Original Paper

HORMONE RESEARCH

Horm Res 2006;66:45–50
DOI: 10.1159/000093473

Received: December 7, 2005
Accepted: April 8, 2006
Published online: May 19, 2006

Iron Deficiency in Goitrous Schoolchildren of Semirom, Iran

Mansour Siavash Dastjerdi Mahin Hashemipour Hasan Rezvanian
Fatemeh Kazemi Alireza Najafian Mohammad Mohammady
Ashraf Aminorroaya Masoud Amini Ali Kachuei Mohammad Hassan Moaddab

Isfahan Endocrine and Metabolism Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

Key Words
Goiter · Iodine deficiency · Iron deficiency · Salt iodization · Transferrin · Ferritin

Abstract
Background: Iodine deficiency produces the spectrum of iodine deficiency disorders (IDDs): endemic goiter, hypothyroidism, cretinism, and congenital anomalies. Other factors, including goitrogens and micronutrient deficiencies, may influence the prevalence and severity of IDDs and response to iodine supplementation. This cross-sectional, descriptive study was performed in 2003 on elementary school children of Semirom, a mountainous region of Iran, where goiter was hyper-endemic in 1994, but the goiter prevalence had not decreased as expected many years after salt iodization and iodine injection. Some possible risk factors associated with goiter in that area were evaluated, and the results of iron study are presented here. ***Methods:*** 1,869 cases were selected by a multistage cluster sampling procedure. Grade 2 goitrous children were compared with equal number of non-goitrous children for serum iron, ferritin, transferrin, thyroxin, TSH and urine iodine concentrations (UIC). ***Results:*** 210 children (105 goiter grade 0 and 105 goiter grade 2) entered this sub-study. Of 210 participants, 70 children had low transferrin saturation, 13 had low serum ferritin and 9 children had both problems. There was no significant difference in goiter rate between children with low iron indices and others. There was no significant correlation between serum iron, ferritin or transferrin saturation with other variables including T4, UIC and goiter stage. ***Conclusion:*** The present study reveals that in the area studied, iron deficiency cannot explain the high prevalence of goiter, so other responsible factors should be investigated.

Introduction

It is estimated that 750 million people worldwide are at risk of iodine deficiency disorders (IDDs) based on goiter prevalence [1].

Iodine deficiency produces a spectrum of disorders, endemic goiter, hypothyroidism, cretinism, and congenital anomalies that are termed IDDs [2].

Iodine deficiency in childhood also impairs neuromotor and intellectual development, with an average reduction in the intelligence quotient of 10 points [3].

On the other hand, in iodine-deficient areas, multiple nutritional factors, including goitrogenic foods, protein-energy malnutrition, and selenium deficiency may influence the prevalence and severity of IDD and modify the response to iodine supplementation [4–7].

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0301–0163/06/0661–0045$23.50/0

Accessible online at:
www.karger.com/hre

Mansour Siavash Dastjerdi, MD
Isfahan Endocrine and Metabolism Research Center
Sedigheh Tahereh Medical Research Complex
Khorram Street, Isfahan (Iran)
Tel. +98 311 335 9933, Fax +98 311 337 3733, E-Mail siavash@med.mui.ac.ir

One of micronutrients that can potentially influence IDDs is iron [8–12], and deficiencies of iron and iodine are both major public health problems [13].

In many developing countries, children are at high risk of both goiter and iron deficiency anemia. Iron deficiency adversely affects thyroid physiology. Animal and human studies suggest that iron deficiency impairs thyroid hormone metabolism and may reduce the efficacy of iodine supplementation in areas of endemic goiter [14]. Iron deficiency anemia decreases plasma thyroxin (T4) and triiodothyronine (T3) concentrations, reduces peripheral conversion of T4 to T3, and may increase concentrations of thyrotropin [14–17].

The two initial steps of thyroid hormone synthesis are catalyzed by thyroperoxidases that are dependent on iron [18]. In addition, iron deficiency may alter the central nervous system control of thyroid physiology and modify nuclear triiodothyronine binding [15, 19].

The therapeutic response to orally given iodized oil is lower in goitrous children with iron deficiency anemia than in iron-sufficient children [12], suggesting that the presence of iron deficiency anemia in children limits the effectiveness of iodine intervention programs [12]. On the other hand, iron treatment of goitrous children with iron deficiency anemia improved their response to orally given iodized oil [14, 20].

Subjects and Methods

This study was performed in 2003, in Semirom, a mountainous region in the central area of Iran, where goiter was hyper-endemic with a prevalence of about 80.5% estimated in 1994.

In Iran, all salt preparations have been iodized since 1988. Production of uniodized house salt has been forbidden by legislation since 1994, and thereafter frequent regular evaluations of salt (at factory, store and house levels) and urine iodine concentrations by provincial organizations and local health officials have confirmed adequate iodine intake [21]. In 1993, all citizens of Semirom were given a single-dose injection of 480 mg of iodized oil intramuscularly.

Because the prevalence of goiter was not decreased as expected 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 were evaluated, and the results of iron indices are presented here.

This was a cross-sectional, descriptive study performed on schoolchildren of Semirom. 108 elementary schools with 4,773 students were considered as primary sampling units. 79 schools were from rural areas with 2,449 students (1,247 male and 1,202 female), and 29 schools from urban areas with 2,324 students (1,126 male and 1,198 female). Subjects were enrolled with a multistage cluster sampling procedure and then appropriate numbers of children were sampled randomly within selected clusters. Informed consent was obtained from parents of children before inclusion.

We excluded subjects with a 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.

Endocrinologists examined all children and goiter grading was done according to WHO classification [1].

These children were classified in 3 groups (grades 0, 1 and 2) with respect to goiter grading. The first group (grade 0) was considered as the control in comparison with others (grades 1 and 2). The sum of grades 1 and 2 provided the total goiter rate (TGR) of the study population.

To evaluate the responsible factors for goiter, grade 2 goitrous children were compared with an equal number of randomly selected children from the control group for serum iron, ferritin, transferrin, thyroxin (T4) and thyroid-stimulating hormone (TSH) and urine iodine concentration.

The blood samples were transported on dry ice to the reference laboratory of the endocrine and metabolism research center. The samples were stored in the freezer at –70°C until analysis. All urine and blood assays were performed within a median time of 26 h of sampling. The same person performed each assay using the same method.

Urine iodine concentration (UIC) was measured by the digestion method based on a modification of the Sandell-Kolthoff reaction [1, 22] (intra-assay CV 1.2% and inter-assay CV 2.2%). Measures less than 10 μg/dl were considered as iodine deficiency [1].

Serum iron was measured by photometric assay (intra-assay CV 2.2% and inter-assay CV 2.9%) and transferrin by immunoturbidometery (intra-assay CV 2.7% and inter-assay CV 3.1%), both with an automated analyzer (Liasys, Italy). Serum ferritin was measured with IRMA by Iran kavoshyar kits (intra-assay CV 5.9% and inter-assay CV 5.5%). Values equal to 50 μg/dl were considered as the normal lower limit of serum iron, and 12 ng/ml as the normal lower limit of serum ferritin. Transferrin saturation between 19 and 50% was considered normal. Iron deficiency was defined as low transferrin saturation and ferritin. 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.

Statistical Analysis

Variables with normal distribution (serum iron level, transferrin and transferrin saturation) are presented as means ± SD. Goiter prevalence was compared between groups with the χ^2 test. Correlation between variables was calculated by Pearson's correlation test. $p < 0.05$ was considered statistically significant. Analyses were performed with SPSS statistical package version 11.5.

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

Table 1. Baseline characteristics of the study population

	Male	Female	Age, years	Height, cm	Weight, kg
All	989 (54.1%)	839 (45.9%)	9.33 ± 1.02	132.39 ± 7.54	26.21 ± 4.58
Selected subgroup with grade 0	61 (57.5%)	45 (42.5%)	9.20 ± 0.85	131.46 ± 7.35	25.56 ± 4.68
Selected subgroup with grade 2	51 (48.6%)	54 (51.4%)	9.47 ± 1.06	134.20 ± 7.47	26.91 ± 3.82

Table 2. Hormonal and biochemical results of participants in iron evaluation groups

	T4, μg/dl	TSH, mIU/ml	Tpo Ab, IU/ml	Tg Ab, IU/ml	UIC, μg/dl	Fe, μg/dl	TIBC, μg/dl	Ferritin, ng/ml
Male	9.02 ± 1.43	2.92 ± 2.72	90.33 ± 485.36	146.63 ± 707.76	19.74 ± 8.94	80.23 ± 33.90	342.71 ± 48.04	32.12 ± 18.73
Female	8.79 ± 1.66	2.57 ± 1.49	20.79 ± 114.60	12.30 ± 23.91	19.56 ± 10.32	75.80 ± 37.55	340.28 ± 45.68	30.26 ± 17.39
Goiter grade 0	9.14 ± 1.47	2.45 ± 1.17	7.86 ± 12.05	11.12 ± 27.35	19.28 ± 9.81	78.16 ± 36.08	344.79 ± 46.58	31.68 ± 19.06
Goiter grade 2	8.65 ± 1.59	3.08 ± 2.95	31.56 ± 154.61	13.29 ± 20.83	21.54 ± 8.42	78.15 ± 35.37	338.31 ± 47.12	30.81 ± 17.15
Total	8.91 ± 1.54	2.75 ± 2.22	57.70 ± 363.12	83.60 ± 519.19	19.65 ± 9.58	78.15 ± 35.64	341.57 ± 46.85	31.25 ± 18.09

Data of variables with normal distribution are presented as mean ± SD.
Tpo Ab = Thyroid peroxidase antibodies; Tg Ab = thyroglobulin antibodies; UIC = urinary iodine concentration.

Results

The results of our studies are given in tables 1–3 and below.

1,869 schoolchildren (899 from urban and 970 from rural areas) were enrolled in this study with male to female ratio of 1.18 and age of 7–13 (mean ± SD: 9.3 ± 1.0 years) (table 1). Of these, 1,199 were classified as goiter grade 0 (64.15%), 556 had goiter grade 1 (29.74%) and 114 had goiter grade 2 (6.09%) with total goiter prevalence of about 36%.

The mean UIC in children was 19.3 ± 9.1 μg/dl. 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 the children were severely iodine deficient (UIC <2 μg/dl).

105 of 114 grade 2 goitrous children and an equal number of randomly selected children from the control group agreed to enrolment into this sub-study of iron evaluation.

Of these 210 children, 70 had low (less than 18%) transferrin saturation, 139 had normal (between 19 and 50%) transferrin saturation, and 1 had high (more than 50%) transferrin saturation. There was no difference between these 3 groups regarding the presence or absence of goiter (p = 0.56).

13 children had low serum ferritin (7 in goiter group and 6 in control group) and 197 children had normal serum ferritin. There was no difference between low and normal ferritin levels in children regarding presence or absence of goiter (p = 0.775) (table 2).

Table 3. Goiter grade in iron-deficient and non-iron-deficient participants

	Goiter grade	Serum iron status		Total
		iron deficient	non-iron deficient	
Control	0	4	101	105
Goitrous	2	5	100	105
Total		9	201	210

Of 210 participants, based on low transferrin saturation and serum ferritin levels, 9 children were found to be iron deficient (5 in the goiter group and 4 in the control group) (table 3).

There was no significant difference in goiter rate between cases with iron deficiency (both transferrin saturation and ferritin level lower than normal) and other cases (at least one normal serum iron index) (p = 0.722).

There was no significant difference between groups with goiter grade 0 and goiter grade 2 in iron indices such as serum iron level (p = 0.999), ferritin (p = 0.729), TIBC (p = 0.316), and transferrin saturation (p = 0.686).

There was also no significant difference of UIC between goitrous and nongoitrous children. Correlation data analysis by Pearson's correlation coefficient for se-

rum iron, ferritin and transferrin saturation and each other variable shows that there is no significant correlation between serum iron level, ferritin and transferrin saturation with other variables including TSH, T4, urine iodine concentration and goiter stage ($p > 0.5$).

None of the students had thyroid dysfunction.

Discussion

As stated, this study shows that goiter prevalence has decreased from 80.55% in 1994 to about 36% in 2003. This implies that iodine deficiency has been the most important cause of endemic goiter and also shows the effective role of a single intramuscular injection of iodized oil and also salt iodization in treating goiter. However, Semirom is still considered an endemic region of goiter and despite the salt iodization program and iodized oil injection, the goiter rate is still high. Although iodine deficiency is present in mild-to-moderate degrees, it cannot truly explain the still high prevalence of goiter.

Some potential explanations for the inadequate response of goiter rate to iodine supplementation in children may exist: first, incomplete regression of enlarged thyroid in children who were iodine deficient during their early years of life [23], and second, the lag period between iodine supplementation and normalization of thyroid size [24]. The first theory cannot explain the results of the present study because since 1988 all people have used iodized salt, so 7- to 13-year-old participants of this study haven't lived in an iodine-deficient area.

Some investigators suggested that after iodine supplementation, there is a lag before the goiter rate normalizes. The duration of this lag is unclear, with experts suggesting that it may last from months to years [24]. With respect to the prolonged interval between iodine supplementation and follow-up assessment in the present study, and also according to the fact that thyroid enlargement regresses more rapidly in response to bolus iodine supplementation in comparison with gradual iodized salt programs [25, 26], the high prevalence of goiter in our study cannot be attributed to a lag period.

The manual goiter palpation technique yields sufficiently precise quantitative results for clinical purposes [27] but it has some limitations. While the goiter rate remains high after iodine supplementation, sonography may reveal significant changes in thyroid volume [28, 29]. Previous studies indicated that measurement of goiters by palpation may not be appropriate in the short-term evaluation of iodization programs, but for a long-term follow-up it could be reliable [30]. However, even if our assessment of response to iodized oil supplementation is biased, the high prevalence of goiter in the area studied is undeniable.

Other explanations for this unexpected high goiter rate are the roles of unknown goitrogens [31], autoimmunity [32], or other micronutrient deficiencies [33–39]. Iron deficiency is one of the suspected candidates [12, 16, 40].

As mentioned, iron deficiency, with or without anemia, can impair thyroid hormone metabolism [8, 11, 19, 41] and results in goiter development. In our study, serum iron, ferritin and transferrin measurements showed that only 9.52% of school-age children were iron deficient. On the other hand, goiter rate and thyroid function tests didn't show a statistical difference between subjects with normal and low serum iron indices. Correlation tests also didn't show any relationship between serum iron and ferritin levels or transferrin saturation and goiter, UIC, serum T4 and TSH concentrations. These data suggest that although iron deficiency is present in the studied area, it has little or no impact on the goiter rate and thyroid hormone profile. This is in contrast with some other studies, as some studies in Iran and other countries have confirmed the above-mentioned association of iron deficiency and IDDs [12, 14, 42]. On the other hand, there was no correlation between iron status and goiter rate or thyroid hormone levels in a survey carried out in Ethiopian children [38, 43] or another study in Turkey [44]. There were also no significant differences in the prevalence of goiter among anemic and nonanemic children and adults in a study in the Philippines [34].

The causes of this difference are unclear but may be attributed to geographic differences and the genetic heterogeneity of the participants in various studies, multiple confounding factors or probably methodological differences. Some studies have used total serum thyroxin as an indicator of thyroid hormone state [15], but total thyroxin per se is not an accurate method of thyroid function evaluation as it is predisposed to multiple disturbing factors like TBG effects and chronic diseases. Combination of TSH and thyroxin as used in this study can give more accurate and interpretable results. We used serum ferritin, iron and transferrin saturation for evaluation of body iron status but not hemoglobin. Low iron indices are not equivalent to iron deficiency anemia, so the negative results of our study may be due to milder degrees of iron deficiency.

Altogether, it seems that factors other than iodine and iron deficiency may be at least partly responsible for the high prevalence of goiter in Semirom. These include protein-energy malnutrition [14, 39, 45], vitamin A [36, 46], selenium and Zn deficiencies [47, 48] or autoimmunity [32].

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 the evaluated subjects, gives more accurate and valuable data for future planning.

In conclusion, the present study reveals that in the area studied, iron deficiency cannot explain the high prevalence of goiter and that other responsible factors should be investigated.

Acknowledgments

This study was funded by the Bureau for Research, Isfahan University of Medical Sciences and Endocrine and Metabolism Research Center. The authors are thankful to the authorities of the provincial and local education offices, the patients who participated in this study and the staff of the Isfahan Endocrine and Metabolism Research Center.

References

1 World Health Organization, United Nations Children's Fund and International Council for the Control of Iodine Deficiency Disorders: Assessment of Iodine Deficiency Disorders and Monitoring Their Elimination, WHO/NHD/01.1. Geneva, WHO, 2001.
2 WHO, UNICEF and ICCIDD: Indicators for Assessing Iodine Deficiency Disorders and Their Control through Salt Iodinization. WHO/NUT.94.6. Geneva, WHO, 1994.
3 Bailey KV, Clugston GA: Iodine deficiency disorders; in Murray CJL, Lopez AD (eds): The Global Burden of Disease and Risk Factors in 1990, Geneva, WHO/World Bank, 1990, pp 36–40.
4 Boyages SC: Clinical review 49: iodine deficiency disorders. J Clin Endocrinol Metab 1993;77:587–591.
5 Furnee CA: Prevention and control of iodine deficiency: a review of a study on the effectiveness of oral iodized oil in Malawi. Eur J Clin Nutr 1997;51(suppl 4):S9–S10.
6 Thilly CH, Vanderpas JB, Bebe N, Ntambue K, Contempre B, Swennen B, Moreno-Reyes R, Bourdoux P, Delange F: Iodine deficiency, other trace elements and goitrogenic factors in the etiopathology of iodine deficiency disorders. Biol Trace Element Res 1992;32:229–243.
7 Zimmermann MB, Adou P, Torresani T, Zeder C, Hurrell RF: Effect of oral iodized oil on thyroid size and thyroid hormone metabolism in children with concurrent selenium and iodine deficiency. Eur J Clin Nutr 2000; 54:209–213.
8 Hess SY, Zimmermann MB: The effect of micronutrient deficiencies on iodine nutrition and thyroid metabolism. Int J Vitam Nutr Res 2004;74:103–115.
9 Hurrell RF: Bioavailability of iodine. Eur J Clin Nutr 1997;51(suppl 1):S9–S12.
10 Karamifar H, Shahriari M, Sadjadian N: Prevalence of endocrine complications in beta-thalassaemia major in the Islamic Republic of Iran. East Mediterr Health J 2003; 9:55–60.
11 Tienboon P, Unachak K: Iron deficiency anaemia in childhood and thyroid function. Asia Pac J Clin Nutr 2003;12:198–202.
12 Zimmermann M, Adou P, Torresani T, Zeder C, Hurrell R: Persistence of goiter despite oral iodine supplementation in goitrous children with iron deficiency anemia in Cote d'Ivoire. Am J Clin Nutr 2000;71:88–93.
13 ACC/SCN: Second Report on the World Nutrition Situation, vol 1. Global and regional results. ACC/SCN: Geneva, 1992.16 Ministry of Health. Plan National d'Action pour la Nutrition. Côte d'Ivoire, Ministry of Health, 1994.
14 Zimmermann M, Adou P, Torresani T, Zeder C, Hurrell R: Iron supplementation in goitrous, iron-deficient children improves their response to oral iodized oil. Eur J Endocrinol 2000;142:217–223.
15 Beard JL, Borel MJ, Derr J: Impaired thermoregulation and thyroid function in iron-deficiency anemia. Am J Clin Nutr 1990;52: 813–819.
16 Beard JL, Brigham DE, Kelley SK, Green MH: Plasma thyroid hormone kinetics are altered in iron-deficient rats. J Nutr 1998; 128:1401–1408.
17 Dillman E, Gale C, Green W, Johnson DG, Mackler B, Finch C: Hypothermia in iron deficiency due to altered triiodothyronine metabolism. Am J Physiol 1980;239:R377–R381.
18 Ackrell BA, Maguire JJ, Dallman PR, Kearney EB: Effect of iron deficiency on succinate- and NADH-ubiquinone oxidoreductases in skeletal muscle mitochondria. J Biol Chem 1984;259:10053–10059.
19 Smith SM: Indices of in vivo and in vitro thyroid hormone metabolism in iron-deficient rats. Nutr Res 1994;14:729–739.
20 Hess SY, Zimmermann MB, Adou P, Torresani T, Hurrell RF: Treatment of iron deficiency in goitrous children improves the efficacy of iodized salt in Cote d'Ivoire. Am J Clin Nutr 2002;75:743–748.
21 Azizi F, Mehran L: Experiences in the prevention, control and elimination of iodine deficiency disorders: a regional perspective. East Mediterr Health J 2004;10:761–770.
22 Pino S, Fang SL, Braverman LE: Ammonium persulfate: a safe alternative oxidizing reagent for measuring urinary iodine. Clin Chem 1996;42:239–243.
23 Aghini-Lombardi F, Antonangeli L, Pinchera A, Leoli F, Rago T, Bartolomei AM, et al: Effect of iodized salt on thyroid volume of children living in an area previously characterized by moderate iodine deficiency. J Clin Endocrinol Metab 1997;82:1136–1139.
24 Delange F, De Benoist B, Pretell E, Dunn JT: Iodine deficiency in the world: where do we stand at the turn of the century? Thyroid 2001;11:437–447.
25 Dunn JT: Iodized oil in the treatment and prophylaxis of IDD; in Hetzel BS, Dunn JT, Stanbury JB (eds): The Prevention and Control of Iodine Deficiency Disorders. Amsterdam, Elsevier, 1987, pp 127–134.
26 Gutekunst R, Benmiloud M, Karmarkar M, Pandav D, Pretell EA, Teichert HM: ICCIDD Iodized oil study group. J Endocrinol Invest 1992;15(suppl 2):122.
27 Nordmeyer JP, Simons M, Wenzel C, Scholten T: How accurate is the assessment of thyroid volume by palpation? A prospective study of 316 patients. Exp Clin Endocrinol Diabetes 1997;105:366–371.

28 Todd CH, Dunn JT: Intermittent oral administration of potassium iodide solution for the correction of iodine deficiency. Am J Clin Nutr 1998;67:1279–1283.
29 Zimmermann MB, Hess SY, Molinari L, De Benoist B, Delange F, Braverman LE, et al: New reference values for thyroid volume by ultrasound in iodine-sufficient schoolchildren: a World Health Organization/Nutrition for Health and Development Iodine Deficiency Study Group Report. Am J Clin Nutr 2004;79:231–237.
30 Jooste PL, Weight MJ, Lombard CJ: Short-term effectiveness of mandatory iodization of table salt, at an elevated iodine concentration, on the iodine and goiter status of schoolchildren with endemic goiter. Am J Clin Nutr 2000;71:75–80.
31 Muros P, Ruiz-Lopez MD, Olea MF: Intake of iodine and major nutrients in an area of endemic goitre. J Nutr Sci Vitaminol (Tokyo) 1992;38:603–607.
32 Dremier S, Coppee F, Delange F, Vassart G, Dumont JE, Van Sande J: Clinical review 84. Thyroid autonomy: mechanism and clinical effects. J Clin Endocrinol Metab 1996;81:4187–4193.
33 Corvilain B, Contempre B, Longombe AO, Goyens P, Gervy-Decoster C, Lamy F, et al: Selenium and the thyroid: how the relationship was established. Am J Clin Nutr 1993;57(suppl 2):244S–248S.
34 Florentino RF, Tanchoco CC, Rodriguez MP, Cruz AJ, Molano WL: Interactions among micronutrient deficiencies and undernutrition in the Philippines. Biomed Environ Sci 1996;9:348–357.
35 Ingenbleek Y, De Visscher M: Hormonal and nutritional status: critical conditions for endemic goiter epidemiology? Metabolism 1979;28:9–19.
36 Keyvani F, Yassai M, Kimiagar M: Vitamin A status and endemic goiter. Int J Vitam Nutr Res 1988;58:155–160.
37 Untoro J, Ruz M, Gross R: Low environmental selenium availability as an additional determinant for goiter in East Java, Indonesia? Biol Trace Elem Res 1999;70:127–136.
38 Wolde-Gebriel Z, Gebru H, Fisseha T, West CE: Severe vitamin A deficiency in a rural village in the Hararge region of Ethiopia. Eur J Clin Nutr 1993;47:104–114.
39 Zimmermann MB, Wegmuller R, Zeder C, Chaouki N, Torresani T: The effects of vitamin A deficiency and vitamin A supplementation on thyroid function in goitrous children. J Clin Endocrinol Metab 2004;89:5441–5447.
40 Beard J, Tobin B, Green W: Evidence for thyroid hormone deficiency in iron-deficient anemic rats. J Nutr 1989;119:772–778.
41 Brigham D, Beard J: Iron and thermoregulation: a review. Crit Rev Food Sci Nutr 1996;36:747–763.
42 Azizi F, Mirmiran P, Sheikholeslam R, Hedayati M, Rastmanesh R: The relation between serum ferritin and goiter, urinary iodine and thyroid hormone concentration. Int J Vitam Nutr Res 2002;72:296–299.
43 Wolde-Gebriel Z, West CE, Gebru H, Tadesse AS, Fisseha T, Gabre P, et al: Interrelationship between vitamin A, iodine and iron status in schoolchildren in Shoa Region, central Ethiopia. Br J Nutr 1993;70:593–607.
44 Yavuz O, Yavuz T, Kahraman C, Yesildal N, Bundak R: The relationship between iron status and thyroid hormones in adolescents living in an iodine deficient area. J Pediatr Endocrinol Metab 2004;17:1443–1449.
45 Pathak P, Singh P, Kapil U, Raghuvanshi RS: Prevalence of iron, vitamin A, and iodine deficiencies amongst adolescent pregnant mothers. Indian J Pediatr 2003;70:299–301.
46 Mesaros-Kanjski E, Kontosic I, Kusic Z, Kaic-Rak A, Dakovic N, Kuser J, et al: Endemic goitre and plasmatic levels of vitamins A and E in the school-children on the island of Krk, Croatia. Coll Antropol 1999;23:729–736.
47 Zhang F, Liu N, Wang X, Zhu L, Chai Z: Study of trace elements in blood of thyroid disorder subjects before and after 131I therapy. Biol Trace Elem Res 2004;97:125–134.
48 Zimmermann MB, Kohrle J: The impact of iron and selenium deficiencies on iodine and thyroid metabolism: biochemistry and relevance to public health. Thyroid 2002;12:867–878.