Received: 17.8.2008 **Accepted: 2.3.2009**

Original Article

Zinc status in goitrous school children of Semirom, Iran

Mohammad Hassan Moaddab[a], Ammar Hassanzadeh Keshteli[b], Mansour Siavash Dastjerdi[a], Hasan Rezvanian[a], Ashraf Aminorroaya[a], Masoud Amini[a], Ali Kachuei[a], Mahin Hashemipour[a]*

Abstract

BACKGROUND: Iodine deficiency produces the spectrum of iodine deficiency disorders (IDDs) including 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. An association between zinc and goiter has previously been reported.

METHODS: A cross sectional study investigating an association between goiter and serum zinc status was performed in 2003 in a mountainous region of Iran. One thousand eight hundred twenty-eight children were selected by multistage cluster sampling. Goiter staging was performed by inspection and palpation. Serum zinc, total thyroxine, thyroid stimulating hormone and urinary iodine concentration were measured in a group of these children.

RESULTS: Thirty six and seven tenth percent of subjects were classified as goitrous. Serum zinc level in goitrous and nongoitrous children was 82.80 ± 17.85 and 83.38 ± 16.25 μg/dl, respectively (p = 0.81). The prevalence of zinc deficiency (serum zinc ≤ 65 μg/dl) in goitrous and nongoitrous children did not differ significantly (9.3 % vs. 10.8%, p = 0.70).

CONCLUSIONS: Goiter is still a public health problem in Semirom. According to the present study zinc status may not play a role in the etiology of goiter in Semirom school children. However, the role of other goitrogens or micronutrient deficiencies should be investigated in this region.

KEYWORDS: Goiter, Iodine Deficiency, Zinc Deficiency, Child.

JRMS 2009; 14(3): 165-170

Goiter is an enlargement of the thyroid gland that often produces a noticeable swelling in the front of the neck. This enlargement can be caused by iodine deficiency, inability of the body to use iodine correctly, or a variety of thyroid disorders, including infections, tumors, and autoimmune diseases.[1-3]

Nutritional deficiencies, including zinc,[4] manganese,[5] vitamin A,[6,7] and severe protein malnutrition[6] also contribute to inability to proper usage of iodine and development of goiter.[7]

In Iran, all salt preparations have been iodized since 1988. Production of uniodized house salt has 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.[8]

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.[9] Besides salt iodization since 1988, in 1993, all

[a] Isfahan Endocrine and Metabolism Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.
[b] Research Center, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.
*Corresponding Author
E-mail: Hashemipour@med.mui.ac.ir

citizens of Semirom were given a single dose of intramuscular injection of 480 mg iodized oil. 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?

Zinc is a trace element with numerous functions in the human organism. It is important for the appropriate functioning of metabolism, growth, immunological system and an essential component of various metalloenzymes in the organism participating in the synthesis of other enzymes.[10] Zinc plays a key role in the thyroid function. It is very important in thyrotropin-releasing hormone synthesis,[11] is essential for thyroxine (T4)-to-T3 conversion,[12] and is required for the biological functioning of the thyroid hormone and related receptors.[13] Zinc deficiency has a suppressing effect on thyroid hormones, whereas zinc supplementation has an opposite effect.[14,15]

The aim of the present study was to investigate the role of zinc deficiency in the endemic goiter in school children of Semirom, Iran.

Methods

This was a cross sectional study performed on school children of Semirom. One hundred and eight elementary schools with 4773 students were considered as primary sampling units. Seventy nine schools were from rural areas with 2449 students (1247 males and 1202 females), and 29 schools from urban areas with 2324 students (1126 males and 1198 females). 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.[16] In a case control sub-study, grade 2 goitrous children were compared with a proper number of randomly selected children from nongoitrous group for serum zinc, total thyroxine (T4), thyroid stimulating hormone (TSH) and urinary iodine concentration (UIC).

Blood samples were transported by dry ice to the reference laboratory of Isfahan Endocrine and Metabolism Research Center. Plastic bottles with screw caps were utilized to collect the urine samples. The samples were stored in the freezer at the temperature of -70°C until analysis. Serum T4 was measured with radioimmunoassay (Iran Kavoshyar Co., Tehran, Iran). Serum 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 zinc concentrations were measured with atomic absorption spectrometry. Zinc deficiency was defined as serum zinc ≤ 65 µg/dl.[17] UIC was measured by digestion method based on a modification of Sandell-Kolthoff reaction. UIC less than 10µg/dl was considered as iodine deficiency .[16]

This study was approved by ethics committee of Goiter Research Center affiliated to Isfahan University of Medical Sciences. Written permission was taken from the provincial organization of education. In Semirom, local official of health and education accompanied us.

Quantitative variables are presented as mean ± SD or median. Normality of data distribution was assessed with Kolmogorov–Smirnov test .Independent sample t-test was used to compare measurements in different groups. Parameters not normally distributed were compared by Mann-Whitney test. Prevalence of zinc deficiency between goitrous and normal children was compared by Chi-square test. Pearson correlation was used to find correlation between serum zinc and different quantitative variables. To explore the association between goiter and other variables, the

logistic regression model was also built up. P value less than 0.05 was considered statistically significant. All analysis was performed using SPSS version 15 (SPPS Corp, Chicago, IL, USA).

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 (9.3 ± 1.0 years). Thirty six and seven tenth percent (36.7%) of subjects were classified as goitrous (Table 1).

Table 1. Thyroid size determined by inspection and palpation in school children of Semirom, Iran.

	Thyroid size		
	Grade 0 (%)	**Grade 1 (%)**	**Grade 2 (%)**
Boys	65	29.2	5.8
Girls	61.4	31.7	6.9
All	63.3	30.4	6.3

Goiter prevalence among girls was 38.6% while 35% of boys were goitrous (p = 0.06). The mean UIC in children was 19.3 ± 9.1 μg/dl. Mild (5 ≤ UIC < 10 μg/dl) and moderate (2 ≤ UIC < 5μg/dl) iodine deficiency was detected in 6.4% and 3.2% of cases, respectively. Only 1.8% of children were severely iodine deficient (UIC < 2μg/dl).

One hundred and eight grade 2 goitrous children and 111 randomly selected children from nongoitrous group agreed to participate in the sub-study of zinc evaluation.

The mean ± SD of serum zinc in goitrous children was comparable to serum zinc level in nongoitrous subjects (82.80 ± 17.85 vs. 83.38 ± 16.25 μg/dl, p = 0.81). Serum zinc in goitrous and nongoitrous boys was 83.10 ± 18.50 and 88.42 ± 17.50 μg/dl, respectively (p = 0.12). Serum zinc level in goitrous girls was not statistically different from that in nongoitrous girls (82.51 ± 17.35 vs. 77.00 ± 11.91μg/dl, p = 0.06).

The prevalence of zinc deficiency in goitrous and nongoitrous children was 9.3% and 10.8%, respectively (p = 0.70). Whilst 13% of goitrous boys had zinc deficiency, 6.5% of nongoitrous boys were zinc deficient (p = 0.23). The prevalence of zinc deficiency in goitrous and nongoitrous girls was 5.6% and 16.3%, respectively (p = 0.07).

Using logistic regression analysis, we showed no association between zinc status and risk of goiter (Table 2).

Table 2. Logistic regression analysis for risk of goiter in school children of Semirom.

Variables	OR	95% CI	P value
Age (years)	1.26	0.63-2.51	0.52
Sex (male/female)	1.30	0.25-6.83	0.76
TSH (mU/l) *	1.91	0.01-25.62	0.80
T4 (μg/dl)	0.63	0.35-1.12	0.11
UIC (μg/dl)	1.05	0.98-1.12	0.15
Serum Zn (μg/dl) *	9.49	0.001-83.53	0.63
BMI (Kg/m2)	1.31	0.88-1.97	0.19

* A logarithmic transformation was used to normalize the distribution

Serum T4 in goitrous and nongoitrous subjects was 8.65 ± 1.59 and 9.16 ± 1.47 μg/dl, respectively (p = 0.02).

Serum TSH in goitrous and nongoitrous children did not differ significantly (3.04 ± 2.93 vs. 2.50 ± 1.19 mU/l, p = 0.09).

There was also no significant difference in TSH, T4, and UIC levels between zinc deficient and zinc sufficient subjects (Table 3).

Table 3. Serum levels of different variables in children with and without zinc deficiency in school children of Semirom, Iran (μg/dl).

	TSH (mU/l)	T4 (μg/dl)	UIC (μg/dl)
Zinc deficient	2.30 ± 0.96	8.93 ± 1.55	18.49 ± 9.31
Zinc sufficient	2.80 ± 2.30	8.78 ± 1.58	24.40 ± 10.56
P value	0.07	0.70	0.10

Serum zinc was not correlated with TSH, T4, age, height, and weight. However, there was a negative weak correlation between Serum zinc and BMI (r = -0.18, p = 0.18).

Discussion

This study shows that goiter prevalence has decreased from 89.55% in 1994 [9] to about 36% in 2003. This implies iodine deficiency has been the most important cause of endemic goi-

ter 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 in spite of the salt iodization program and iodized oil injection; goiter rate is still high in this area. It should also be noted that according to WHO/UNICEF/ICCIDD recommended criteria,[16] there is no biochemical iodine deficiency or no inadequacy in iodine intake of the studied population.

In iodine deficient areas, multiple nutritional and environmental influences may contribute to the prevalence and severity of iodine deficiency disorders.[18] We had previously showed that neither selenium deficiency [19] nor iron deficiency[20] play a role in the etiology of residual goiter in schoolchildren of Semirom.

Zinc is an essential nutrient that is required in human and animals for many physiological functions.[21] It is a component of more than 300 enzymes including metal containing enzymes which participate in nucleic acid and carbohydrate metabolism, along with protein metabolism.[22] The biological effects of zinc are remarkably diverse. Thirty percent of cellular zinc is found within the nucleus,[23] and a large numbers of proteins that play a role in the regulation of gene expression have been either shown or suspected to contain zinc. It has been suggested that nuclear zinc-binding proteins may be more susceptible to zinc deficiency than zinc metaloenzymes because they have a lower affinity for the cation.[24]

Triiodo-L-thyronine (T_3) receptors, in common with other members of the nuclear receptor family, are thought to be included among the nuclear zinc-binding proteins.[25]

In the present study we showed that there was no significant difference in serum zinc level between goitrous and nongoitrous children. We also did not find any significant difference between the prevalence of zinc deficiency in children with and without goiter. There are controversial data about the role of zinc status in development of goiter. In one study in Turkey, Ozata et al showed that zinc deficiency might contribute to the pathogenesis of endemic goiter.[4] On the other hand, Hampel et al showed that zinc deficiency did not contribute to endemic goiter in Germany.[26] The present study is the second investigation to find the role of zinc status in endemic goiter in an Iranian population. The study which was published recently [17] and used almost similar method to the present work, did not find any association between zinc status and endemic goiter in Iranian schoolchildren too.

In a zinc deletion–repletion study carried out in humans, TSH, total T4 and free T4 tented to decrease during the depletion phase and returned to control levels after zinc repletion.[27] In the present study we showed that zinc deficiency does not affect thyroid hormones significantly. This was also showed by Dabbaghmanesh et al.[17]

There are several studies that revealed serum TSH is in upper normal range in area with endemic goiter.[28-30] In our study, although goitrous subjects had higher TSH level than nongoitrous ones, the difference was not statistically significant. In contrast to Semiz et al who showed that serum T_4 and TSH were not affected significantly in endemic goiter area,[31] our data revealed that goitrous subject may have lower T4 levels than nongoitrous ones.

In the present study we only measured serum zinc level to determine zinc status. Measurement of zinc in other tissues such as different blood cell types, hair, and nails, and a variety of a zinc-binding proteins, such as metallothionein and other zinc metalloenzymes, have also been investigated as possible indicators of zinc status. However, these approaches do not seem to provide any greater sensitivity or analytic convenience than using serum zinc concentration.[32] In the present study dietary intake of zinc was not assessed and we can not discuss about it here.

The main limitation of our study was that, we categorized participants into goitrous and nongoitrous group by inspection and palpation. Zimmermann et al has questioned the role of inspection and palpation in detection of goiter.[33] It would be more accurate if we used

thyroid ultrasonography to determine goiter size. It should be added that we tried to solve this problem by including nongoitrous subject and children with grade 2 of goiter who has significant enlarged thyroid, in the study.[34]

Conclusions

In conclusion, goiter is still a public health problem in Semirom. Iodine deficiency can not explain the high prevalence of goiter in this region. We did not find any association between zinc status and goiter in Semirom school children. We suggest another study with larger sample size and using thyroid ultrasonography, investigating the role of different possible contributors of goiter be done in this region.

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 students who participated in this study and the Isfahan Endocrine and Metabolism Research Center staff.

Conflict of Interests

Authors have no conflict of interests.

Authors' Contributions

MH carried out the design and coordinated the study. MHM and AHK and MSD have assistance in the statistical analysis and prepared the manuscript. HR, AA, MA, and AK provided assistance in the design of the study, coordinated and carried out all the experiments.
All authors have read and approved the content of the manuscript.

References

1. Prescott E, Netterstrom B, Faber J, Hegedus L, Suadicani P, Christensen JM. Effect of occupational exposure to cobalt blue dyes on the thyroid volume and function of female plate painters. Scand J Work Environ Health 1992;18(2):101-4.
2. Gaitan E. Goitrogens. Baillieres Clin Endocrinol Metab 1988;2(3):683-702.
3. Gaitan E. Goitrogens in food and water. Annu Rev Nutr 1990;10:21-39.
4. Ozata M, Salk M, Aydin A, Sayin S, Oktenli C, Beyhan Z, et al. Iodine and zinc, but not selenium and copper, deficiency exists in a male Turkish population with endemic goiter .Biol Trace Elem Res 1999;69(3):211-6.
5. Kawada J, Nishida M, Yoshimura Y, Yamashita K. Manganese ion as a goitrogen in the female mouse. Endocrinol Jpn 1985;32(5):635-43.
6. Ingenbleek Y, Luypaert B, De Nayer P. Nutritional status and endemic goiter. Lancet 1980;1(8165):388-91.
7. Osman AK, Fatah AA. Factors other than iodine deficiency contributing to the endemicity of goiter in Darfur Province (Sudan). J Hum Nutr 1981;35(4):302-9.
8. Azizi F, Mehran L. Experiences in the prevention, control and elimination of iodine deficiency disorders: a regional perspective. East Mediterr Health J 2004;10(6):761-70.
9. Emami A, Amini M, Azizzadeh A. The effect of lipiodol in prevention of iodine deficieniy goiter in school students of Hana. Journal of Isfahan Medical School 1994;38:47-53. (Persian)
10. Ferraz IS, Daneluzzi JC, Vannucchi H, Jordão AA Jr, Ricco RG, Del Ciampo LA, et al. Zinc serum levels and their association with vitamin A deficiency in preschool children. J Pediatr 2007;83(6):512-7.
11. Pekary AE, Lukaski HC, Mena I, Hershman JM. Processing of TRH precursor peptides in rat brain and pituitary is zinc dependent. Peptides 1991;12(5):1025-32.
12. Chen MD, Lin PY, Lin WH. Zinc supplementation on serum levels and hepatic conversion of thyroid hormones in obese (ob/ob) mice. Biol Trace Elem Res 1998;61(1):89-96.
13. Freake HC, Govoni KE, Guda K, Huang C, Zinn SA. Actions and interactions of thyroid hormone and zinc status in growing rats. J Nutr 2001;131(4):1135-41.
14. Baltaci AK, Mogulkoc R, Bediz CS, Kul A, Ugur A. Pinealectomy and zinc deficiency have opposite effects on thyroid hormones in rats. Endocr Res 2003;29(4):473-81.

15. Baltaci AK, Mogulkoc R, Kul A, Bediz CS, Ugur A. Opposite effects of zinc and melatonin on thyroid hormones in rats. Toxicology 2004;195(1):69-75.
16. WHO, UNICEF, ICCIDD. Assessment of iodine deficiency disorders and monitoring their elimination. A guide for programme managers. WHO/NHD/01.1. 2nd ed. Geneva: WHO; 2001.
17. Dabbaghmanesh MH, Sadegholvaad A, Zarei F, Omrani G. Zinc status and relation to thyroid hormone profile in Iranian school children. J Trop Pediatr 2008;54(1):58-61.
18. 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(10):867-78.
19. Hashemipour M, Siavash M, Amini M, Aminorroaya A, Rezvanian H, Kachuei A, et al. Goiter persistence after iodine replenishment, the potential role of selenium deficiency in goitrous school children of Semirom, Iran. Exp Clin Endocrinol Diabetes 2008;116(2):75-9.
20. Siavash Dastjerdi M, Hashemipour M, Rezvanian H, Kazemi F, Najafian A, Mohammady M, et al. Iron deficiency in goitrous school children of Semirom, Iran. Horm Res 2006;66(1):45-50.
21. Sun JY, Jing MY, Weng XY, Fu LJ, XU ZR, Zi NT, et al. Effects of dietary zinc levels on the activities of enzymes, weights of organs, and the concentrations of zinc and copper in growing rats. Biol Trace Elem Res 2005;107(2):153-65.
22. Vallee BL. Falchuk KH. The biochemical basis of zinc physiology. Physiol Rev 1993;73(1):79-118.
23. Smeyers-Verbeke J, May C, Drochmans P, Massart DL. The determination of Cu, Zn and Mn in subcellular rat liver fractions. Anal Biochem 1977;83(2):746-53.
24. Chesters JK. Trace element–gene interactions with particular reference to zinc. Proc Nutr Soc 1991;50(2):123-9.
25. Evans RM. The steroid and thyroid hormone receptor superfamily. Science 1988;240(4854):889-95.
26. Hampel R, Kuhlberg T, Schneider KP, Glass A, Zollner H. Serum zinc levels and goiter epidemiology in Germany. Z Ernahrungswiss 1997;36(1):12-5.
27. Wada L, King JC. Effect of low zinc intakes on basal metabolic rate, thyroid hormones and protein utilization in adult men. J Nutr 1986;116(6):1045-53.
28. Bachtarzi H, Benmiloud M. TSH-regulation and goitrogenesis in severe iodine deficiency. Acta Endocrinol (Copenh) 1983;103(1):21-7.
29. Chopra IJ, Hershman JM, Hornabrook RW. Serum thyroid hormone and thyrothropin levels in subjects from endemic goiter regions of New Guinea. J Clin Endocrinol Metab 1975;40(2):326-33.
30. Thakur C, Saikia TC, Yadav RN. Total serum levels of triiodothyronine (T3), thyroxine (T4) and thyrotropine (TSH) in school going children of Dibrugarh district: an endemic goiter region of Assam. Indian J Physiol Pharmacol 1997;41(2):167-70.
31. Semiz S, Senol U, Bircan O, Gumuslu S, Korgun DK, Akcurin S, et al. Thyroid hormone profile in children with goiter in an endemic goiter area. J Pediatr Endocrinol Metab 2001;14(2):171-6.
32. Hess SY, Peerson JM, King JC, Brown KH. Use of serum zinc concentration as an indicator of population zinc status. Food Nutr Bull 2007;28(3 Suppl):S403-29.
33. Zimmermann M, Saad A, Hess S, Torresani T, Chaouki N. Thyroid ultrasound compared with World Health Organization 1960 and 1994 palpation criteria for determination of goiter prevalence in regions of mild and severe iodine deficiency. Eur J Endocrinol 2000;143(6):727-31.
34. Adibi A, Sirous M, Aminorroaya A, Roohi E, Mostafavi M, Fallah Z, et al. Normal values of thyroid gland in Isfahan, an iodine replete area. J Res Med Sci 2008;13(2):55-60.