.8	13.5	12.1	13.6	5.4	5.4	5.2
110	F	HighI	3.9	40.4	7.5	12.3	6.2	13.5	4.5	4.3	5.9
14	M	Se+highI	4.0	13.4	2.3	14.7	12.8	16.1	5.3	5.3	5.2
18	M	Se+highI	4.1	10.8	2.4	13.1	9.0	12.5	5.3	4.6	4.6
72	F	Se+highI	3.7	6.5	2.4	15.0	13.8	15.1	4.6	5.3	4.6
83	M	Se+highI	4.5	12.3	4.6	12.7	8.1	14.4	5.5	6.3	5.5
103	F	Se+highI	2.0	8.1	2.2	13.8	10.8	13.8	4.9	4.8	5.1
118	M	Se+highI	4.2	9.8	3.6	14.2	11.7	13.1	4.2	4.2	4.0
Hyperthyroidism											
46	F	HighI	1.14	0.07	0.01	15.2	21.3	24.4	5.4	6.5	6.9
81	F	Se+highI	1.15	0.03	NM	13.2	17.4	17.1	5.4	8.4	6.1
97	M	HighI	0.35	0.05	0.05	17.0	29.1	32.5	5.4	8.2	8.9

FT₄, free thyroxine; FT₃, free triiodothyronine; NM, not measured. For clinical assessment, normal ranges of thyroid hormone concentrations given by Southern Community Laboratories were as follows: TSH, 0.3–5.0 mIU TSH/l; FT₄, 10–23 pmol FT₄/l; FT₃, 2.8–6.8 pmol FT₃/l.

older adults who have lived many years in an iodine-deficient area and those with underlying thyroid disease are more likely to respond adversely to increased iodine intake than are those who live in iodine-sufficient areas or who have normal thyroid glands.

The major factor determining the occurrence of iodine-induced hypothyroidism or hyperthyroidism as a public health problem is the sudden increment of iodine (2), as experienced by our participants. However, the response to excess iodate was variable with some individuals tolerating the high intake without side effects, whereas some responded adversely. A significant proportion of our participants (25%) who received excess iodate for 8 weeks developed subclinical hypothyroidism as a result of inhibition of synthesis of thyroid hormones, while the remaining participants showed no effect. On the other hand, only three participants showed signs of iodate-induced hyperthyroidism, which is most commonly encountered in populations that have had long exposure to iodine deficiency and in older individuals who have long-standing nodular goiter (autonomous thyroid nodules) (3, 8).

Our observations may reflect age-related changes in thyroid function and increased risk of thyroid insufficiency in the elderly (23), although this was evident in only one of our older individuals (participant no. 97). Many of our older participants would have been born in the 1930s when iodine deficiency goiter was prevalent in many parts of New Zealand until adequate iodization of salt was introduced in the early 1940s. From that time until the 1980s was a time of adequate iodine status throughout the country because of high iodine content of dairy products as a result of the use of iodophor cleaning agents in the dairy industry, as well as iodized salt use (12). In the past 10–15 years, the use of iodophors has reduced resulting in a decrease in iodine status and a return to mild iodine deficiency from the early 1990s (11–13). Thus, our participants may have had varied historical exposure to iodine deficiency depending on their place of residence in New Zealand during their lifetime. Females are more susceptible to the effects of excess iodine intake than are males (8), but this was not evident in our small sample with six males and four females developing hypothyroidism, and one male and two females developing hyperthyroidism.

In this study, participants received 50 mg/day of iodine as iodate for 8 weeks, equivalent to 2800 mg iodine. Two other studies on the effects of high intake of iodine for prolonged periods have reported similar transient effects on thyroid status. An increase in serum TSH and thyroid volume was observed in ten male volunteers given 27 mg iodine daily for 4 weeks (total dose 756 mg) (24). Both TSH and thyroid volume had returned to normal within 1 month. Similarly, in 33 euthyroid patients given Lugol solution (80–100 mg/day) for 15 days (total dose 1200–1500 mg), TSH increased and returned to normal

after iodine withdrawal, but there were no demonstrable changes in serum T_4 or T_3 (25). We cannot explain why some participants developed thyroid dysfunction while others did not. There is likely to be a large variation in individual response to excess iodate intake, related to factors outlined above, such as previous exposure to iodine deficiency, nutritional status of the individual, sex, age, body size, thyroid health, and general health (8). In this respect, a major limitation of the study is that we did not measure thyroperoxidase antibody (TPO-Ab) levels of the participants. We speculate that high TPO-Ab titers were present in those participants who developed subclinical or clinical hypothyroidism, reflecting an underlying autoimmune thyroid problem. The presence of TgAbs did not seem to be a contributing factor as only three of those affected had elevated levels, while another three did not develop thyroid disease.

The UL of intake for iodine for the USA and Canada was set at 1100 $\mu\text{g}/\text{day}$ (26) as is the Australian and New Zealand upper limit (27). This was based on observations of elevated TSH concentrations after supplemental intake indicating a lowest-observed-effect level of 1700 $\mu\text{g}/\text{day}$. An uncertainty factor of 1.5 was applied to give a no-observed-adverse-effect level that is the basis for the upper limit of intake. However, this guideline should be exercised with caution as individuals with chronic iodine deficiency or with underlying thyroid disease may respond to intake lower than these (1). In our older population, most abnormalities had returned to normal after only 4 weeks, indicating that long-term adverse effects were unlikely. However, a longer follow-up of these participants would have been desirable. Prolonged exposure to excess iodate at this level, particularly in susceptible individuals, might have more serious adverse consequences affecting their health and well-being. Ocular toxicity has occurred in humans after exposure to doses of 600–1200 mg/individual, and in several animal species, oral exposures to high doses of iodate have pointed to corrosive effects in the gastrointestinal tract, hemolysis, nephrotoxicity, and hepatic injury (10).

Other nutritional determinants of thyroid function such as selenium, vitamin A, and iron may influence the effects of high iodine intake (1). In particular, several studies have reported an interaction between selenium status and thyroid function (15, 28, 29). Selenium regulates thyroid hormone metabolism through its action as a component of the iodothyronine deiodinases in converting T_4 to T_3 . In selenium deficiency, conversion of T_4 to T_3 is impaired (17, 18). However, the interaction is modest when subjects are not sufficiently iodine and/or selenium deficient (16, 19). Beneficial effects of selenium supplementation on autoimmune thyroiditis have been reported, possibly through the action of GPx in enhancing the immune system and protecting the thyroid gland against oxidant stress (30–32). In a recent randomized controlled trial with patients with autoimmune thyroiditis,

physiological doses of selenium improved thyroid structure and reduced autoantibody titer (33). We did not see any protective effect of selenium supplemented with high iodine in comparison with high iodine on the development of thyroid disease in our participants; however, the number of subjects affected adversely by high iodate intake was too small to draw any such conclusions.

This is the first study to our knowledge to report an effect of high iodate intake on GPx activity as a measure of selenium status in humans. Selenium supplementation increased GPx activity, confirming many other intervention studies carried out in New Zealand, which indicate that the baseline selenium status of New Zealanders is insufficient for maximization of GPx activity (12). However, we observed a statistically significant smaller increase in GPx in the Se+highI group than in the other selenium-supplemented groups. In addition, there was a decrease in GPx activity in the highI group that was greater than that for the other two groups not supplemented with selenium. This may partly reflect the smaller but non-significant increase in PISe in the Se+highI group, but this is unlikely to be the only reason. However, these differences are more likely to be due to higher oxidant stress induced by high iodate intake, resulting in a larger decrease in GPx activity or a smaller increase in response to selenium supplementation because of higher consumption of WBGpx. Our results agree with those of Xu *et al.* (34) who showed in mice that decreased activities of GPx resulting from excessive iodine intake could be restored through supplementing with selenium. These observations indicate that when high iodate supplements are used to eliminate iodine deficiency, it would appear important to co-administer selenium to ensure adequate selenium intake.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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