Selenium and iodine supplementation: effect on thyroid function of older New Zealanders[1–3]

Christine D Thomson, Jennifer M Campbell, Jody Miller, Sheila A Skeaff, and Vicki Livingstone

ABSTRACT

Background: The New Zealand population has both marginal selenium status and mild iodine deficiency. Adequate intakes of iodine and selenium are required for optimal thyroid function.

Objective: The aim of the study was to determine whether low selenium and iodine status compromises thyroid function in an older New Zealand population.

Design: We investigated the effects of selenium and iodine supplementation in a double-blind, randomized, placebo-controlled trial in 100 Dunedin volunteers aged 60–80 y. Participants received 100 μg Se/d as L-selenomethionine, 80 μg I, 100 μg Se + 80 μg I, or placebo for 3 mo. Thyroid-stimulating hormone (TSH), free triiodothyronine (T_3), free thyroxine (T_4), thyroglobulin, plasma selenium, whole-blood glutathione peroxidase (GPx) activity, and urinary iodine concentrations (UICs) were measured.

Results: Plasma selenium ($P < 0.0001$) and whole-blood GPx activity ($P<0.0001$) increased from baseline to week 12 in the selenium and selenium plus iodine groups in comparison with the placebo group. Median UIC at baseline was 48 μg/L (interquartile range: 31–79 μg/L), which is indicative of moderate iodine deficiency. UIC increased in the iodine and selenium plus iodine groups and was significant only for the iodine group ($P = 0.0014$). Thyroglobulin concentration decreased by 24% and 13% of baseline in the iodine and selenium plus iodine groups in comparison with the placebo group ($P = 0.009$ and $P = 0.108$, respectively). No significant treatment effects were found for TSH, free T_3, free T_4, or ratio of T_3 to T_4.

Conclusions: Additional selenium improved GPx activity but not the thyroid hormone status of older New Zealanders. Iodine supplementation alleviated the moderate iodine deficiency and reduced elevated thyroglobulin concentrations. No synergistic action of selenium and iodine was observed. The trial was registered at www.anzctr.org.au/registry/ as ACTRN012605000368639. *Am J Clin Nutr* 2009;90:1038–46.

INTRODUCTION

Adequate intakes of both iodine and selenium are required for optimal thyroid function (1–3). Iodine is an essential component of the thyroid hormones thyroxine (T_4) and triiodothyronine (T_3), and deficiency will impair synthesis of these hormones. Selenium is essential for the biosynthesis and function of the iodothyronine deiodinases that control the conversion of T_4 to T_3. In addition, selenium-dependent glutathione peroxidases (GPxs) are implicated in the protection against oxidative damage to the thyroid gland (1–4). Selenium deficiency will decrease conversion of T_4 to T_3, and it increases oxidant stress on the thyroid gland as a result of reduced GPx activity (2, 4). Both selenium and iodine deficiencies may exacerbate the effects of individual deficiencies such that selenium deficiency, in the presence of severe iodine deficiency, with the associated hyperstimulation of the thyroid and increased H_2O_2 production, results in reduced GPx activity and subsequent reduction in the clearance of H_2O_2 (1, 4).

The interaction between selenium and iodine status is of particular interest in New Zealand where intakes of both trace elements are relatively low (5). New Zealanders have experienced a return to mild-moderate iodine deficiency, with elevated serum thyroglobulin and enlarged thyroid glands (6–8). Although selenium status has increased, intakes for many New Zealanders are still insufficient for maximal GPx activity (8–10). In a 1995 study, selenium supplementation resulted in a small but significant decrease in plasma T_4 and an increase in the ratio of T_3 to T_4 (T_3:T_4) (9); however, in later studies, changes were small and not significant (11).

Older people are particularly vulnerable to suboptimal selenium and iodine status as a result of imbalanced nutrition (12, 13). In a study of 103 New Zealand women aged 70–80 y, selenium intake was 34 μg/d and plasma selenium concentration was 0.86 μmol/L, significantly lower than those of younger adult women assessed at the same time (14). The iodine status of older New Zealanders has not been determined, but it is expected to be low along with the rest of the adult population (8). In addition, the elderly are at increased risk of thyroid insufficiency, and age-related changes in thyroid-stimulating hormone (TSH), T_4, and T_3 have been observed (15). The elderly are a growing segment of the population, and impaired thyroid function as a result of low selenium and iodine status may have consequences on health and well-being which will strain health care resources.

[1] From the Departments of Human Nutrition (CDT, JMC, SAS, and JM) and Preventive and Social Medicine (VL), University of Otago, Dunedin, New Zealand.

[2] Supported by Otago Medical Research Foundation and the University of Otago Research Fund.

[3] Address correspondence to CD Thomson, Department of Human Nutrition, University of Otago, PO Box 56, Dunedin, New Zealand. E-mail: christine.thomson@otago.ac.nz.

Received June 6, 2009. Accepted for publication July 28, 2009.

First published online August 19, 2009; doi: 10.3945/ajcn.2009.28190.

We hypothesized that current selenium and iodine intakes of older New Zealanders might be inadequate for optimal conversion of T_4 to T_3. A recent study by Rayman et al (16) did not find any effect of selenium intervention on thyroid function in British elderly residents with similar selenium status, but they did not assess iodine status, which they reported to be adequate, nor did they supplement with iodine in addition to selenium. Similarly, Combs et al (17) did not find an effect of selenium supplementation alone on thyroid function in US residents with adequate selenium status. The aim of our study was to investigate the effect of selenium and iodine supplementation separately and together on selenium and iodine status and thyroid function.

SUBJECTS AND METHODS

A randomized controlled trial was carried out with older male and female residents of Dunedin in the South Island of New Zealand from August to November 2005. Participants were aged between 60 and 80 y; were noninstitutionalized, were free from serious medical illness such as cancer, diabetes, or cardiovascular disease; were not using medications for thyroid function or with any known thyroid problems, and were not taking multivitamin-multimineral or other dietary supplements that contained selenium or iodine. Subjects were recruited by advertisements in regional and community newspapers, club and church newsletters, on notice boards in retirement villages, supermarkets, hospitals, and leisure centers; by letters sent to participants in a previous study conducted in the Department of Human Nutrition; and by visits and presentations to various senior citizen organizations. All participants gave their informed consent, and the Ethics Committee of the University of Otago, Dunedin, New Zealand, approved the protocol.

Study design

Potential participants were screened by telephone with the use of a brief questionnaire that included questions on age, health, and inclusion criteria. Respondents who met the inclusion criteria were mailed information sheets and consent forms, and after consent they were randomly assigned into treatment groups. Block randomization with stratification by sex was used to assign 76 participants into 1 of 3 treatment groups (November 2005): 100 μg Se (n = 26), 80 μg I (n = 25), and placebo (n = 25). The randomization scheme was generated by using the website Randomization.com (www.randomization.com). The fourth group, 100 μg Se + 80 μg I (n = 26), was part of another earlier randomization of 4 groups of subjects (August 2005). An error in the manufacturer of some supplements used for the first randomization and intervention resulted in very high intakes of iodine for participants in 3 of the groups, and it was necessary to terminate their intervention. No significant differences were observed in baseline measures of selenium, iodine, or thyroid hormone status of the final 4 groups (**Table 1**).

A decrease of 2 pmol/L in serum-free T_4 concentration in the treatment groups was considered to be a clinically important change. To have a power of 90% to detect a true difference of 2 pmol/L in serum-free T_4 between a treatment group and the control group, a sample size of 22 people per group is required. This calculation is based on the assumption that the SD is 2 pmol/L. We assumed a 2-sided statistical test and a 5% level of significance. Assuming 15% attrition over the study duration, 25 people per group were required.

A staff member not involved with the recruitment of participants for the study was in charge of the randomization list and kept the list private, only revealing the treatment allocation for a participant after receiving the information that the patient was eligible for the study and had consented to take part. The staff member responsible for assigning participants to their groups had no direct contact with the patients; hence allocation was independent of recruitment (ie, the sequence was concealed until interventions were assigned). The participants, investigators administering the interventions, and investigators assessing the outcomes of the intervention were blinded to the treatment assignment.

TABLE 1
Baseline markers of selenium and iodine status and thyroid function in study participants[1]

Treatment group	All (n = 100)	Placebo (n = 24)	100 μg Se (n = 25)	80 μg I (n = 25)	100 μg Se + 80 μg I (n = 26)
Age (y)	72.4 ± 4.8[2]	73.2 ± 4.7	71.4 ± 5.5	70.9 ± 5.1	74.1 ± 3.4
BMI (kg/m^2)	26.8 ± 5.8	25.2 ± 6.5	28 ± 3.8	27.8 ± 5.2	25.5 ± 6.7
Male (%)	45	44	46	40	46
PlSe (μmol/L)	1.20 ± 0.33	1.23 ± 0.29	1.23 ± 0.31	1.22 ± 0.36	1.11 ± 0.33
WBGPx (U/g hemoglobin)	43.6 ± 9.8	44.1 ± 8.9	43.8 ± 12.3	43.2 ± 9.1	43.5 ± 8.9
UIC (μg/L)	48 (31, 79)[3]	44 (28, 104)	52 (34, 68)	40 (18, 64)	59 (42, 93)
Free T_3 (pmol/L)	4.82 ± 0.47	4.85 ± 0.47	4.70 ± 0.46	4.90 ± 0.51	4.84 ± 0.42
Free T_4 (pmol/L)	14.3 ± 2.1	14.7 ± 2.0	14.0 ± 2.0	13.9 ± 2.2	14.6 ± 2.1
Free T_3:T_4	0.34 (0.31, 0.38)	0.33 (0.31, 0.37)	0.34 (0.30, 0.39)	0.35 (0.32, 0.39)	0.33 (0.31, 0.37)
TSH (mIU/L)	2.23 (1.73, 3.21)	2.35 (1.59, 3.41)	2.58 (1.76, 3.23)	2.20 (1.53, 3.00)	2.15 (1.77, 3.07)
Tg (μg/L)[4]	15.8 (10.0, 29.2)	13.4 (9.1, 22.9)	15.3 (10.2, 29.5)	16.3 (9.5, 32.8)	15.9 (13.9, 30.4)

[1] PlSe, plasma selenium concentration; WBGPx, whole-blood glutathione peroxidase; UIC, urinary iodine concentration; T_3, triiodothyronine; T_4, thyroxine; T_3:T_4, ratio of T_3 to T_4; TSH, thyroid-stimulating hormone; Tg, thyroglobulin. No significant differences were found between treatment groups: ANOVA for continuous data, chi-square test for categorical data, Kruskal-Wallis test for skewed data.

[2] Mean ± SD (all such values).

[3] Median; interquartile range in parentheses (all such values).

[4] Tg concentration is reported for 89 participants; 9 participants were excluded because of Tg antibodies, and 2 participants had insufficient sample volume, which left n = 22, 23, 23, and 21 in the placebo, selenium, iodine, and selenium plus iodine groups, respectively.

Participants completed a brief questionnaire that included questions on demographics, dietary habits, supplement and medication use, smoking habits, consumption of foods high in selenium or iodine such as seafood and Brazil nuts, and self-reported health status. Fasting blood samples were collected at baseline and at weeks 2, 4, 8, and 12, and casual morning urine samples were collected at baseline and week 12. Duplicate height and weight measurements were made at baseline for calculation of body mass index (BMI; in kg/m^2).

Treatments

Tablets, identical in size, shape, and color, were produced by Alaron Products (Port Nelson, New Zealand). Iodine tablets contained potassium iodate, and selenium tablets contained L-selenomethionine. One batch only of each supplement was produced. Ten tablets were randomly selected from each group and analyzed for iodine and selenium content by Hill Laboratories Ltd (Hamilton, New Zealand) with the use of inductively coupled plasma mass spectrometry with a detection limit of 0.01 μg Se/tablet and 0.02 μg I/tablet, respectively. Placebo tablets contained $<$0.01 μg selenium or iodine per tablet, selenium tablets contained a median of 108 μg Se [interquartile range (IQR): 100–110 μg Se] with negligible iodine; iodine tablets contained negligible selenium and a median of 79 μg I (IQR: 76–82 μg I); and selenium plus iodine tablets contained 94 μg Se (IQR: 88–99 μg Se) and 80 μg I (IQR: 71–103 μg I) per tablet.

Participants consumed 1 tablet daily for 12 wk; they were encouraged to maintain their normal diets and to avoid supplements that contained selenium or iodine for the study duration. Compliance was monitored by completion of a daily checklist and from the number of tablets returned at study conclusion.

Sample collection

Blood was collected in EDTA-coated tubes (Becton Dickinson, Franklin Lakes, NJ) for separation of whole blood and plasma and additive free evacuated tubes 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) urine samples were collected in clean, plastic specimen containers and stored at –20°C until analysis.

Analytic methods

Plasma selenium concentrations were determined in duplicate by graphite furnace Atomic Absorption Spectroscopy with Zeeman background correction (AA-800; Perkin-Elmer Corp, Norwalk, CT) by a modification of the method of Jacobson and Lockitch (18). Accuracy was assessed by analysis of certified reference materials (CRMs) with each batch; Seronorm Reference Serum (batch no. JL4409; Laboratories of SERO AS, Billingstad, Norway), with a certified selenium concentration of 0.92 μmol Se/L (95% CI: 0.84, 1.00 μmol Se/L), gave a mean ($\pm$SD) concentration of 0.88 $\pm$ 0.04 μmol/L (CV: 4.9%; n = 45). Analysis of Utak Reference Plasma (batch no. 66816, lot 7081; UTAK Laboratories Inc, Valencia, CA), with a certified selenium concentration of 1.52 μmol Se/L (95% CI: 1.14, 1.90 μmol Se/L), gave a mean of 1.39 $\pm$ 0.09 μmol Se/L (CV: 6.2%; n = 45).

GPx activity was measured in whole blood with the use of RANSEL kits (no. RS 505, 506; Randox Laboratories Ltd, Antrim, United Kingdom) and automated on a Cobas Fara autoanalyser (Hoffman-La Roche, Basel, Switzerland). Whole-blood GPx 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 (19). 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 $\pm$ 2.8 U/g hemoglobin (CV: 6.2%; n = 196).

Urinary iodine concentration (UIC) was determined with Method A recommended by the World Health Organization/UNICEF/International Council for the Control of Iodine Deficiency Disorders (WHO/UNICEF/ICCIDD) (20). Analysis of a CRM, Seronorm Trace Elements Urine (lot no. NO2525; Sero AS, Asker, Norway), with a certified iodine concentration of 141 μg I/L (95% CI: 132, 150 μg I/L) gave a mean of 131 $\pm$ 8 μg I/L (CV: 5.7%; n = 92). Analysis of pooled aliquots of urine with each batch of samples gave a mean of 45 $\pm$ 10 μg I/L (CV: 4.4%; n = 43).

Analyses of serum TSH, free T_3, and free T_4 concentrations were performed by Southern Community Laboratories, Dunedin. TSH was assayed with the use of a 2-site sandwich chemiluminescent immunoassay with a lower limit of detection of 0.004 μU/L. Serum free T_4 and free T_3 were analyzed with the use of a competitive chemiluminescent immunoassay with a lower limit of detection of 1.3 pmol free T_4/L and 0.3 pmol free T_3/L. Analysis of CRM (BioRad Immunoassay Plus material; Irvine, CA), with certified concentrations of 0.60 mIU TSH/L (95% CI: 0.48, 0.72 mIU TSH/L), 10.5 pmol free T_4/L (95% CI: 8.4, 12.7 pmol free T_4/L), and 3.6 pmol free T_3/L (95% CI: 2.9, 4.3 pmol free T_3/L) gave mean concentrations of 0.6 $\pm$ 0.03 mIU TSH/L (CV: 4%), 9.3 $\pm$ 0.7 pmol free T_4/L (CV: 8.5%), and 3.3 $\pm$ 0.14 pmol free T_3/L (CV: 4.2%), respectively.

Serum thyroglobulin concentrations were determined by Endolab, Christchurch Hospital, (Christchurch, New Zealand). Baseline samples were tested for the presence of thyroglobulin antibodies because these can interfere with measurement of thyroglobulin by immunologic methods. If the antibody was present at baseline, then the participant's corresponding week 12 sample was not analyzed, and results from this subject were not included in the data analysis. Both thyroglobulin and thyroglobulin antibodies were measured by immunoenzymatic (2-site) assays with chemiluminescent detection with the use of an Access 2 analyzer (Beckman Coulter Inc, Fullerton, CA), with a lower limit of detection of 0.1 ng thyroglobulin /mL and 2.2 kIU thyroglobulin antibody/L, respectively. External quality control samples used were CRM 457 thyroglobulin standard (European Community Bureau of Reference) and the thyroglobulin antibody WHO 65/93 International standard. Interassay CVs for thyroglobulin were 5.1% at 35.1 μg/L and 6.9% at 288 μg/L (n = 46), and for thyroglobulin antibody, 18% at 4.5 kIU/L and 7.7% at 307 kIU/L (n = 48). For all analytic methods, all samples from each participant were analyzed in the same batch.

Statistical analysis

All statistical analyses were conducted with the use of SAS 9.1.3 (SAS Institute Inc, Cary, NC) or SPSS Version 14.0 for

Windows (SPSS Inc, Chicago, IL). Statistical significance was assessed at $P < 0.05$.

Descriptive statistics are presented for all baseline characteristics. Although it is not considered good practice in a randomized control trial to test for baseline differences between groups, because the process of randomization means any differences will simply be due to chance (21, 22), we chose to test for baseline differences as our recruitment was undertaken in 2 stages. Positively skewed data were described with the use of median (IQR). Categorical baseline characteristics were described with number of participants (%). Differences between groups of normally distributed variables were tested with the use of one-factor analysis of variance for continuous data and chi-squared test for categorical data. Differences between groups of skewed variables were tested with the Kruskal-Wallis test. Associations between biological indexes of selenium (plasma selenium, whole-blood GPx), iodine (UIC), and thyroid status (free T_4, free T_3, T_3:T_4, TSH, thyroglobulin) at baseline were assessed with the use of Pearson's correlation coefficient. Initially, univariate analyses with the variables plasma selenium and UIC were performed to investigate factors associated with these outcomes at baseline. The factors considered were age, sex, BMI, the 2001 New Zealand Index of Deprivation (NZDep2001; an index based on an individual's residential address) (23), smoking status, and medication and supplement use. Multiple linear regression was used to determine which factors were independently associated with the outcome variables.

For the intervention study, linear mixed effects regression models, including both fixed and random effects, were used to examine the effect of treatments on the continuous outcomes. Positively skewed data were log-transformed before the statistical analysis. The random effects allowed for possible correlation between repeated measures over time within a subject. This was necessary for our data because plasma selenium, whole-blood GPx, TSH, free T_4, and free T_3 were measured at 5 time points (weeks 0, 2, 4, 8, and 12), and thyroglobulin and UIC were measured at 2 time points (weeks 0 and 12). The models contained treatment group, time, and the treatment-by-time interaction as fixed effects and subject as the random effect. The participant characteristics of age, sex, BMI, medication and supplement use, and individual baseline plasma selenium concentrations were also included in the model because these were potential confounders. The primary measure of interest was the change in mean response from baseline to week 12 for the outcome variables. Pairwise comparisons were made between groups only if the treatment-by-time interaction was significant ($P < 0.05$).

Random coefficients or mixed means models were used to analyze the data. The choice of model was based on the Akaike Information Criterion values for the models. In a means model, the pattern of covariance between repeated measurements is modeled. However, no structure is imposed on the mean response trend over time (time is a categorical variable in the model); hence, the time ordering of the observations is ignored (24). In a random coefficients model, it is assumed that there is a linear relation between the outcome variable and time. The random coefficients model allows the slopes and intercepts to vary randomly between the study subjects; hence, a separate regression line is fitted for each subject (25). If there was a nonlinear relation between the outcome variable and time, we investigated the use of a quadratic curve or a linear spline. Outcome variables were log-transformed if it improved the model fit. The mixed models were fitted with the use of SAS PROC MIXED (SAS Institute Inc).

A 2-factor analysis was not considered, because our main focus was to compare the effect of selenium and iodine together with the separate effects of selenium alone, iodine alone, and the placebo on the outcomes of interest. This would not be possible if both selenium groups or both iodine groups were combined. We did not consider a post hoc 2-factor analysis appropriate, because this would not have strengthened the effects of treatments on serum T_3 or T_4 concentrations, the primary outcomes of interest.

RESULTS

Of the 102 participants initially randomly assigned to treatment groups, 1 participant was excluded from all analyses because her test results indicated thyroid disease, 1 participant did not attend the baseline clinic, leaving 100 participants for whom baseline characteristics are reported (Table 1). By week 12, a further 3 participants had dropped out, leaving 97 participants who completed the trial (23, 25, 24, 25 in the placebo, selenium, iodine, and selenium plus iodine groups, respectively). A further 9 participants did not provide urine samples for reasons that included difficulty in passing urine or were unwilling to provide a sample. Compliance with supplement use was excellent with 90% of all participants consuming all supplements and 10% consuming between 97% and 99% of their supplements.

Baseline selenium, iodine, and thyroid hormone status

Mean ages and BMIs of participants in the 4 groups were similar, and no significant differences were observed among the treatment groups at baseline for measures of selenium, iodine, or thyroid hormone concentrations (Table 1). Plasma selenium concentrations and whole blood GPx activities at baseline were normally distributed (Table 1). Univariate analysis of independent factors, including age, sex, BMI, NZDep2001 score, use of medication or supplements, and smoking status showed no significant associations with baseline plasma selenium. Similarly, multiple linear regression showed that these factors explained little of the variation in baseline plasma selenium concentrations (R^2 = 4.7%). A moderate correlation was observed between plasma selenium and whole blood GPx activity at baseline (r = 0.329, P = 0.001).

Urinary iodine concentrations were positively skewed, and baseline data are reported as median (Table 1). The unadjusted median UIC (MUIC) of all participants at baseline was 48 μg/L (IQR: 31–79 μg/L), which is indicative of moderate iodine deficiency (20). UIC was $<$100 μg/L in 83% of participants and $<$50 μg/L in 53%. Univariate analysis of factors, including age, sex, BMI, NZDep2001 score, use of medication or supplements, smoking status, and use of iodized salt, showed no significant associations with UIC. Multiple linear regression analysis showed a tendency for participants classified in the highest categories of deprivation (7–10) to have a higher UIC than participants in the lowest categories (1–3) (P = 0.056). However, overall these factors explained little of the variation in UIC (R^2 = 0.063).

Free T_3 concentrations were all within the manufacturer's reference range (2.8–6.8 pmol/L). Two participants had free T_4 concentrations below the manufacturer's reference range (10–23 pmol/L) and 2 had TSH concentrations outside the reference range (0.3–5 mIU/L).

Nine participants had detectable thyroglobulin antibodies, and their thyroglobulin results were excluded from analysis. The median thyroglobulin concentration of 15.8 μg/L (IQR: 10.0–29.2 μg/L) was indicative of mild iodine deficiency (range: 10.0–19.9 μg/L) (26). Four people had thyroglobulin concentrations outside the reference range of 0–58 μg/L, and 37 participants (42%) had thyroglobulin concentrations >20 μg/L. Neither plasma selenium nor whole blood GPx was significantly associated with measures of iodine or thyroid hormone status at baseline.

Effect of selenium and iodine supplementation

Effect on selenium status

The relation between plasma selenium concentration and time was not linear (**Figure 1**); therefore, plasma selenium was modeled with the use of a linear spline with a knot at week 4 and adjusted for possible confounders. At week 12, unadjusted plasma selenium concentrations had increased by 0%, 82%, 8%, and 79% of baseline values in the placebo, selenium, iodine, and selenium plus iodine groups, respectively. When adjusted for age, sex, BMI, medication use, and supplement use and compared with the placebo group, the overall change was statistically significant for the selenium (0.99 μmol/L; 95% CI: 0.84, 1.14 μmol/L; $P < 0.0001$) and selenium plus iodine (0.96 μmol/L; 95% CI: 0.81, 1.16 μmol/L; $P < 0.0001$) groups but not for the iodine group. Pairwise comparisons between the groups showed that adjusted overall changes in plasma selenium concentrations of both the selenium and selenium plus iodine groups differed significantly from both the iodine and placebo groups ($P < 0.0001$ for all) but not from each other.

The relation between whole-blood GPx activity and time was linear and modeled with the use of a random coefficients model, similarly adjusted for confounders (**Figure 2**). By week 12 unadjusted changes in whole-blood GPx activity were 0%, 9%, −1%, and 9% of baseline values in the placebo, selenium, iodine, and selenium plus iodine groups, respectively. When adjusted for baseline measures and compared with the placebo group, the overall change was significant in the selenium group (GPx activity of 4.5 U/g; 95% CI: 2.7, 6.2 U/g; $P < 0.0001$) and the selenium plus iodine group (GPx activity of 5.2 U/g; 95% CI: 3.3, 7.1 U/g; $P < 0.0001$) but not in the iodine group. Pairwise comparisons between the treatment groups showed that adjusted overall changes in whole-blood GPx activity were significantly greater in the selenium and selenium plus iodine groups than in the iodine group ($P < 0.0001$ for both) but not from each other.

Effect on iodine and thyroid status

The relations between time and UIC, TSH, thyroglobulin, free T_3, free T_4 concentrations, and T_3:T_4 were linear and were modeled with the use of a random coefficient model that adjusted for potential confounders. With the exception of free T_3 and free T_4, all data were log-transformed, and the geometric mean (95% CI) at baseline and week 12 was reported.

By week 12, UIC (geometric mean) had changed by −7%, −1%, 120%, and 27% of baseline values in the placebo, selenium, iodine, and selenium plus iodine groups, respectively, after adjustment for age, sex, BMI, medication use, and supplement use (**Table 2**). This change was significant only in the iodine group ($P < 0.001$). The adjusted mean ratio for the selenium, iodine, and selenium plus iodine groups, respectively, was 6%, 136%, and 37% more than the adjusted mean ratio for the placebo group. This was statistically significant for the

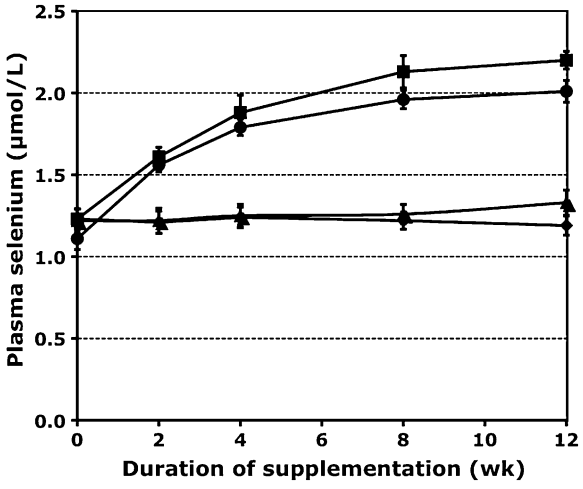

FIGURE 1. Mean (±SE) plasma selenium concentrations during daily supplementation for 12 wk with 100 μg Se/d as L-selenomethionine (■), 80 μg I as potassium iodate (▲), 100 μg Se + 80 μg I (●), or placebo (♦). A mixed model with a linear spline with a knot at week 4 was used to test for differences between the intervention and placebo groups in the change from baseline to week 4 and the change from week 4 to week 12, with adjustment for age, sex, BMI, medication use, and supplement use. Significant time-by-treatment effects were found ($P < 0.0001$ for both). The overall change from baseline to week 12 in comparison with the placebo group was significant for the selenium and selenium plus iodine groups ($P < 0.0001$ for both).

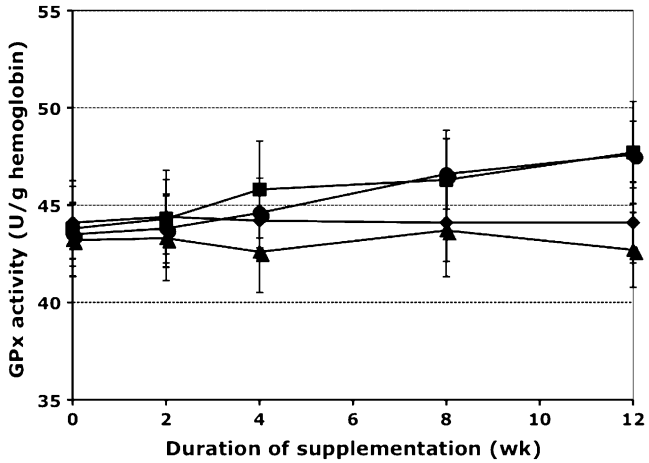

FIGURE 2. Mean (±SE) whole-blood glutathione peroxidase (GPx) activity during daily supplementation for 12 wk with 100 μg Se/d as L-selenomethionine (■), 80 μg I as potassium iodate (▲), 100 μg Se + 80 μg I (●), or placebo (♦). Random coefficients model was used to test differences between intervention and placebo groups, with adjustment for age, sex, BMI, baseline plasma selenium, medication use, and supplement use. A significant time-by-treatment effect was found ($P < 0.0001$). The change in comparison with the placebo group was significant for the selenium and selenium plus iodine groups ($P < 0.0001$ for both).

TABLE 2
Urinary iodine concentrations and their ratios by treatment group at baseline and after the 12-wk intervention period[1]

Treatment group	*n*	Week 0	Week 12	Ratio[2]	Ratio adjusted for change in the placebo group[3]
		μg/L	*μg/L*		
Placebo	21	49.0 (35.6, 67.6)	43.9 (33.2, 58.2)	0.93 (0.64, 1.36)	—
100 μg Se	24	44.7 (33.3, 59.9)	43.7 (34.7, 54.9)	0.99 (0.70, 1.40)	1.06 (0.65, 1.73)
80 μg I	21	33.4 (21.8, 51.1)	70.6 (51.6, 96.7)	2.20 (1.54, 3.13)[4]	2.36 (1.44, 3.87)[5]
100 μg Se + 80 μg I	20	62.8 (50.0, 78.9)	84.2 (61.9, 114.7)	1.27 (0.83, 1.95)	1.37 (0.78, 2.41)

[1] Values are unadjusted geometric means; 95% CIs in parentheses. Significant time-by-treatment interaction, $P = 0.004$ (random-coefficients model).
[2] Ratio of geometric means of week 12 relative to baseline, with adjustment for age, sex, BMI, baseline plasma selenium, medication use, and supplement use.
[3] Ratio of geometric means of the intervention group (week 12 relative to baseline) relative to the placebo group, with adjustment for age, sex, BMI, baseline plasma selenium, medication use, and supplement use.
[4] $P < 0.001$.
[5] $P = 0.0014$.

iodine group only ($P = 0.0014$). Pairwise comparisons between all treatment groups showed that the adjusted change in the UIC of the iodine group was significantly greater than that of the selenium group (the adjusted mean ratio for the iodine group was 122% more than the adjusted mean ratio for the selenium group; 95% CI: 35, 265%; $P = 0.0019$), and there was a trend for the change in the UIC of the iodine group to be greater than the change of the selenium plus iodine group (the adjusted mean ratio for the iodine group was 72% more than the adjusted mean ratio for the selenium plus iodine group; 95% CI: −1, 200%; $P = 0.054$).

At week 12 median UICs of participants in the 2 iodine-supplemented groups were still indicative of mild iodine deficiency (UIC < 100 μg/L) (26) (68 μg/L; IQR: 41, 131 for the iodine group; 97 μg/L; IQR: 51, 146 for the selenium plus iodine group) . Sixty-eight percent and 52% of participants in the 2 groups had UICs indicative of iodine deficiency. These proportions were smaller than those reported at baseline (88%, 76%, respectively).

Mean thyroglobulin concentrations decreased from baseline to week 12 by 5%, 3%, 27%, and 18% in the placebo, selenium, iodine, and selenium plus iodine groups, respectively, after adjustment for age, sex, BMI, medication use, and supplement use (**Table 3**). The decrease was significant in the iodine ($P < 0.0001$) and selenium plus iodine (P = 0.0053) groups. After adjustment for the change in the placebo group, the change (24%) in thyroglobulin was significant for the iodine group ($P = 0.0009$), but the change in the selenium plus iodine group (13%) was no longer significant ($P = 0.108$). Despite the decrease in thyroglobulin concentrations from baseline, median concentrations in the iodine (12.0 μg/L) and selenium plus iodine (11.6 μg/L) groups at week 12 were still indicative of mild iodine deficiency (26), although the proportion of people with thyroglobulin concentration > 20 μg/L was lower than that at baseline in the iodine (30% cf 39%) and selenium plus iodine groups (25% cf 33%).

Changes in mean TSH, free T_3, free T_4 concentrations, and geometric mean T_3:T_4 with supplementation were not statistically significant, and there were no time-by-treatment interactions (**Table 4**). There was a nonsignificant trend for free T_3 concentration to increase in both the selenium (increase of 0.15 pmol/L; 95% CI: −0.02, 0.31 pmol/L; $P = 0.080$) and the iodine (0.14 pmol/L; 95% CI: −0.02, 0.30 pmol/L; $P = 0.089$).

DISCUSSION

Our study is unique in that the effect on thyroid status of supplementation with both selenium and iodine was investigated. Daily supplementation with 100 μg Se for 12 wk did not significantly affect thyroid function in older New Zealanders,

TABLE 3
Serum thyroglobulin concentrations and their ratios by treatment group at baseline and after the 12-wk intervention period[1]

Treatment group	*n*	Week 0	Week 12	Ratio[2]	Ratio adjusted for change in the placebo group[3]
		μg/L	*μg/L*		
Placebo	22	14.4 (9.1, 22.8)	14.0 (8.4, 23.2)	0.95 (0.85, 1.06)	—
100 μg Se	22	15.4 (11.2, 21.3)	15.2 (11.2, 20.7)	0.97 (0.86, 1.09)	1.01 (0.87, 1.19)
80 μg I	23	21.2 (12.5, 35.9)	15.4 (8.9, 26.7)	0.73 (0.66, 0.81)[4]	0.76 (0.65, 0.89)[5]
100 μg Se + 80 μg I	20	17.3 (11.7, 25.5)	14.7 (9.2, 23.6)	0.82 (0.73, 0.94)[6]	0.87 (0.73, 1.03)

[1] Values are unadjusted geometric means; 95% CIs in parentheses. Significant time-by-treatment interaction, $P = 0.0012$ (random-coefficients model).
[2] Ratio of geometric means of baseline to week 12, with adjustment for age, sex, BMI, baseline plasma selenium, medication use, and supplement use.
[3] Ratio of geometric means of the intervention groups relative to the placebo group, with adjustment for age, sex, BMI, baseline plasma selenium, medication use, and supplement use.
[4] $P < 0.0001$.
[5] $P = 0.0009$.
[6] $P = 0.0053$.

TABLE 4
Biomarkers of thyroid function at baseline and after the 12-wk intervention period, their adjusted differences or ratios, and corresponding *P* values[1]

	n	Week 0	Week 12	Adjusted difference[2]	Adjusted ratio[3]	*P* value
Free T_3 (pmol/L)						
Placebo	22	4.85 ± 0.47[4]	4.73 ± 0.41	−0.10 (−0.27, 0.08)[5]	—	0.267
100 μg Se	25	4.70 ± 0.46	4.80 ± 0.44	0.15 (−0.02, 0.31)	—	0.080
80 μg I	25	4.91 ± 0.51	5.01 ± 0.64	0.14 (−0.02, 0.30)	—	0.089
100 μg Se + 80 μg I	24	4.84 ± 0.42	4.88 ± 0.39	0.0005 (−0.18, 0.18)	—	0.995
Free T_4 (pmol/L)						
Placebo	22	14.70 ± 2.03	14.36 ± 1.64	−0.16 (−0.65, 0.33)	—	0.521
100 μg Se	25	14.04 ± 1.99	14.08 ± 2.09	0.04 (−0.43, 0.51)	—	0.881
80 μg I	25	13.87 ± 2.16	13.72 ± 1.73	0.03 (−0.43, 0.48)	—	0.908
100 μg Se + 80 μg I	24	14.58 ± 2.13	13.97 ± 1.96	−0.28 (−0.80, 0.25)	—	0.300
Free T_3:T_4						
Placebo	22	0.33 (0.31, 0.35)	0.33 (0.31, 0.35)	—	0.99 (0.95, 1.02)	0.493
100 μg Se	25	0.34 (0.31, 0.36)	0.34 (0.32, 0.37)	—	1.03 (0.99, 1.07)	0.076
80 μg I	25	0.36 (0.34, 0.38)	0.37 (0.35, 0.38)	—	1.02 (0.99, 1.06)	0.166
100 μg Se + 80 μg I	24	0.33 (0.32, 0.35)	0.35 (0.33, 0.37)	—	1.01 (0.98, 1.06)	0.302
TSH (mIU/L)						
Placebo	21	2.24 (1.81, 2.77)	2.40 (2.01, 2.89)	—	1.09 (0.96, 1.24)	0.176
100 μg Se	25	2.30 (1.86, 2.84)	2.36 (1.87, 2.98)	—	1.00 (0.89, 1.13)	0.939
80 μg I	24	2.03 (1.56, 2.64)	2.04 (1.53, 2.73)	—	0.99 (0.87, 1.11)	0.812
100 μg Se + 80 μg I	24	2.22 (1.81, 2.73)	2.18 (1.87, 2.55)	—	0.92 (0.80, 1.05)	0.218

[1] T_3, triiodothyronine; T_4, thyroxine; TSH, thyroid-stimulating hormone. A random-coefficients mixed model was used to test for the change from baseline and week 12, with adjustment for age, sex, BMI, baseline plasma selenium, medication use, and supplement use.
[2] Difference between week 12 and baseline from the regression model.
[3] Ratio of geometric means of baseline to week 12 relative to baseline from the regression model.
[4] Mean ± SD (all such values).
[5] Unadjusted geometric mean; 95% CI in parentheses (all such values).

despite significant increases in plasma selenium and whole-blood GPx activities. No changes were found for TSH, free T_3, free T_4, or thyroglobulin concentrations, apart from a nonsignificant increase in free T_3 ($P = 0.080$). A recent study of British elderly also did not show an effect of selenium intervention on thyroid hormones, although there was an association between baseline plasma selenium and free T_4 (16). Similarly, selenium supplementation alone did not affect thyroid hormones in US individuals with more than adequate selenium status, apart from an increase in T_3 concentration in men but not women (17). One human cross-sectional study has shown an association between selenium and free T_3, but the relation was no longer significant after controlling for sex and other thyroid hormone variables (27). An increase in free T_3 concentration with selenium supplementation is biologically plausible; it suggests that deiodinase activity was up-regulated, increasing the conversion of T_4 to T_3. In our study, there was no concurrent decrease in free T_4 concentration, and the free T_3:T_4 was unchanged. Furthermore, similar changes were not observed in the selenium plus iodine group; therefore, the clinical significance of this change in free T_3 is questionable. There was no additional beneficial effect of selenium added to iodine in improving thyroid hormone status.

Five randomized controlled trials in healthy human adults have shown a decrease in serum T_4 with selenium intervention (9, 11, 28, 29), although in only 2 were changes statistically significant (9, 29). Our trial differed from earlier studies in that mean plasma selenium concentration at baseline (1.20 μmol/L) was higher, as was that of elderly British subjects (1.16 μmol/L) (16) and US subjects (1.78 μmol/L) (17), compared with 0.83 μmol/L (9) and 0.81 μmol/L (29) in the 2 earlier trials. In studies of children severely deficient in selenium and iodine (30) or phenylketonuria (31), when selenium supplementation decreased T_4 concentration, baseline plasma selenium was very low (34 and 0.26 μmol/L, respectively).

Our results suggest that plasma selenium concentrations in our elderly participants were not low enough to affect thyroid function to any extent. In deficiency, selenium is well maintained in the thyroid gland, and the deiodinases are high on the hierarchy of selenoproteins, such that selenium status must be very low to modify activity of these enzymes (32, 33). We saw no interaction between mild iodine deficiency and low selenium status in our subjects. The mean plasma selenium concentration of our elderly participants (1.20 μmol/L) was higher than in an earlier cohort of older New Zealand women (0.90 μmol/L) (14), a 1977 study of older adults (0.48 μmol/L) (34), and New Zealand adults (1.14 μmol/L) (10). We had expected the selenium status of our older adults to be lower than that of younger adults, as shown in several studies (27, 34, 35), a likely result of low micronutrient intake in older adults (36, 37). The higher than expected selenium status of our older participants reflects the trend of increasing selenium status among New Zealand residents (8, 38). Whole-blood GPx activity increased along with plasma selenium concentration, indicating that GPx in our older population was suboptimal. However, the increase was smaller than observed in earlier studies (9, 19) (9% cf 12–15%), suggesting that activity of GPx is approaching maximal values as a person's selenium status increases.

The iodine status (MUIC, 48 μg/L) of our older New Zealand participants was indicative of mild-to-moderate iodine deficiency, which confirms recent observations of a re-emergence of iodine deficiency in New Zealand. This has resulted in signs of

increased thyroid volume and thyroglobulin concentrations (6, 7, 39), although, to date, little evidence of any associated disease. A supplement of 80 μg I significantly increased geometric mean UIC in the iodine group, with a smaller increase in the selenium plus iodine group. Median UIC for participants with UIC available for both week 0 and week 12 increased from 35 μg/L (IQR: 17–65 μg/L) to 68 μg/L (IQR: 42–131 μg/L) in the iodine group ($n = 21$) and 67 μg/L (IQR: 42–106 μg/L) to 97 μg/L (IQR: 51–146 μg/L) in the selenium plus iodine group ($n = 20$), but at week 12 MUICs of both groups were still indicative of mild iodine deficiency (<100 μg/L). Supplementation at a higher amount appears necessary to adequately improve iodine status. There are several possible reasons for the lack of significant change in iodine excretion of the selenium plus iodine group. Although analysis of the selenium plus iodine supplements showed they contained an average of 80 μg I, the variability was greater than for the iodine supplements, and 10 supplements chosen for analysis may not have been representative of all supplements consumed. Because of the greater variability, some participants may have received more supplements that did not contain the full complement of iodine. Alternatively, the increase may have been lower because baseline geometric mean UIC (62.8 μg/L) of the selenium plus iodine group was higher than the iodine group (33.4 μg/L). In addition, the small sample size of 20 people who gave a urine sample at week 12 may not have been sufficient to detect a significant change.

Serum concentrations of TSH, free T_3, and free T_4 of most participants fell within the manufacturers' reference ranges. However, the median thyroglobulin concentration of 15.8 μg/L was indicative of mild iodine deficiency (10.0–19.9 μg/L) (26), as was the MUIC. Cross-sectional studies have shown that high thyroglobulin concentrations are associated with low UICs (6, 40), and thyroglobulin is considered the most sensitive indicator of iodine status. A decrease in its concentration in our participants suggests that thyroid hyperplasia was present, which may clinically manifest as increased thyroid volume or goiter (6). Iodine supplementation alone significantly reduced thyroglobulin concentration ($P = 0.009$), whereas the decrease with selenium plus iodine supplementation was not significant after adjustment for change in the placebo group. Other studies in iodine-deficient populations have similarly shown thyroglobulin concentration to decrease with iodine prophylaxis (41, 42). However, at week 12 the median thyroglobulin concentrations of the iodine group (12.0 μg/L) and the selenium plus iodine group (11.6 μg/L) were still indicative of mild iodine deficiency (26), confirming that a supplement of 80 μg iodine was not sufficient to raise iodine status to be adequate for optimal thyroid hormone function.

In conclusion, we found little evidence of an improvement in thyroid function with selenium supplementation, apart from a nonsignificant increase in free T_3 concentrations. This suggests that selenium intake is adequate for thyroid function in New Zealand, although not for maximal GPx activity. However, our mild-to-moderate iodine deficiency appears to be compromising thyroid function, because MUICs and thyroglobulin concentrations have approached amounts that the WHO/UNICEF/ICCIDD (20, 26) classify as a public health problem. Iodine supplementation improved thyroid function as shown by a decrease in thyroglobulin concentration; however, daily supplementation with 80 μg I for 12 wk was insufficient to attain adequate iodine or thyroid status in this population. Combined selenium and iodine supplementation did not significantly affect thyroid function, suggesting that in this population selenium was not acting synergistically with iodine to further exacerbate effects of low iodine status on thyroid function.

We thank the participants for their enthusiastic support of this project. We thank Michelle Harper, Karl Bailey, and Ashley Duncan for technical assistance in carrying out the study and Margaret Waldron for assistance with venipuncture.

The authors' responsibilities were as follows—CDT: designed the study, obtained funding support, and was responsible for interpretation of the data and writing the manuscript; JMC: was responsible for recruitment of subjects, data collection, and laboratory analyses and assisted with interpretation of the data; JM: assisted in subject recruitment and laboratory analyses; SAS: assisted in study design and supervision; and VL: carried out statistical analysis and contributed to manuscript preparation. None of the authors had a conflict of interest.

REFERENCES

1. Arthur JR, Beckett GJ, Mitchell JH. The interactions between selenium and iodine deficiencies in man and animals. Nutr Res Rev 1999;12:55–73.
2. Arthur JR, Beckett GJ. Thyroid function. Br Med Bull 1999;55:658–68.
3. Schomburg L, Kohrle J. On the importance of selenium and iodine metabolism for thyroid hormone biosynthesis and human health. Mol Nutr Food Res 2008;52:1235–46.
4. Beckett GJ, Arthur JR. Selenium and endocrine systems. J Endocrinol 2005;184:455–65.
5. Thomson CD. Interaction between selenium and iodine in thyroid status. Met Ions Biol Med 2004;8:552–4.
6. Thomson CD, Woodruffe S, Colls AJ, Joseph J, Doyle TC. Urinary iodine and thyroid status of New Zealand residents. Eur J Clin Nutr 2001;55:387–92.
7. Skeaff SA, Thomson CD, Gibson RS. Mild iodine deficiency in a sample of New Zealand schoolchildren. Eur J Clin Nutr 2002;56:1169–75.
8. Thomson CD. Selenium and iodine intakes and status in New Zealand and Australia. Br J Nutr 2004;91:661–72.
9. Duffield AJ, Thomson CD, Hill KE, Williams S. An estimation of selenium requirements for New Zealanders. Am J Clin Nutr 1999;70:896–903.
10. Thomson CD, Chisholm A, McLachlan SK, Campbell JM. Brazil nuts: an effective way to improve selenium status. Am J Clin Nutr 2008;87:379–84.
11. Thomson CD, McLachlan SK, Grant AM, Paterson E, Lillico AJ. The effect of selenium on thyroid status in a population with marginal selenium and iodine status. Br J Nutr 2005;94:962–8.
12. Horwath CC. Dietary intake studies in elderly people. World Rev Nutr Diet 1989;59:1–70.
13. McClain CJ, McLean M, Barve S, Boosalis MG. Trace metals and the elderly. Clin Geriatr Med 2002;18:801–18.
14. de Jong N, Gibson RS, Thomson CD, et al. Selenium and zinc status are suboptimal in a sample of older New Zealand women in a community-based study. J Nutr 2001;131:2677–84.
15. Weissel M. Disturbances of thyroid function in the elderly. Wien Klin Wochenschr 2006;118:16–20.
16. Rayman MP, Thompson AJ, Bekaert B, Caterick J, Galassini R, Hall E. Randomized controlled trial of the effect of selenium supplementation on thyroid function in the elderly in the United Kingdom. Am J Clin Nutr 2008;87:370–8.
17. Combs GFJ, Midthune DN, Patterson KY, et al. Effects of selenomethionine supplementation on selenium status and thyroid hormone concentrations in healthy adults. Am J Clin Nutr 2009;89:1808–14.
18. Jacobson BE, Lockitch G. Direct determination of selenium in serum by graphite-furnace atomic absorption spectrometry with deuterium background detection and a reduced palladium modifier: age-specific reference ranges. Clin Chem 1988;34:709–14.
19. Thomson CD, Robinson MF, Butler JA, Whanger PD. Long-term supplementation with selenate and selenomethionine: selenium and glutathione peroxidase (EC 1.11.1.19) in blood components of New Zealand women. Br J Nutr 1993;69:577–88.

20. WHO/UNICEF/ICCIDD. Assessment of iodine deficiency disorders and monitoring their elimination: a guide for programme managers. 2nd ed. Geneva, Switzerland: World Health Organization, 2001.
21. Altman DG. Comparability of randomised groups. Statistician 1985;34: 125–36.
22. Schulz KF, Chalmers I, Grimes DA, Altman DG. Assessing the quality of randomization from reports of controlled trials published in obstetrics and gynecology journals. JAMA 1994;272:125–8.
23. Salmond C, Crampton R. NZDep2001 index of deprivation. Wellington, New Zealand: Department of Public Health Wellington School of Medicine and Health Sciences, University of Otago, 2002.
24. Fitzmaurice GM, Laird NM, Ware JH. Applied longitudinal analysis. Hoboken, NJ: Wiley-IEEE, 2004.
25. Brown H, Prescott R. Applied mixed models in medicine. 2nd ed. Chichester, United Kingdom: John Wiley, 2006.
26. WHO/UNICEF/ICCIDD. Indicators for assessing iodine deficiency disorders and their control through salt iodization. Geneva, Switzerland: World Health Organization, 1994.
27. Ravaglia G, Forti P, Maioli F, et al. Blood micronutrient and thyroid hormone concentrations in the oldest-old. J Clin Endocrinol Metab 2000;85:2260–5.
28. Arthur JR, Nicol F, Mitchell JH, Beckett GJ. Selenium and iodine deficiencies and selenoprotein function. Biomed Environ Sci 1997;10:129–35.
29. Olivieri O, Girelli D, Azzini M, et al. Low selenium status in the elderly influences thyroid hormones. Clin Sci 1995;89:637–42.
30. Contempré B, Duale NL, Dumont JE, Ngo B, Diplock AT, Vanderpas J. Effect of selenium supplementation on thyroid hormone metabolism in an iodine and selenium deficient population. Clin Endocrinol (Oxf) 1992;36:579–83.
31. Calomme MR, Vanderpas JB, Francois B, et al. Thyroid function parameters during a selenium repletion/depletion study in phenylketonuric subjects. Experientia 1995;51:1208–15.
32. Behne D, Kyriafopoulos A. Effects of dietary selenium on the tissue concentrations of type 1 iodothyronine 5′-deiodinase and other selenoproteins. Am J Clin Nutr 1993;57(suppl):310S–2S.
33. Arthur JR, Brown KM, Fairweather-Tait SJ, Crews HM. Dietary selenium: why do we need it and how much is enough? Nutr Food Sci 1997;97:225–8.
34. Thomson CD, Rea HM, Robinson MF, Chapman OW. Low blood selenium concentrations and glutathione peroxidase activities in elderly people. Proc Univ Otago Med Sch 1977;55:18–9.
35. Olivieri O, Girelli D, Stanzial AM. Selenium, zinc, and thyroid hormones in healthy subjects. Biol Trace Elem Res 1996;51:31–41.
36. Shahar D, Shai I, Vardi H, Fraser D. Dietary intake and eating patterns of elderly people in Israel: who is at nutritional risk? Eur J Clin Nutr 2003;57:18–25.
37. de Jong N, Green TJ, Skeaff CM, et al. Vitamin B-12 and folate status of New Zealand older women: a cause for concern? Asia Pac J Clin Nutr 2003;12:85–91.
38. Thomson CD, Robinson MF. The changing selenium status of New Zealand residents. Eur J Clin Nutr 1996;50:107–14.
39. Thomson CD, Colls AJ, Conaglen JV, Macormack M, Stiles M, Mann J. Iodine status of New Zealand residents as assessed by urinary iodide excretion and thyroid hormones. Br J Nutr 1997;78:901–12.
40. Skeaff SA, Thomson CD, McLachlan S, Morgen A. Thyroid hormone status of children from the 2002 National Children's Nutrition Survey 2002. Wellington, New Zealand: Ministry of Health, 2005:1–13.
41. van den Briel T, West CE, Hautvast JG, Vulsma T, de Vijilder JJ, Ategbo EA. Serum thyroglobulin and urinary iodine concentration are the most appropriate indicators of iodine status and thyroid function under conditions of increasing iodine supply in schoolchildren in Benin. J Nutr 2001;131:2701–6.
42. Zimmermann MB, Moretti D, Chaouki N, Torresani T. Development of a dried whole-blood spot thyroglobulin assay and its evaluation as an indicator of thyroid status in goitrous children receiving iodized salt. Am J Clin Nutr 2003;77:1453–8.