Goiter Persistence After Iodine Replenishment, the Potential Role of Selenium Deficiency in Goitrous Schoolchildren of Semirom, Iran

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Key words
- selenium
- goiter
- selenoproteins
- thyroid
- cretinism

Abstract

Background: Despite long-standing iodine supplementation in Iran, the prevalence of goiter remains high in some areas. This suggests other nutritional deficiencies may be considered as responsible factors of goiter persistence. Therefore, we assessed the prevalence of selenium deficiency in children living in a mountainous area in Iran to evaluate its correlation with goiter.

Methods: In this cross-sectional study, 1828 students from the 108 primary schools of urban and rural areas of Semirom in central Iran were selected by multistage random cluster sampling. After obtaining written consent from their parents, the children were examined for goiter grading. Grade 2 goitrous children (108 cases) were compared with non-goitrous children (111 children) as control group for serum selenium concentration.

Results: Overall, 36.7% of 1828 students had goiter. The mean and median urinary iodine excretion level was 19.3 and 18.5 μg/dl respectively. This was within normal limits. Of 219 evaluated cases, 109 children had selenium deficiency. Mean serum levels of selenium in the goitrous and control groups were 62.7 μg/l and 60.8 μg/l, respectively (p=0.42). There was a borderline significant difference of the goiter prevalence in selenium deficient and selenium sufficient subjects (40.8% vs. 54.3%, p=0.037). Twelve children had clinical or subclinical hypothyroidism. The mean (SD) serum selenium concentration of euthyroid and hypothyroid students were 61.9 (17.2) μg/l and 66.4 (11.9) μg/l respectively (p=0.35).

Conclusion: In the area studied, selenium deficiency cannot explain high prevalence of goiter and other responsible factors should be investigated. Selenium deficiency may also have mild borderline significant protective effects on thyroid function and goiter.

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Introduction

It is estimated that 750 million people worldwide are at risk of iodine deficiency disorders (IDDs); endemic goiter, hypothyroidism, endemic cretinism, and congenital anomalies (World Health Organization, 2001; WHO, 1994). Within populations with severe endemic iodine deficiencies, higher percentages of mental retardation occur. This complication of iodine deficiency is called endemic cretinism with two characteristic forms of myxedematous and neurological cretins. The former shows, aside from mental retardation, signs of severe hypothyroidism without goiter, and the later exhibits goiter without signs of hypothyroidism.

On the other hand in iodine-deficient areas, multiple nutritional factors, including goitrogenic foods, protein-energy malnutrition, and micronutrient deficiencies, may influence the prevalence and severity of IDDs and modify the response to iodine supplementation (Boyages, 1993; Furnee, 1997; Zimmermann et al., 2000c).

In Iran, all salt preparations have been iodized since 1988. Production of uniodized house salt have also been forbidden by legislation since 1994, and thereafter frequent regular evaluations of salt (at factory, store and house levels) and also urine iodine by provincial organization and local officials of health have confirmed adequate iodine intake (Azizi and Mehran, 2004).

This study was performed in 2003, in Semirom, a mountainous region in the central area of Iran, where goiter was endemic with a prevalence of about 89.5% estimated in 1994. Besides salt iodization since 1988, in 1993, all citizens of Semirom were given a single dose of intramuscular injection of 480 mg iodized oil.

Table 1 Baseline data of the participants

		Age (mean ± SD)	non goitrous n (%)	goiter stage1 n (%)	goiter stage2 n (%)	Total n (%)
	male	9.3 ± 1.0	643 (65.0%)	289 (29.2%)	57 (5.8%)	989 (100.0%)
sex	female	9.3 ± 1.0	515 (61.4%)	266 (31.7%)	58 (6.9%)	839 (100.0%)
	total	9.3 ± 1.0	1158 (63.3%)	555 (30.4%)	115 (6.3%)	1828 (100.0%)

Because the goiter prevalence was not decreased as expected (less than 5% till 2000) many years after iodine injection and salt iodization described above, an important question emerged: which factors other than iodine deficiency are responsible for persistence of goiter in that area? We performed this study to evaluate these probable factors. Multiple risk factors like thiocyanate, iron (Siavash et al., 2006), vitamin A, autoimmunity (Hashemipour et al., 2007), and zinc were evaluated.

One of the trace elements that can potentially influence IDDs is selenium (Aydin et al., 2002; Contempre et al., 1995).Animal and human studies suggest that selenium deficiency impairs thyroid hormone metabolism (Corvilain et al., 1993; Fordyce et al., 2000; Hou et al., 2004). By decreasing intracellular glutathione peroxidase (GPx) activity, selenium deficiency may increase hydrogen peroxide (H_2O_2) supply and lead over several weeks to the thyroid atrophy observed in myxoedematous cretins. On the other hand, by improving thyroid hormone synthesis and by decreasing peripheral thyroxine (T4) deiodination, selenium deficiency could protect fetal brain T4 supply and thus prevent neurologic cretinism. Selenium deficiency may protect against iodine deficiency by decreasing T4 metabolism and thus iodide leakage and, perhaps also by increasing H_2O_2 supply and thyroid hormone synthesis and thus thyroid efficiency (Kohrle et al., 2005). Here we present the results of selenium evaluation in Semirom and discuss its potential roles in goiter and thyroid function.

Material and Methods

This was a cross sectional, descriptive study performed on schoolchildren of Semirom.

108 Elementary schools with 4773 students were considered as primary sampling units.79 schools were from rural areas with 2449 students (1247 male and 1202 female), and 29 schools from urban areas with 2324 students (1126 male and 1198 female). Subjects were enrolled with a multistage cluster sampling procedure and then, appropriate numbers of children were sampled randomly within selected clusters. Written consent was obtained from parents of children before inclusion.

We excluded subjects with history of exposure to radioactive iodine, thyroid surgery or significant underlying disease such as cardiopulmonary, liver or renal problems. Information for exclusion was collected based on available medical records of students and interviews with parents, teachers and participants.

We examined all children and goiter grading was performed according to WHO classification in three groups (World Health Organization, 2001). To evaluate responsible factors for goiter, grade two goitrous children were compared with equal number of randomly selected children from control group for serum selenium, thiocyanate, thyroxine (T4), thyroid-stimulating hormone (TSH) and urine iodine.

The blood samples were transported on dry ice to reference laboratory of endocrine and metabolism research center. The samples were stored in the freezer at −70 °C until analysis. The same person and method performed each assay.

Urine iodine concentration (UIC) was measured by digestion method on the spot urine samples, based on a modification of Sandell-Kolthoff reaction (Pino et al., 1996; World Health Organization, 2001) (Intra-assay CV 1.2% and inter-assay CV 2.2%). Measures less than 10 μg/dl were considered as iodine deficiency (World Health Organization, 2001).

Serum T4 concentrations were measured with radio- immunoassay (RIA) by Iran kavoshyar kits (Intra-assay CV 4.7% and inter-assay CV 4.9%). Serum TSH concentrations were measured with IRMA by Iran kavoshyar kits (Intra-assay CV 1.5% and inter-assay CV 1.9%). The normal range of T4 was 4.5 −12 μg/dl and for TSH was 0.3–3.9 mU/l. Plasma selenium was measured by atomic absorption. Levels less than 61 μg/l was considered selenium deficiency. As we did not have normal selenium levels for the study population, we considered this level based on more than two SDs below mean for normal healthy children living in Tehran (central of Iran) in a recent study (Safaralizadeh et al., 2005).

Statistical analysis

Variables with normal distribution (serum selenium level) are presented as mean ± SD. Goiter and selenium deficiency prevalence between groups were compared by chi-square test. We also divided participants into four groups based on serum selenium levels and compared different variables between them by ANOVA.

P-values less than 0.05 were considered statistically significant. Analyses were performed with SPSS statistical package version 11.5.

The study was approved by the ethics committee of Goiter Research Center affiliated to Isfahan University of Medical Sciences. Written permission was taken from the Provincial Organization of Education. At Semirom, local official of health and education accompanied us.

Results

A total of 1828 school children (879 from urban and 949 from rural areas) were enrolled in this study with male to female ratio of 1.18 and age of 7 to 13 (mean ± SD:9.3 ± 1.0 years) (**Table 1**). Of these, 1158 were classified as goiter grade 0 (63.3%), 555 had goiter grade 1 (30.4%) and 115 had goiter grade 2 (6.3%) with total goiter prevalence of about 36%. The mean (SD) and median urinary iodine excretion level was 19.3 (9.1) and 18.5 μg/dl respectively. Mild (UIC < 10 μg/dl) and moderate (UIC < 5 μg/dl) iodine deficiency was detected in 6.4% and 3.2% of cases, respectively. Only 1.8% of children were severely iodine deficient (UIC < 2 μg/dl). Of 115 grade two goitrous students, 108 children as well as 111 of randomly selected children from control group agreed to enrolment in this sub-study of selenium evaluation.

Mean serum levels of selenium in the goitrous and control groups were 62.7 μg/l and 60.8 μg/l, respectively (p = 0.42). There

Table 2 Serum levels of different variables in selenium deficient and sufficient subjects

	Zinc μg/dl	Selenium μg/l	Ferritin ng/ml	Vitamin A μg/dl	TSH mU/l	T4 μg/dl	TPO Ab IU/ml	TG Ab IU/ml	Thiocyanate mg/dl	Iodine μg/dl
selenium deficient	82.9 (1.8)	48.2 (0.96)	31.8 (1.8)	38.4 (1)	2.6 (0.1)	9.1 (0.16)	68 (38)	132 (69)	0.6 (0.06)	20.1 (1.4)
selenium adequate	83.4 (1.5)	75.5 (1.0)	31.1 (1.7)	39.4 (1.0)	2.9 (0.3)	8.8 (0.15)	45 (30)	45 (16)	0.6 (0.1)	18.4 (1.6)
P	ns	<0.001	ns	ns	ns	ns	ns	ns	ns	ns

Data reported as mean (SE), ns, non significant

Table 3 Serum levels of different variables based on serum selenium concentration

Selenium Groups	Zinc μg/dl	Selenium μg/l	Ferritin ng/ml	Vitamin A μg/dl	TSH mU/l	T4 μg/dl	TPO Ab IU/ml	TG Ab IU/ml	Thiocyanate μg/dl	Iodine μg/dl
0 Se ≤61	82.9 (18.4)	48.2 (10.1)	31.8 (18.8)	38.5 (10.5)	2.9 (1.5)	9.1 (1.6)	68 (397)	131 (718)	0.6 (0.4)	20.1 (9.2)
1 62>Se≤73	83.7 (14.6)	67.7 (3.1)	32.8 (18.7)	40.0 (12.1)	3.1 (3.3)	8.9 (1.6)	9 (27)	47 (219)	0.5 (0.2)	17.6 (9.8)
2 74>Se≤95	83.5 (17.7)	81.3 (5.9)	29.9 (16.6)	38.4 (9.8)	2.7 (1.7)	8.7 (1.3)	96 (496)	48 (114)	0.7 (0.4)	19.1 (11.2)
3 Se >95	80.2 (6.2)	101.5 (5.6)	24.6 (12.9)	40.8 (8.6)	2.6 (1.2)	8.7 (1.6)	10 (10)	9 (6)	0.8 (0.4)	19.8 (8.1)
P	ns	0.001	ns	ns	ns	ns	ns	ns	ns	ns

Data reported as mean (SE), ns, non significant

were not any correlation between serum selenium concentration and baseline data of the patients including height, weight, BMI and age.

Twelve children had clinical or subclinical hypothyroidism. The mean (SD) serum selenium concentration of euthyroid and hypothyroid students were 61.9 (17.2) μg/l and 66.4 (11.9) μg/l respectively (p=0.35).

Based on the serum level of selenium, the subjects were divided in two groups, those with selenium deficiency (109 children) and those who were selenium sufficient (110 children). There was a borderline significant difference of the goiter prevalence in selenium deficient and selenium sufficient subjects (40.8% vs. 54.3%, p=0.037).There was no significant difference in the serum zinc, ferritin, vitamin A,TSH,T4, antiTPO Ab and antiTg Ab, thiocyanate and urinary iodine between subjects with selenium deficiency and those who were selenium sufficient (**Table 2**), although a trend to higher antibodies in selenium deficient group is visible. We further divided participants to four groups based on SD serum selenium concentration (**Table 3**). Here the results were similar to the above, but the p values were toward less significance. The prevalence of selenium deficiency was not significantly different between males and females (53% vs. 45.6%, p=0.17).

Students aged 10 or more, who had received i.m. injection of iodized oil 10 years earlier, had higher concentrations of serum anti thyroid antibodies (93.0 versus 27.4 for anti TPO, p=0.184 and 145.0 versus 41.6 for anti Tg, p=0.148).

Thiocyanate levels were normal in all students except one with mild elevation (5.14 mg/dl).

Discussion

As stated, this study shows that goiter prevalence has decreased from 89.55% in 1994 to about 36% in 2003. This implies iodine deficiency has been the most important cause of endemic goiter in the area and shows the effective role of single intramuscular injection of iodized oil and also salt iodization in decreasing goiter rate. However, Semirom is still considered an endemic region of goiter and despite the salt iodization program and iodized oil injection, goiter rate is still high in this area.

Although manual goiter palpation technique yields sufficiently precise quantitative results for clinical purposes (Nordmeyer et al., 1997) it has some limitations. While goiter rate remains high after iodine supplementation, sonography may reveal significant changes in thyroid volume (Todd and Dunn, 1998; Zimmermann et al., 2004a). Previous studies indicated that measurement of goiters by palpation may not be appropriate in short-term evaluation of iodization programs, but for long-term follow-up it can be reliable (Jooste et al., 2000). However, even if our assessment of response to iodine replenishment is not adequately sensitive, the high prevalence of goiter in the area studied is undeniable. Although iodine deficiency is present in mild to moderate degrees, it cannot truly explain the yet high prevalence of goiter. Other explanations for this unexpected high goiter rate are the role of unknown goitrogens (Muros et al., 1992), autoimmunity (Kabelitz et al., 2003), or other micronutrient deficiencies (Florentino et al., 1996; Ingenbleek and De Visscher, 1979; Keyvani et al., 1988; Untoro et al., 1999; Wolde-Gebriel et al., 1993; Zimmermann et al., 2004b). Selenium deficiency is one of the suspected candidates (Brauer et al., 2006; Beard et al., 1998; Zimmermann et al., 2000b).

Our study reveals that selenium deficiency is quite prevalent in the area affecting near to 50% of the participants.

Berzelius discovered selenium, an essential trace element as early as 1817.

It is incorporated into an atypical amino acid named selenocysteine to make selenoproteins, which are important antioxidant enzymes, help regulate thyroid function and play a role in the immune system. Plant foods were the major dietary sources

of selenium. The content of selenium in food depends on the selenium content of the soil where plants are grown or animals are raised. Today the main human selenium source in the areas with lower soil selenium, beside seafood, originates from the animal foods like red meat, chicken and eggs, as in many parts of the world, animal livestock is supplemented with minerals and trace elements, especially also selenium, in order to improve their health status, reproduction and growth.

The first discovered mammalian selenoprotein was the cytosolic glutathione peroxidase (GPx) and its family.D1 was the first member of a second group of selenoproteins, the iodothyronine deiodinases. Recently, another selenium containing enzyme family of three members, the mammalian thioredoxin reductases was identified.

Three specific diseases have been associated with selenium deficiency:

- Keshan Disease, with enlarged heart and poor heart function, in selenium deficient children
- Kashin-Beck Disease, which results in osteoarthropathy.
- Myxedematous Endemic Cretinism, which results in mental retardation.

Selenium affects thyroid physiology at least by two mechanisms of antioxidation and deiodinase activity. The thyroid gland, which produces H_2O_2 for thyroid hormone synthesis, is exposed to free radical damage if H_2O_2 is not properly reduced to H_2O by intracellular defense mechanisms or during the hormone synthesis process (Farber et al., 1990). Protection against H_2O_2 and resulting free radicals entails vitamins C and E and enzymes such as catalase, superoxide dismutase, and selenium -containing enzymes. GPx and other selenium dependent enzymes are present in the thyroid and involved in antioxidant defenses (Rotruck et al., 1973; Howie et al., 1998; Behne and Kyriakopoulos, 1993; Kohrle, 1999; Kohrle, 2005).Thus, iodine deficiency increases H_2O_2 generation, whereas selenium deficiency decreases H_2O_2 disposal,. selenium deficiency also increases the sensitivity of the thyroid gland to necrosis caused by iodide overload in iodine-deficient thyroid glands (Contempre et al., 1993; Mahmoud et al., 1986; Many et al., 1986; Many et al., 1992) especially if associated by thiocyanate overload (Contempre et al., 2004). Se deficiency increases the inflammatory reaction initiated by iodide overload that then evolves to fibrosis, whereas the non- selenium deficient thyroid exhibits no fibrosis (Contempre et al., 1995). The association of three factors, i.e., iodine and selenium deficiencies plus thiocyanate overload, mimics in rats the phenotype of Central Africa myxedematous cretinism (Contempre et al., 2004).

All three iodothyronine deiodinases are selenoenzymes, and Type I (D1) is the most abundant and best characterized of the three deiodinases. D1 is extensively expressed in the liver, kidney, thyroid, and pituitary of adult higher mammals (Baur et al., 2002; Kohrle, 2002). Selenium deficiency decreases activities of the type I and II enzymes. Correction of the iodine and selenium deficiencies appears the logical prevention strategy in endemic myxedematous cretinism, but correcting the selenium deficiency first would be an inappropriate strategy, because it induces T_4 deiodination and consequently increases loss of inadequate iodine, which worsens the hypothyroidism and might lead to catastrophic thyroid failure (Contempre et al., 1992).

The protective role of selenium deficiency on decreasing goiter prevalence in Semirom may represent the first mechanism. In this regard, thyroid fibrosis may be a consequence of decreased antioxidant potency of selenium deficient patients. If this is the case, their lower TSH and higher T4 can hardly be explained. Normal thiocyanate in the area also makes this mechanism less likely, as in animal and human studies, selenium deficiency has resulted in thyroid fibrosis only on the presence of thiocyanate excess (Kohrle et al., 2005).

Lower TSH and higher T4 in selenium deficient students, and also higher selenium concentration in the hypothyroid children, although not significant statistically, may represent the second mechanism. In this regard, selenium deficiency may be a protective factor against iodine loss and hypothyroidism. By this mechanism, observed in animal studies, selenium deficient patients may also be at risk of iodine overload after i.m. iodized oil injection. This iodine overload is by itself a risk factor for autoimmune thyroid disease as observed also in our participants.

An interesting finding in our study is higher serum concentrations of TPO and Tg antibodies in selenium deficient children compared to normal participants. Although not statistically significant, it is in accordant to recent findings that selenium deficiency may be a risk factor for autoimmune thyroid disease and its supplementation may be of value for prevention and also treatment of that (Duntas, 2006; Woenckhaus and Girlich, 2005).

Altogether, it seems that factors other than iodine and selenium deficiency may be, at least partly, responsible for high prevalence of goiter in Semirom. These include protein-energy malnutrition (Pathak et al., 2003; Zimmermann et al., 2000a),Vitamin A (Keyvani et al., 1988; Mesaros-Kanjski et al., 1999; Zimmermann et al., 2004b), and Zn deficiencies (Zhang et al., 2004; Zimmermann and Kohrle, 2002) or autoimmunity (Hashemipour et al., 2007; Kabelitz et al., 2003).

Further investigations for evaluating other micronutrient deficiencies and autoimmunity in goitrous children would contribute to plan more effective goiter control programs. Assessment of change in thyroid size of goitrous children by ultrasound, even in a part of evaluated subjects, gives more accurate and valuable data for future planning.

In conclusion, the present study reveals that in the area studied, selenium deficiency, although prevalent, cannot explain high prevalence of goiter, and other responsible factors should be investigated. Selenium deficiency may also have mild borderline significant protective effect on thyroid function and goiter.

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