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Original Article

The Role of Iron Deficiency in Persistent Goiter

Mohammad-Hossein Dabbaghmanesh MD*, Abdolsamad Sadegholvaad MD*, Fardad Ejtehadi MD*, Gholamhossein Ranjbar-Omrani MD•*

Background: **Iodine deficiency has been identified as a significant public health problem in Iran. The main strategy for controlling iodine deficiency was nationwide salt iodination. Over 10 years after starting this program, goiter is still endemic in school children. Iron deficiency may have interfered with the iodine intervention program. The objective of the present study was to evaluate the relationships between iron status, thyroid hormone profile, and the prevalence of goiter 11 years after implementation of the salt iodination program.**

Methods: **In this study which was conducted in Marvdasht, Shiraz, 1188 students aged eight to 13 years were enrolled. Goiter was graded according to the classification by the World Health Organization (WHO). Serum concentrations of thyroid hormones and thyroid stimulating hormone were determined using commercial kits. The urinary iodine level was measured using the digestion method.**

Results: **Goiter was endemic (39.6%); the majority of participants had grade 1 thyromegally. Despite the endemic status of goiter in southern Iran, the urine content of iodine reflected a normal iodine intake. The prevalence of iron deficiency was 16.4%.The iron-deficient patients had a significantly higher thyroid stimulating hormone level and lower free T4 concentrations than those with a normal serum ferritin level (*P*<0.001).**

Conclusion: **Iron supplementation may improve thyroid metabolism in children but we still have to investigate the role of other goitrogens in this area.**

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Keywords: Epidemiology • goiter • Iran • iron • prevalence

Introduction

Iodine deficiency has several important consequences on health which are generally termed "iodine deficiency disorders".[1] Several national surveys reported states of endemic goiter and iodine deficiency in all provinces of Iran.[2] Salt iodination was considered to be the first line of public health measures to prevent and control endemic goiter. Iran was declared an iodine sufficient area in year 2000.[3] Nevertheless, goiter is still endemic among Iranian school children.[4] The efficiency of salt iodination may be influenced by multiple nutritional and environmental factors.[5–7] Iron deficiency, which impairs thyroid metabolism and may limit the effectiveness of iodine intervention programs, is still one of the most important nutritional issues in developing countries.[8–10] This study was undertaken to investigate the relationship between the iron status, thyroid function tests, and the prevalence of goiter among Iranian school children, 11 years after implementing the iodine intervention program.

Authors' affiliation: *Endocrine and Metabolism Research Center, Nemazee Hospital, Shiraz University of Medical Sciences, Shiraz, Iran.
•**Corresponding author and reprints:** Gholamhossein Ranjbar-Omrani MD, Endocrine and Metabolism Research Center, Nemazee Hospital, Shiraz University of Medical Sciences Shiraz, Iran.
Tel: +98-711-628-14-73, Fax: +98-711-628-14-73,
E-mail: dabbaghm@sums.ac.ir.
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Materials and Methods

This study was carried out in Marvdasht, an urban community situated 50 km north of Shiraz, the capital of Fars Province in southern Iran, between April and November 2005. The target population was all children aged eight to 13 years from 97 schools. The sampling frame consisted of the list of schools, from which we selected 40 clusters by random cluster sampling. From these

40 clusters, 200 school children from each age group were chosen at random. All selected children (600 boys and 600 girls) and their parents were invited to be explained about the study. All but 12 persons accepted to participate in this study. The children (598 boys and 590 girls) were enrolled after their parents provided informed written consents. None of them was receiving thyroid medication. Examinations were done by an endocrinologist and goiter was graded according to the World Health Organization (WHO) criteria which consider a nonpalpable thyroid tissue as grade 0, palpable but non-visible goiter as grade 1, and palpable and visible goiter as grade 2.[11] Simple random sampling was used for recruiting 500 of 1188 school children to be tested for urinary iodine excretion (UIE), serum free thyrotoxin (FT4), free tri-iodothyronin (FT3), thyroid stimulating hormone (TSH), and ferritin levels. Urine samples were collected in the morning and were frozen until urinary iodine was measured using the digestion method (WHO/ICCIDD recommendation for the median UIE to be ≥10 μg/dL).[11]

FT4 and FT3 were analyzed by radioimmunoassay (RIA-Gnost CIS, Bio International, France). TSH was measured using the immunoradiometric assay technique (Biosource Europe SA, Belgium). The normal range for FT4, FT3, and TSH was considered 7 – 18 pg/mL, 2 – 4.25 pg/mL, and 0.3 – 3.9 μIU/mL, respectively. Serum ferritin (SF) was evaluated using the immunoradiometric assay method with a normal range of 15 – 200 ng/mL; iron deficiency was defined as a SF <15 ng/mL.[12] To eliminate the influence of factors such as fever, infection, liver disease or cancer on SF, only healthy children were examined. Data were expressed as mean ±standard deviation (SD) and compared by one-way analysis of variance (ANOVA) and Student's *t*-tests. Variables not normally distributed were expressed as median and compared by Mann-Whitney U and Kruskal-Wallis tests. Comparisons between frequencies were made by χ^2 test. Statistical significance was considered at $P<0.05$. The study protocol was approved by the Reviewer Board of Shiraz Endocrine Research Center and Shiraz University of Medical Sciences.

Results

Prevalence of goiter

Thyroid enlargement of grade 1 and 2 was observed in 37% and 2.6% of the students, respectively. Among girls, 40.1% had goiter; grade 1 in 37.6% and grade 2 in 2.5%. Thirty-nine percent of the boys had goiter; 36.3% had grade 1 and 2.7% had grade 2 disease. The prevalence did not have any significant association with age or gender ($P=0.326$) (Figure 1).

Urinary iodine excretion

The median urinary iodine concentration was 18.8 μg/dL without any significant difference between the boys (17 μg/dL) and girls (22.4 μg/dL); 12.2% of the children had values <5 μg/dL ($P=0.345$). UIE was unrelated to age or gender and its values did not differ significantly between children with and without goiter (20 μg/dL vs. 18 μg/dL, $P=0.213$)

TSH, FT4, FT3

The mean TSH concentration was 2.5 μIU/mL. The mean concentrations for FT4 and FT3 were 13.1 pg/mL and 3.8 pg/mL, respectively without any age-or gender-related differences.

Subclinical hypothyroidism was found in 2.5% of the school children whose TSH concentrations were >3.9 μIU/mL; in 0.8% of the cases, TSH was >10 μIU/mL. The prevalence of subclinical hyper-

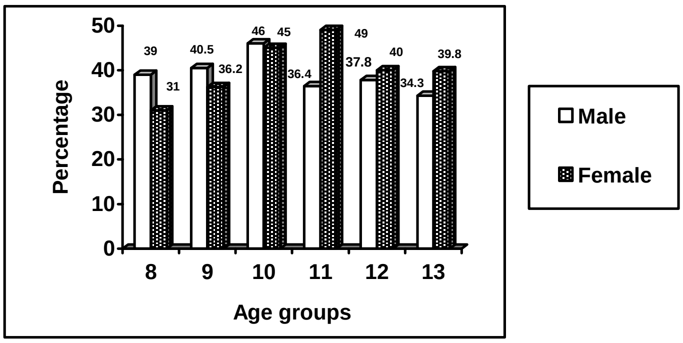

Figure 1. Prevalence of goiter (grade 1 and 2) in different age groups (years of age) of the studied school children.

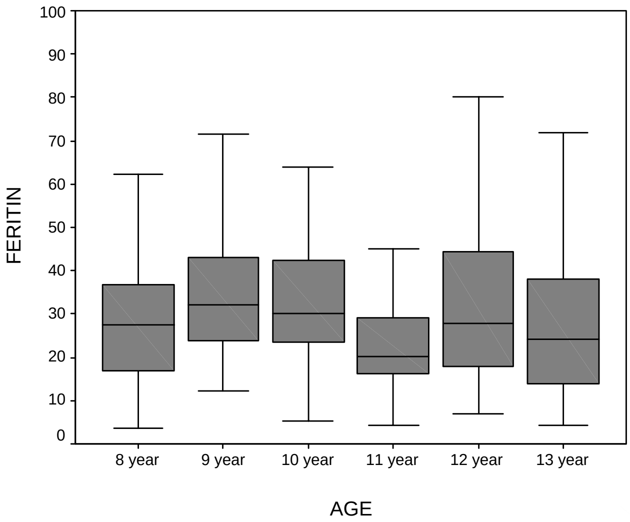

Figure 2. Distribution of ferritin levels (ng/mL) in different age groups.

thyroidism was 0.2%.

Iron status

The mean±SD SF concentration was 32.3±22.3 ng/mL without any significant differences between the boys and girls (33.5±12.4 vs. 30.8±23.4; *P*=0.205). Of the school children studied, 16.4% had iron deficiency (SF<15 ng/mL). The prevalence rates were not significantly different between the boys (16.6%) and girls (16.1%) and had no relationship with age (Figure 2). The mean±SD SF (31.3±21.6 ng/mL) in the goiterous children was comparable to those without goiter (32.9±22.8 ng/mL) (*P*=0.711).

The subjects were then stratified according to their SF, using a cutoff point of 15 ng/mL. Significant differences between the two groups were only observed for FT4, TSH, UIE, and the prevalence of goiter (Table 1).

Discussion

The endemic goiter is still present in Iran, despite a significant success in its reduction after salt iodination.[3] In contrast to fairly high prevalence rates of goiter in southern Iran, the median urinary iodine concentration indicated an adequate iodine supply, implying that iodine deficiency is no longer the cause of persistent goiter in this region. Deficiencies of iron and iodine are major public health problems and found concurrently in developing countries. The mean SF in our study was 32.3±22.3 ng/mL; 16.4% of the school children had SF <15 ng/mL which was lower than that reported from other developing countries (25 – 35%).[13] Nevertheless, it was still more common than in industrialized nations (5 – 9%).[14,15]

The presence or absence of goiter had no relation to iron status, although a decrease in serum FT4 and an increase in TSH concentration were present in those with SF<15 ng/mL. Studies in human and animals have shown that iron deficiency impairs thyroid metabolism. In rats, iron deficiency decreases plasma thyroid hormone concentration, impairs peripheral conversion of T4 to T3, reduces the activity of hepatic thyroxine 5'-deiodinase, and blunts the thyrotropin response to thyrotropin releasing hormone.[16–18] On the other hand, low T4 and T3 concentrations were found in iron-deficient adults.[19,20] In addition, higher TSH concentrations were observed in iron-deficient adolescents.[21] It seems that the initial steps of thyroid hormone synthesis involve iodine incorporation into tyrosine residues of thyroglobulin and that the covalent bridging of the residues are catalyzed by iron-containing thyroperioxidase.

Table 1. Mean±SD thyroid hormone concentrations stratified by serum ferritin level.

Thyroid hormone profile	Ferritin<15 ng/mL (*n*=82)	Ferritin>15 ng/mL (*n*=418)	*P* value
Free T4 (pg/mL)	12.2±3.2	13.2±2.8	0.001
Free T3 (pg/mL)	3.6±0.4	3.7±0.5	0.192
TSH (μIU/mL)	3.2±6.4	2.4±1.9	0.001

Other hem-containing enzymes such as cytochrome C oxidase, myeloperoxidase, and succinate dehydrogenase are also sensitive to iron depletion.[22,23] Severe iron deficiency could therefore, interfere with thyroid hormone synthesis and decrease the thyroperoxidase activity.[24] In one study, iron deficiency was associated with a high prevalence of goiter in Iranian school children.[25] On the other hand, a survey of Ethiopian children showed no correlation between iron status and goiter prevalence or thyroid hormone concentration.[26] There were no significant differences in the goiter rate between the anemic and nonanemic Filipinos children either.[27]

In conclusion, after 10 years of salt iodination, goiter is still prevalent among children. Although there was no significant difference in the prevalence of goiter between those with low and normal ferritin levels, iron deficiency was associated with increased TSH and decreased FT4 concentrations. Therefore, iron supplementation may improve thyroid metabolism in school children. However, it is necessary to elucidate the roles of other goitrogens, possible trace elements and vitamin A deficiencies,[26,28] or increasing prevalence of thyroid autoimmunity after salt iodination.[29]

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