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Selenium Deficiency as a Possible Contributor of Goiter in Schoolchildren of Isfahan, Iran

Ammar H. Keshteli · Mahin Hashemipour · Mansour Siavash · Masoud Amini

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Abstract The prevalence of goiter still remains high in some areas of Iran in spite of iodine supplementation. In the present study, we investigated the role of selenium (Se) deficiency in the etiology of goiter in Isfahan. Two thousand three hundred thirty-one schoolchildren were selected by multistage random sampling. Thyroid size was estimated in each child by inspection and palpation. Urinary iodine concentration (UIC) and plasma Se were measured. Overall, 32.9% of the 2,331 children had goiter. The median UIC was 19.55 μg/dl. Plasma Se was measured in 96 goitrous and 72 nongoitrous children. The mean±SD of plasma Se in goitrous and nongoitrous children was 66.86±21.82 and 76.67±23.33 μg/l, respectively (P=0.006). Goitrous girls had lower plasma Se level than nongoitrous girls (65.62±21.64 vs. 76.51±22.61 μg/dl, P=0.02). Goitrous boys had lower plasma Se level than nongoitrous boys (68.45±22.21 vs. 76.91±24.76 μg/l, P=0.14). The prevalence of Se deficiency was significantly higher in goitrous boys and girls than nongoitrous children. Se deficiency is among the contributors of goiter in Isfahan goitrous schoolchildren. However, the role of other micronutrient deficiencies or goitrogens should be investigated in this region.

Keywords Goiter · Selenium deficiency · Iodine deficiency · Iran

Introduction

Iodine deficiency disorders (IDDs) are still a major health problem estimated to affect 750 million people worldwide [1]. The spectrum of these disorders includes endemic goiter, hypothyroidism, endemic cretinism, and other congenital anomalies [2].

A. H. Keshteli
Medical Students Research Center, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

A. H. Keshteli · M. Hashemipour (✉) · M. Siavash · M. Amini
Isfahan Endocrine and Metabolism Research Center, Seddigheh Tahereh Research Complex, Isfahan University of Medical Sciences, Khorram street, Isfahan, Iran
e-mail: hashemipour@med.mui.ac.ir

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.

Selenium (Se) is one of the trace elements that can potentially influence IDDs [3]. Animal and human studies suggest that Se deficiency impairs thyroid hormone metabolism [4, 5]. Se deficiency may protect against iodine deficiency (ID) 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 [6]. Conflicting data exist on the possible role of Se status in goiter [7]. While Se deficiency was mentioned as a cause of goiter in schoolchildren of Iran [8] and Turkey [3, 9], other studies did not find any correlation between Se status and goiter [7, 10].

Endemic goiter was present in most part of Iran [11], and for several years, ID was considered a contributing factor for endemic goiter in this country [12]. Iran's National Committee for Control of IDD was initiated in 1989 by the order of the Minister of Health and Medical Education. The production and distribution of iodized salt, with 40 mg of potassium iodide per kilogram of sodium chloride, began and the education of policy-makers, health personnel, and public initiated in 1990. However, rapid survey of iodized salt consumption showed that less than 50% of the population consumed iodized salt in 1993 with mean urinary iodine concentration (UIC) of 5.0 to 8.2 μg/dl. Therefore, the first law requiring the mandatory iodization of all salts for household use was proclaimed in 1994 [13]. Isfahan is a city in the central part of Iran with an approximate population of 2,000,000. The prevalence of goiter in Isfahan had been estimated to be 92% in girls and 85% in boys in 1989 [14]. According to another study that was conducted in 1997, the prevalence of goiter among 6–18 year-old children in Isfahan was estimated to be 62% [15].

The present study was carried out to estimate the goiter prevalence and iodine status and investigate the role of Se status as a possible contributor of endemic goiter in Isfahan schoolchildren, 15 years after the initiation of salt iodization program.

Methods and Materials

This was a cross-sectional study performed on schoolchildren of Isfahan in 2005. Subjects were enrolled with a multistage cluster random sampling. We excluded subjects with a history of exposure to radioactive iodine, thyroid surgery, or significant underlying disease such as cardiopulmonary, liver, or renal problems based on available medical records and interviewing with parents and teachers.

Body mass index (BMI) was calculated using the following formula: BMI=weight (kg)/height $(m)^2$. Body surface area (BSA) was calculated by the formula: weight $(kg)^{0.425} \times$ height $(cm)^{0.725} \times 71.84 \times 10^{-4}$.

Goiter grading was performed by two endocrinologists according to WHO/UNICEF/ICCIDD classification [1]:

Grade 0: No palpable or visible goiter
Grade 1: A goiter that is palpable but not visible when the neck is in the normal position, (i.e., the thyroid is not visibly enlarged)
Grade 2: A swelling in the neck that is clearly visible when the neck is in a normal position and is consistent with an enlarged thyroid when the neck is palpated.

The blood samples were transported on dry ice to the reference laboratory of the Isfahan Endocrine and Metabolism Research Center. The samples were stored at −70°C until analysis. All urine and blood assays were performed within a median of 26 h of sampling. The same person performed each assay using the same method.

UIC was measured by the digestion method based on a modification of Sandell–Kolthoff reaction [1, 12].

Serum T4 was measured with radioimmunoassay (Iran Kavoshyar Co., Tehran, Iran). Serum thyroid-stimulating hormone (TSH) concentration was measured using immunoradiometric assay (Iran Kavoshyar Co., Tehran, Iran). The normal range of T4 was 4.5–12 μg/dl and for TSH was 0.3–3.9 mU/l.

Serum anti-thyroglobulin antibody (anti-Tg Ab) and anti-thyroperoxidase antibody (anti-TPO Ab) were measured by rapid enzyme-linked immunosorbent assay (Genesis Diagnostics, Littleport, UK).

Plasma Se was measured by atomic absorption method. Se deficiency was defined as plasma Se less than 80 μg/l [8].

Quantitative variables are presented as mean±SD. Normality of data distribution was assessed with Kolmogorov–Smirnov test. Independent sample *t* test and one-way analysis of variance were used to compare measurements in different groups. Parameters not normally distributed were compared by Mann–Whitney test. Prevalence of Se deficiency between goitrous and normal children was compared by chi-square test. Pearson correlation was used to find correlation between Se and different quantitative variables. *P* value less than 0.05 was considered statistically significant. All analysis was performed by using SPSS version 15 (SPPS Corp., Chicago, IL, USA).

Written consent was obtained from all children's parents who were informed about the study. The study was approved by the ethics committee of the Isfahan Endocrine and Metabolism Research Center.

Results

Two thousand three hundred thirty-one schoolchildren were enrolled in this study, with female to male ratio of 1.60. Their age ranged from 6 to13 years. The mean age±SD was 9.39±1.18 for girls and 9.47±1.12 for boys. Thirty-two and nine tenths of subjects were classified as goitrous (Table 1). Goiter prevalence among girls was 32.4%, while 33.7% of boys were goitrous (*P*=0.51).

UIC was measured in 454 schoolchildren. The mean±SD and median UIC was 220.66±17.33 and 195.50 μg/l, respectively. Of the total samples, 15.8% had iodine excretion level below 100 μg/l, and 3.7% had iodine level below 50 μg/l. Of the subjects, 25.6% had UIC between 200 and 300 μg/l and 23.8% had UIC more than 300 μg/l. UIC in goitrous and nongoitrous children was 220.91±119.44 and 220.16±114.64 μg/l, respectively (*P*=0.57).

Table 1 Thyroid Size Determined by Inspection and Palpation in Schoolchildren of Isfahan, Iran

	Number of subjects	Thyroid size		
		Grade 0 (%)	Grade 1 (%)	Grade 2 (%)
Boys	898	66.3	27.3	6.4
Girls	1,433	67.6	29.0	3.4
All	2,331	67.1	28.3	4.6

The mean±SD of UIC in goitrous and nongoitrous boys was 215.70±118.02 and 223.92±127.09 μg/l, respectively (P=0.66). UIC in goitrous and nongoitrous girls was 223.68±112.49 and 218.33±112.85 μg/l, respectively (P=0.72).

Table 2 shows Se status in the study participants. Plasma Se was measured in 96 goitrous (42 boys and 54 girls) and 72 nongoitrous children (29 boys and 43 girls) as the control group. The mean±SD of plasma Se in goitrous and nongoitrous children was 66.86±21.82 and 76.67±23.33 μg/l, respectively (P=0.006). Se level in goitrous and nongoitrous boys was 68.45±22.21 and 76.91±24.76 μg/l, respectively (P=0.14). Plasma Se level in goitrous and nongoitrous girls was 65.62±21.64 and 76.51±22.61 μg/dl, respectively (P=0.02).

The prevalence of Se deficiency in goitrous and nongoitrous children was 75.0% and 51.4%, respectively (odds ratio, 2.84; 95% CI, 1.48–5.45, P=0.002). While 71.4% of goitrous boys had Se deficiency, 48.3% of nongoitrous boys were Se-deficient (odds ratio, 2.68; 95% CI, 1.00–7.20, P=0.05). The prevalence of Se deficiency in goitrous and nongoitrous girls was 77.8% and 53.5%, respectively (odds ratio, 3.04; 95% CI, 1.26–7.32, P=0.01).

There was no statistically significant difference between the mean serum TSH, T4, anti-Tg Ab, anti-TPO Ab, and UIC in subjects with and without Se deficiency (Table 3)

There was also no significant difference between these parameters in different Se concentration quartiles (Table 4).

In children whom Se was measured, there were 25 subjects (14.9%) with subclinical hypothyroidism.

In goitrous children, Se level was reversely correlated with age (r=−0.24, P=0.02), BMI (r=−0.20, P=0.05) and BSA (r=−0.26, P=0.01) and was positively correlated with T4 (r=0.22, P=0.03).

Discussion

According to the present study, goiter prevalence in Isfahan has decreased from about 89% in 1989 [12] and 62% in 1997 [16] to 32.9% in 2005. This implies that ID has been the most important cause of endemic goiter and also shows the effective role of the legislation and salt iodization in treating goiter. However, goiter is still endemic in this iodine-replenished area and a severe public health problem according to WHO/UNICEF/ICCIDD recommended criteria [1].

According to WHO/UNICEF/ICCIDD recommended criteria, the indicator of ID elimination is a median value for UIC of 100 μg/l, and UIC should not be below 50 μg/l in more than 20% of samples [1]. In the studied population, the median UIC was 195.50 μg/l, and 3.7% of the population had UIC below 50 μg/l. It means that there is no biochemical ID or inadequacy in iodine intake of the overall population. According to WHO/UNICEF/

Table 2 Plasma Selenium (Se) Concentration and Se Deficiency Status in Goitrous and Nongoitrous Schoolchildren of Isfahan, Iran

		Goitrous	Nongoitrous	P value
Plasma Se (μg/l)	Boys	68.45±22.21	76.91±24.76	0.14
	Girls	65.62±21.64	76.51±22.61	0.02
Se deficiency (percent)	Boys	71.4	48.3	0.05
	Girls	77.8	53.5	0.01

Table 3 Serum Levels of Different Variables in Children with and without Selenium Deficiency in Isfahan

	TSH (mU/l)	T4 (μg/dl)	anti-TPO Ab (IU/mL)	anti-Tg Ab (IU/mL)	UIC (μg/l)
Selenium deficient	3.28±4.70	8.58±1.32	38.27±132.93	85.36±430.26	224.46±122.93
Selenium sufficient	2.55±1.41	8.98±1.56	34.38±95.96	29.72±92.17	218.70±118.19
P value	ns	ns	ns	ns	ns

ICCIDD criteria, 25.6% of subjects in our study had iodine intake more than adequate and 23.8% had excessive iodine intake. This indicates the risk of iodine-induced hyperthyroidism [1] or other harmful effects. We suggest evaluating the iodine content of salt in this region.

While the iodine status is normal and satisfactory, other environmental and genetic factors should be evaluated to explain the residual goiter prevalence [8]. In the present study, we found a relationship between Se deficiency and goiter in schoolchildren of Isfahan.

Se is a trace mineral with a role in multiple biologic functions. It is the second essential trace element for thyroid function [16]. Se 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 [17]. Protection against H_2O_2 and resulting free radicals entails vitamins C and E and enzymes such as catalase, superoxide dismutase, and Se-containing enzymes. Glutathione peroxidase and other Se-dependent enzymes are present in the thyroid and involved in antioxidant defenses [18–21]. Thus, ID increases H_2O_2 generation, whereas Se deficiency decreases H_2O_2 disposal.

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 [22, 23]. Se deficiency decreases activities of types I and II enzymes. Correction of the iodine and Se deficiencies appears the logical prevention strategy in endemic myxedematous cretinism, but correcting the Se deficiency first would be an inappropriate strategy because it induces T4 deiodination and consequently increases loss of inadequate iodine, which worsens the hypothyroidism and might lead to catastrophic thyroid failure [24]

Beckett et al. [25] showed increased thyroid weight in rats with concurrent iodine and Se deficiency in comparison with rats fed with ID diet. There are a few studies about the role of Se status in thyroid function in humans. Decreased Se concentration was observed in hyperthyroid patients within a Se-deficient population [26].

Table 4 Different Variables Concentration Based on Quartiles of Plasma Selenium in Schoolchildren of Isfahan

Plasma selenium (Se) concentration (μg/l)	TSH (mU/l)	T4 (μg/dl)	anti-Tg Ab (IU/mL)	anti-TPO Ab (IU/mL)	UIC (μg/l)
Se≤55.5	2.92±1.62	8.51±1.41	64.40±208.65	30.92±76.08	210.16±119.26
55.5<Se≤69	3.65±7.10	8.45±1.32	139.20±646.25	23.88±100.56	213.98±123.03
69<Se≤89.75	2.80±1.59	9.12±1.07	29.66±92.10	63.86±184.50	240.22±109.94
Se>89.75	2.65±1.40	8.82±1.72	24.75±75.12	31.12±100.43	220.05±126.57
P value	ns	ns	ns	ns	ns

In the present study, goitrous subjects had significant lower Se levels than nongoitrous ones. This is in agreement with previous studies in Turkey [3, 9], Poland [27], and Iran [8]. Derumeaux et al. [28] also showed that Se was inversely related to thyroid volume and risk of goiter in French women with mild ID and low prevalence of Se deficiency. However, they did not find similar such association in men.

Brauer et al. [7] showed a higher urinary Se excretion in probands with goiter in comparison with subjects with normal thyroid volume in a population with borderline iodine sufficiency. However, they concluded that that finding was a coincidence and urinary Se was not an independent risk factor for the development of goiter. To the best of our knowledge, two previous studies were performed in Iranian population to determine the role of Se in the high prevalence of goiter. Dabbaghmanesh et al. [8] showed that Se concentration was significantly lower in goitrous children, and there was modest impairment of peripheral thyroid hormone metabolism in Se-deficient subjects. In contrast to the present study, our group did not find any evidence about the role of Se deficiency in goitrous schoolchildren of Semirom, a city near Isfahan [10]. Although Dabbaghmanesh et al. [8] showed a significant increase in free T4 level in Se-deficient subjects, Se deficiency did not cause any significant impairment in thyroid hormone metabolism in the present study.

The association between thyroid autoantibodies and goiter has been described [29]. A few works have been done to discover the relation between Se deficiency and thyroid autoantibodies. In a study by Gartner et al. [30], Se supplements of 200 μg selenite produced a significant decline in TPO Ab concentration in patients with autoimmune thyroiditis. The mechanism by which Se exerts effects on TPO Ab production is likely to be due to the ability of high doses of Se to modify the inflammatory and immune responses [31]. We tried to test the hypothesis that Se deficiency might increase the concentration of thyroid autoantibodies and consequently results in goiter. Although Se-deficient subjects had higher levels of those antibodies than Se-sufficient ones, the difference was not statistically significant.

The main limitation of our study was that we categorized participants into goitrous and nongoitrous group by inspection and palpation. Zimmermann et al. [32] showed the low sensitivity and specificity of palpation in areas of mild to moderate IDD. Classification of subjects into different goiter groups would be more accurate if we used thyroid ultrasonography instead of inspection and palpation.

In the present study, we showed the high prevalence of goiter in schoolchildren of Isfahan. There was satisfactory iodine intake of the studied subjects. Se deficiency plays a role in the still high prevalence of goiter in this region. Se supplementation might be beneficial to reduce the prevalence of goiter. However, the role of other goitrogens should be investigated.

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