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Effect of oral iodized oil on thyroid size and thyroid hormone metabolism in children with concurrent selenium and iodine deficiency

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Objectives: To determine the efficacy of oral iodized oil in goitrous children who are both selenium (Se) and iodine deficient; to investigate if Se status modifies the response of iodine deficient, goitrous children to oral supplementation with iodized oil.
Design: A longitudinal intervention trial.
Setting: Two rural villages in the western Côte d'Ivoire.
Subjects: 51 goitrous non-anemic schoolchildren with both iodine and Se deficiency.
Intervention: Each child received an oral dose of 0.4 ml iodized poppyseed oil containing 200 mg of iodine. They were followed for 1 y with measurements of urinary iodine (UI), thyrotropin (TSH), thyroxine (T4), and thyroid volume by ultrasound.
Results: At baseline all children were goitrous and Se deficient; median UI was 29 μg/l and mean serum Se (s.d.) was 14.8 (10.7) μg/l. After receiving iodized oil, thyroid volume decreased significantly *vs* baseline at 10, 15, 30 and 50 weeks ($P < 0.001$). At 50 weeks mean percentage change in thyroid volume from baseline was −46.6% and only five children remained goitrous. Median TSH values at 5, 10, 15, 30 and 50 weeks were reduced significantly ($P < 0.001$) compared to baseline. Among individual children the severity of Se deficiency predicted the degree of response to iodized oil. Baseline serum Se and percentage change in thyroid volume from baseline at 50 weeks were strongly correlated ($r^2 = 0.554$). Baseline Se and percentage decrease in TSH from baseline at 30 weeks were also well-correlated ($r^2 = 0.467$).
Conclusion: Although more severe Se deficiency partially blunts the thyroid response to iodine supplementation, oral iodized oil is an effective method for iodine repletion in goitrous children who are Se deficient.
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Introduction

Iodine deficiency produces a spectrum of disorders—endemic goiter, hypothyroidism, cretinism and congenital anomalies—that are termed the iodine deficiency disorders (IDD; WHO/UNICEF/ICCIDD, 1994). Mild iodine deficiency also impairs intellectual development and can reduce average population cognitive scores by 10–15% (Maberley, 1998). In Western and Central Africa, it is estimated that 250 million people are at risk for IDD and 50 million have goiter (Bailey & Clugston, 1990).

Multiple nutritional and environmental influences contribute to the prevalence and severity of IDD in iodine-deficient areas (Gaitan, 1990; Boyages, 1993). Se is an essential component of the iodothyronine 5′-deiodinases, which convert thyroxin (T_4) to the more biologically active 3,5,3′-triiodothyronine (T_3) (Arthur *et al*, 1999). Glutathione peroxidase (GPX), another Se-containing enzyme, is an important antioxidant in the thyroid gland. In animals, Se deficiency can lower deiodinase activity and adversely affect thyroid metabolism (Beech *et al*, 1995; Beckett *et al*, 1991). In humans, cross-sectional studies have suggested that poor Se nutrition may be associated with impaired thyroid metabolism in iodine-deficient populations (Vanderpas *et al*, 1990; Thilly *et al*, 1993). There are no published data describing the use of oral iodized oil to treat iodine deficiency in children who are both iodine and Se deficient. Also, there have been no published prospective studies describing the influence of Se status on the response to iodine supplementation in iodine deficient populations.

Severe deficiencies of Se and iodine coexist in China, Southeast Asia, Russia, Egypt and Central Africa (Utiger, 1998). In these regions, interactions between Se and iodine deficiency may be important determinants of patterns of disease. In Tibet, where severe Se deficiency is endemic,

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iodine deficiency is a risk factor for Kashin–Beck disease (Moreno-Reyes *et al*, 1998). In rural Zaire, combined iodine and Se deficiency is associated with increased risk for endemic myxoedematous cretinism (Vanderpas *et al*, 1990).

In the mountainous western regions of the Côte d'Ivoire, Se deficiency is common and the prevalence of goiter among school age children approaches 50% (Ministry of Health, 1994). Therefore, the aims of this study were: (a) to determine the efficacy and safety of oral iodized oil in goitrous children who are both Se and iodine deficient; and (b) to investigate if Se status modified the response of iodine-deficient, goitrous children to oral supplementation with iodized oil.

Methods

The study was carried out in two isolated villages (total population = 1450) in an area of endemic goiter in the mountains of the western Côte d'Ivoire (Latapie *et al*, 1981). The villages are 5 km apart and are similar ethnically. The staple foods are rice and cassava. The study was approved by the Ethical Review Board of the University Hospital of Zürich, the National Institute of Public Health and the Ministry of Research of the Côte d'Ivoire. Oral informed consent was obtained from the chiefs of the villages and the families of the subjects.

All children aged 6–15 y in the two villages ($n = 419$) were screened. Weight and height were measured and goiter was graded using WHO criteria (WHO/UNCF/ICCIDD, 1994). Spot urine samples were collected for measurement of Urinary Iodine (UI). Blood was collected by venipuncture for determination of hemoglobin (Hb) and spotted onto filter paper for measurement of whole blood TSH and serum T_4. The complete results of the screening have been described previously (Zimmermann *et al*, 2000).

All 6–12 year old children with Grade 1 goiter and who were not anemic (Hb > 120 g/l) were invited to join an intervention study with oral iodized oil. After a brief physical examination, 53 children were enrolled. Baseline measurements in the morning before administration of the iodized oil included iodine in spot urines, TSH and serum T_4 on blood spotted onto filter paper, serum retinol and serum Se. Thyroid gland volume was measured using an Aloka SSD-500 Echocamera (Aloka, Mure, Japan) with a high-resolution 7.5 MHz linear transducer (DeLange *et al*, 1997).

Each child then received an oral dose of 0.4 ml iodized poppyseed oil (Lipiodol, Guerbet, France) containing 200 mg of iodine. At 1, 5, 10, 15, 30 and 50 weeks post-intervention, spot urines were collected for measurement of UI and dried blood spots for determination of TSA and T_4. At 10, 15, 30 and 50 weeks, thyroid volume was measured using ultrasound. To avoid interobserver variability, all ultrasound measurements were performed by a single investigator (MBZ). At 15 weeks, spot urines were collected for measurement of urinary thiocyanate. At 10, 15, 30 and 50 weeks height and weight were remeasured to account for the potential affect of growth on thyroid volume. Of the 53 children who began the study, 51 completed it.

In countries with a high prevalence of child growth retardation, thyroid volume is considered to be more directly a function of total body surface area (BSA) than of age. Therefore, BSA was calculated from weight and height measurements taken with each ultrasound measurement, and normative values for thyroid volume in children aged 6–12 y according to sex, age and BSA were used to define the presence or absence of goiter (WHO/ICCIDD, 1997).

Blood and urine samples were aliquoted and frozen at −20°C until analysis. UI was measured using a modification of the Sandell–Kolthoff reaction (Pino *et al*, 1996). Serum Se was measured by atomic absorption spectrometry with the Zeeman background correction (Perkin-Elmer Model 4100 ZL, Norwalk, CT) with a limit of sensitivity of 6.5μg/l; undetectable concentrations were assigned a value of 6.5μg Se/l (Van Dael *et al*, 1995). Serum retinol was measured by HPLC (Catignani & Bieri, 1983). Hb was measured using the cyanmethemoglobin method with kits (Sigma Diagnostics, St Louis, USA). Dried blood spots in filter paper were analysed for whole blood TSH and serum T_4 using immunossay (Torresani & Scherz, 1986). Urinary thiocyanate (SCN) was analyzed by a colorimetric method (Bowler, 1944). Normal reference values are: UI, 50–250 μg/l; UI/SCN, > 3 μg/mg (DeLange *et al*, 1983); serum Se, 65–105 μg/l; serum retinol, 0.35–1.75 μmol/l; whole blood TSH, < 3.5 mU/l; serum T_4, 65–165 nmol/l.

Data which were normally distributed were expressed as means (s.d.) and were compared by Student's *t*-test. Parameters not normally distributed (UI, TSH, UI/SCN ratio) were expressed as medians with 95% confidence intervals, and were compared by Mann–Whitney tests. *P*-values were adjusted for multiple comparisons (Bonferroni correction). Multiple regression was used to test for associations.

Results

Baseline characteristics of the subjects are shown in Table 1. There were no visible signs of acute protein-energy malnutrition in any of the subjects and the mean BMI of the children was near the 50th percentile for black children from the US (Must *et al*, 1991). Median UI was 29 μg/l; 20% and 90% of children had UI < 20 μg/l and < 50 μg/l, respectively, indicating moderate to severe iodine

Table 1 Baseline characteristics of the selenium-deficient goitrous children

Characteristic	*Goitrous subjects (n = 51)*
Age (y)	8.6 (1.9)
Gender	23 females, 28 males
Weight (kg)	25.9 (6.2)
Height (cm)	128 (13)
BMI (kg/m^2)	15.8 (1.5)
Hemoglobin (g/l)	125 (4)
Grade 1 goiter (number of subjects)	49
Grade 2 goiter (number of subjects)	2
Median urinary iodine (μg/l)	29 (30–47)
Number of subjects < 20 μg/l(%)	15 (29.4%)
Number of subjects < 50 μg/l(%)	45 (88.2%)
Number of subjects < 100 μg/l(%)	51 (100%)
Whole blood thyrotropin (mU/l)	1.1 (1.1–1.3)
Serum thyroxine (nmol/l)	111 (23)
Thyroid volume (ml)	8.5 (2.0)
Serum retinol (μmol/l)	0.65 (0.39)
Urinary iodine/thiocyanate ratio (μg/mg)	1.9 (1.9–3.5)
Serum selenium (μg/l)	14.8 (10.7)

Values are means (s.d.), with the exception of urinary iodine, thyroptropin, and urinary iodine/thiocyanate ratio, which are presented as medians (95% CI).

deficiency (WHO/UNICEF/ICCIDD, 1994). None of the children showed signs of cretinism. Thyroid volume by ultrasound in all children was above WHO upper limits of normal calculated according to BSA (WHO/ICCIDD, 1997). On inspection, 49 children had Grade 1 goiter and two had Grade 2 goiter. Median whole blood TSH and mean serum total T_4 were within normal ranges. Cassava is one of the staple foods of the western Côte d'Ivoire and the median UI/SCN ratio was low (< 3 μg/mg), indicating increased risk for exacerbation of goiter by thiocyanate (DeLange *et al*, 1983). Mean serum retinol (s.d.) was 0.65 (0.39) μmol/l and 24% of children were vitamin A deficient (< 0.35 μmol/l). All of the children were Se deficient and mean serum Se (s.d.) was only 14.8 (10.7) μg/l. Over 90% had values < 30 μg/l and 22% had values < 6.5 μg/l, the limit of sensitivity of our assay.

Table 2 shows the changes in thyroid volume after receiving the iodized oil. Thyroid volume was decreased significantly *vs* baseline at 10, 15, 30 and 50 weeks ($P < 0.001$). At 15 and 50 weeks the mean percentage change in thyroid volume from baseline was -30.7% and -46.6%, respectively. There was a sharp reduction in goiter prevalence at 10,15, 30 and 50 weeks; at 50 weeks only five children remained goitrous. Table 2 also shows the changes in TSH, T_4 and UI over the 50 weeks of follow-up. UI was significantly increased above baseline at all time points ($P < 0.001$). Median UI at 50 weeks was 97 μg/l, just below the WHO cut-off value (100 μg/l) for risk of IDD (WHO/UNICEF/ICCIDD, 1994). Although baseline and follow-up median TSH and mean serum T_4 were within the normal range, median TSH values at 5, 10, 15, 30 and 50 weeks were reduced significantly ($P < 0.001$) compared to baseline. Mean serum T_4 increased significantly from baseline at 30 weeks ($P < 0.01$).

To test for associations, multiple regression of percentage change in thyroid volume at 30 and 50 weeks on serum Se, serum retinol, UI, UI/SCN ratio and BMI was done. The regression of percentage change in thyroid volume at both 30 and 50 weeks on Se was highly significant ($P < 0.005$). Adding serum retinol, UI, BMI, or UI/SCN ratio did not improve the prediction at either time point. Regression of percentage decrease in TSH at 30 and 50 weeks on serum retinol, serum Se, UI, UI/SCN ratio and BMI was also done. The regression of percentage change on Se was significant at 30 weeks ($P < 0.01$) and at 50 weeks ($P < 0.5$). Adding serum retinol, UI, BMI or UI/SCN ratio did not improve the prediction. Figure 1 shows the strong correlation ($r^2 = 0.554$) between baseline Se and percentage change in thyroid volume at 50 weeks

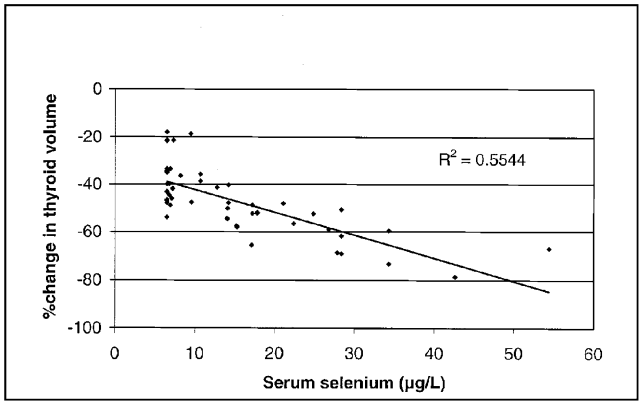

Figure 1 Correlation between serum selenium and percentage change in thyroid volume from baseline at 50 weeks after 200 mg oral iodine in 51 selenium-deficient goitrous children.

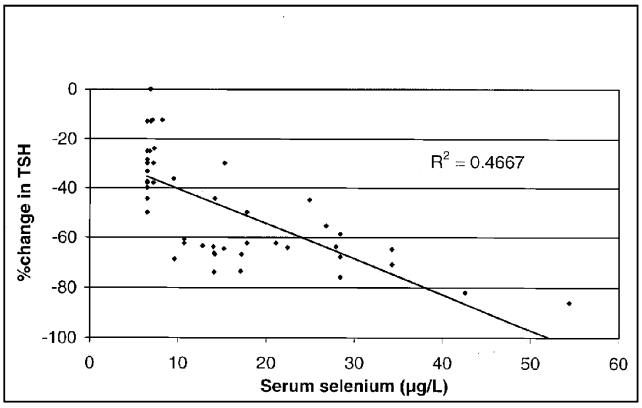

Figure 2 Correlation between serum selenium and percentage change in TSH from baseline at 30 weeks after 200 mg oral iodine in 51 selenium-deficient goitrous children.

after oral iodine. Because the correlation between baseline Se and percentage change in TSH was stronger at 30 weeks than at 50 weeks (although both were significant), we have shown the correlation ($r^2 = 0.467$) at 30 weeks in Figure 2.

Discussion

Selenocysteine has been identified in the active center of the iodothyronine deiodinases, which regulate the formation and degradation of active thyroid hormone, 3,5,3′-triiodothyronine (T_3; Arthur *et al*, 1999). In animals, Se

Table 2 Thyroid volume, percentage change in thyroid volume, prevalence of goiter. TSH, T_4, and UI in selenium-deficient goitrous children ($n = 51$) at baseline and 1, 5, 10, 15, 30 and 50 weeks after receiving 200 mg oral iodine

Week	*Thyroid volume (ml)*	*Percentage change from baseline*	*Prevalence of goiter (%)*	*TSH (mU/l)*	*T_4 (nmol/l)*	*Urinary iodine (μg/l)*
Baseline	8.5 (2.0)		100	1.1 (1.1–1.4)	110 (22)	29 (30–47)
1				1.1 (1.1–1.5)	113 (22)	992** (919–1500)
5				0.6** (0.5–0.7)	115 (21)	281** (262–358)
10	6.5 (1.7)**	− 22.3 (17.3)	56	0.6** (0.5–0.8)	110 (26)	168** (165–231)
15	5.1 (1.5)**	− 30.7 (14.8)	31	0.5** (0.4–0.6)	122 (24)	181** (165–218)
30	4.6 (1.5)**	− 45.5 (12.0)	12	0.6** (0.5–0.6)	156* (30)	125** (115–143)
50	4.3 (1.3)**	− 46.6 (13.1)	10	0.8* (0.7–0.9)	132 (36)	97** (88–120)

Values for TSH and urinary iodine are medians (95%CI). All other values are means (s.d.). *$P < 0.01$ *vs* baseline; **$P < 0.001$ *vs* baseline. Thyroid volume was not measured at 1 and 5 weeks. To reduce the effects of variability among individuals, percentage change from baseline was calculated for each child before deriving means.

deficiency lowers deiodinase activity (Beech *et al*, 1995). In addition, Se deficiency can reduce GPX activity and increase oxidative damage to the thyroid by hydrogen peroxide, which is produced in high amounts in the iodine-deficient thyroid as a result of stimulation by TSH (Corvilain *et al*, 1993). In a study in rats by Beckett *et al*, concurrent Se and iodine deficiency produced a significant increase in both thyroid weight and TSH and a decrease in thyroidal iodine when compared with either single Se or iodine deficiency, suggesting that Se deficiency can exacerbate the hypothyroidism observed in iodine deficiency (Beckett *et al*, 1991).

In humans, cross-sectional studies have demonstrated that poor Se nutrition may be associated with impaired thyroid metabolism. In a study of children and young adults in iodine-deficient areas of Malawi and Zaire, severe Se deficiency was implicated in the high frequency of myxoedematous cretinism in Ubangi, Zaire (Thilly *et al*, 1993). In Egypt, Samir found low levels of serum Se in subjects with multinodular goiter, as well as a weak correlation between serum Se and Serum T_4 and T_3 levels (Samir & el-Awady, 1998). Vanderpas *et al* studied Zairean schoolchildren and cretins in areas of endemic goiter and control areas and found that subjects in the area of endemic goiter had sharply lower serum Se and erythrocyte glutathione peroxidase (RBC-GPX) levels. Low RBC-GPX was associated with increased TSH levels. They concluded that combined iodine and Se deficiency may be associated with the elevated frequency of endemic myxoedematous cretinism in Central Africa (Vanderpas *et al*, 1990).

The severity of Se deficiency in the children in this study is comparable to that described in the most Se deficient areas of Zaire and China (Thilly *et al*, 1993; Moreno-Reyes *et al*, 1998). Despite very low serum Se levels, the children in this study showed a rapid and sustained response to the oral iodized oil. There was a striking reduction in thyroid size and goiter prevalence during the 50 weeks of follow-up. Thyroid size was reduced by nearly half at 30 and 50 weeks and the goiter rate fell to near 10%. This reduction in goiter prevalence is more pronounced than those described by most previous authors (Bautista *et al*, 1982; Zitai, 1983; Eltom *et al*, 1985; Dunn, 1987; Benmiloud *et al*, 1994; Furnée *et al*, 1995), but because of varying conditions in these studies (age of subjects, severity of iodine deficiency, geographic location, ultrasound *vs* palpation for goiter grading, follow-up intervals), it is difficult to compare results. In an area of endemic goiter in the Sudan, 200 mg of iodine as iodized oil reduced goiter prevalence as measured by palpation by 60% at 1 y (Elnager *et al*, 1995). In a study of goitrous adults in Zaire, 118 mg oral iodine reduced thyroid size as measured by a thyroid tracing method by 36% at 3 months and 52% at 1 y (Tonglet *et al*, 1992). In the present study, we used thyroid ultrasonography, a more precise and objective method of measuring goiter size (Vitti *et al*, 1994).

Among individual children the severity of Se deficiency predicted the degree of response to iodized oil. As shown in Figures 1 and 2, the most severely Se deficient children showed a less vigorous response to the intervention. Both an anatomic indicator of response (percentage change in thyroid volume at 30 and 50 weeks) and a biochemical indicator of thyroid function (percentage decrease in TSH at 30 and 50 weeks) were significantly correlated with serum Se at baseline. Thus, although more severe Se deficiency may partially blunt the thyroid response to iodine supplementation, the use of oral iodized oil is a safe and effective method for iodine repletion in goitrous children who are Se deficient.

The present study describes the influence of Se status on the response to iodine supplementation in iodine deficient children. However, Se may be only one of many nutritional influences that influence the pathogenesis of IDD in iodine-deficient areas. We have recently shown that concurrent iron deficiency impairs the response of iodine-deficient, goitrous children to oral iodized oil. In the iron deficient children in that study, Se status was not correlated with response to iodine repletion (Zimmermann *et al*, 2000). In the present study, all of the children had Hb > 120 mg/l. Food goitrogens (Gaitan, 1990) and vitamin A deficiency (Wolde-Gebriel *et al*, 1993) may also adversely affect thyroid metabolism. Although many of the children in this study had low levels of serum retinol and very low UI/SCN ratios, multiple regression indicated that serum Se was the only significant determinant of their response to oral iodized oil.

A limitation of the study design was the use of a single baseline measurement of serum Se as the only measure of Se status in the children. It would have been preferable to have repeated measurements of serum Se during the study and/or functional measures of Se status such as RBC-GPX (Foster & Sumar, 1997). The chiefs and the families of the children involved were reluctant to have blood drawn from the children and so we were unable to do repeated venipuncture. However, in this region, dietary supply of Se probably varies only minimally throughout the year due to the consumption of a fairly monotonous diet consisting mainly of cassava and rice.

In these goitrous, Se-deficient children, there were no apparent adverse effects from the 200 mg oral dose of iodine. None of the children showed signs of iodine induced hyper- or hypothyroidism or other adverse effects. Studies in Zaire have shown that correcting Se deficiency before improving iodine status of hypothyroid iodine- and Se-deficient subjects can aggravate hypothyroidism (Contempre *et al*, 1991). Therefore, it is important to correct iodine deficiency first and, based on the results of this study, the use of iodized oil appears to be safe and effective in children who are both iodine and Se deficient.

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