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Reappraisal of the risk of iodine-induced hyperthyroidism: An epidemiological population survey

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ABSTRACT. The occurrence of iodine-induced hyperthyroidism (IIH) has been reported after iodine supplementation from clinics and hospitals, but not following an epidemiologic survey. We studied the prevalence of thyroid derangement in a population following iodine supplementation. One yr after more than 75% of the population had been consuming 40 ppm iodized salt; information regarding history of endemic goiter and iodized salt production, distribution, consumption and monitoring were collected in four cities of the Islamic Republic of Iran. A total of 6048 subjects were randomly selected. All subjects were assessed for size of goiter, and urinary iodine and serum T_4, T_3, TSH, anti-thyroglobulin and anti-thyroperoxide were measured. Before iodine supplementation, all four cities were areas of endemic goiter. The rate of household consumption of iodized salt was 50, 75 and 90% in 1994, 1995 and 1996, respectively. Ninety-one percent of the salt samples contained 15-55 ppm iodide. Total goiter rate was 57, 62 and 68%; median urinary iodine was 188, 197 and 190 µg/l in the age groups of 6-18, 19-40 and >40 yr, respectively. Prevalence of clinical and subclinical hyperthyroidism was 0.34 and 0.41 and those of clinical and subclinical hypothyroidism were 0.51 and 1.07%, respectively. Nine point eight and 18% in the 19-40 yr age group and 17.6 and 25.6% in >40 yr old subjects had positive anti-thyroperoxidase and anti-thyroglobulin, respectively. This systemic epidemiologic study in an iodine deficient population showed that, following a well-executed iodine supplementation program, the occurrence of IIH is rare.
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INTRODUCTION

Iodine-induced hyperthyroidism (IIH), the occurrence of thyrotoxicosis after administration of iodine, was described more than a century ago (1) and has been the subject of many studies thereafter. A number of excellent reviews and editorials have been reported on IIH (2-4). Until 1994, IIH was considered a rather rare condition during iodide supplementation. Reports of high incidence of IIH following iodine supplementation in African countries, including several deaths (5, 6), prompted thyroidologists (7) and WHO (8) to pay more attention to the IIH problem and to implement surveys and monitor this previously unforeseen complication of iodide supplementation.
Detailed review of IIH discloses that this condition has occurred mainly with excess iodine intake (5, 6) and that in iodine supplementation programs with optimal iodine intake, an increase in incidence of hyperthyroidism has been reported from clinics and hospitals, but not as a result of systemic epidemiologic survey (9-14).
The Islamic Republic of Iran (I.R. Iran) was long considered an iodine deficient country (15). Several studies (16-18), including a national survey in 1989 (19), clearly demonstrated that goiter was prevalent as both endemic and hyperendemic in many regions. In 1985, four years before iodine supplementation began, an epidemiologic survey had shown prevalence of hypo-and hyperthyroidism of 2.3 and 3.7%, respectively (16).
The aim of this study was to determine the occurrence of thyroid derangement and antithyroid antibody positivity in the populations of four cities of the I.R. Iran with varying degrees of iodine consumption, one year after the iodide consumption rate had reached 75% of households.

Key-words: Iodine-induced hyperthyroidism, thyrotoxicosis, iodized salt, hypothyroidism, urinary iodine.

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MATERIAL AND METHODS

Study plan

Selection of provinces: a national survey of more than 30,000 schoolchildren in 1996 demonstrated that in all provinces of I.R. Iran median

urinary iodine was above 100 µg/l (20). Sari, Tehran, Rasht, and Ilam, the capital cities of the four provinces of Mazandaran, Tehran, Guilan and Ilam, respectively, were selected for this study. The geographic locations of these cities are shown in Figure 1.

Collection of information: detailed data on the history of IDD and the steps taken to control iodine deficiency were collected for each province. These included data on endemic goiter before introduction of iodized salt and the characteristics of the salt iodization program. Names of iodized salt factories, level of iodization in the factory and retailers and methods used for quality control of iodization process were obtained. This information was acquired from national and provincial authorities, from databases and literature (21) available.

Sampling: 5553 samples were required based on estimated prevalence of IIH in an endemic goiter area of 1.7% (22), with z 41.96 and a maximum acceptable error (d) of 0.34. In each city cluster sampling of households was performed. A total of 6048 subjects were selected randomly with probability proportionate to size method in four cities.

Collection of samples: each subject completed a questionnaire regarding past or present history of thyroid disorders and taking of L-T_4, T_3 or antithyroid medications. A trained physician then examined the subject and goiter was graded according to WHO-UNICEF-ICCIDD classification (23). The prevalence of goiter in each city was determined in three age groups: 6-18, 19-40 and ≥40 yr. A casual urine sample and a non-fasting blood sample were obtained between 8:00-11:00 h am from all subjects.

Visits to salt factories: salt factories producing iodized salt for the areas surveyed were visited and the logbook of the factory was reviewed.

Iodized salt monitoring: the records of salt monitoring for the years 1994 and 1995 were reviewed at the Ministry of Health and Medical Education (MHME).

This study was approved by the human research review committee and oral consent was obtained from all participants.

Fig. 1 - *Geographic locations of 4 cities surveyed in 1996. Sari, Tehran, Rasht and Ilam are the capital cities of the Mazandaran, Tehran, Guilan and Ilam provinces, respectively*

Biochemical measurements

In each city, serum was separated and promptly frozen. Frozen serum and urine samples were transferred to the research laboratory of the Endocrine Research Center where all biochemical measurements were performed.

Hormone assays: Serum concentrations of T_4, T_3, TSH and T_3 uptake test were performed using commercial kits from Fenzia, Finland. Free T_4 index (FT_4I) and free T_3 index (FT_3I) were then calculated. In all assays performed, the interassay and intraassay coefficient of variation was 11 and 9%, respectively. Reference ranges for euthyroid subjects were: T_4: 4.5-12.5 µg/dl, T_3: 80-210 ng/dl, TSH: 0.2-4.5 mU/l, T_3 uptake: 25-35%, FT_4I: 4.5-12.5 and FT_3I: 70-200.

Thyroid antibodies: anti-thyroperoxidase (TPO) and anti-thyroglobulin (Tg) titers were measured, using Elisa kits from Radim, Italy, in 600 serum samples, 300 in each of the age groups of 19-40 and >40 yr selected randomly. Values above 100 IU/ml were considered positive.

Iodine assays: urinary iodine was measured by acid digestion method. Iodine in salt was measured by titration method (24).

Methods of analysis

Statistical analyses of all data collected in four cities were centralized in the laboratory of the Endocrine Research Center. The definitions used for subclinical and clinical thyroid derangements were as follows: subclinical hyperthyroidism: suppressed serum TSH and normal free thyroid indices; overt hyperthyroidism: suppressed serum TSH and increased FT_4I and/or FT_3I; subclinical hypothyroidism; increased serum TSH and normal FT_4I; overt hypothyroidism: increased serum TSH and low FT_4I.

Descriptive statistical descriptions such as means, median, range, standard deviation and proportions were used. Differences between mean values for quantitative variables were evaluated using the student *t*-test. Chi Square was used for analysis of goiter size results. All *p* values were obtained from two-tailed tests, and only values below 0.05 were considered significant. The conversion ratios for T_4 and T_3 from µg/dl and ng/dl to nmol/l are 12.87 and 0.01536, respectively.

RESULTS

Collection of information

Before the national IDD control program was implemented, all four cities and their respected provinces were areas of endemic goiter. The past history of IDD and the major activities in the prevention and correction of iodine deficiency in the four cities are summarized in Table 1. A more detailed description of these aspects is available in records of MHME in Farsi. The information relevant to the present study indicates that, following iodized salt production in 1989, household consumption of iodized salt increased gradually; however, the rapid survey in 1994 showed that less than half of the households consumed iodized salt (21). Median urinary iodine excretion tested in spot locations was between 50 to 82 µg/l and goiter was prevalent. After the passage of mandatory law for production of only io-

Table 1 - *Past history of iodine deficiency disorder (IDD) and attempts for the prevention of iodine deficiency in the four cities studied.*

City	Past history of IDD (surveys in schoolchildren)			Attempts for the prevention of IDD	
Tehran	1984*	TGR†	88% in girls and 72% in boys	1989	Beginning of distribution of iodized salt
	1988	MUI	67 µg/l		
	1989	TGR	87% in girls and 72% in boys		
	1996	TGR	40% in girls and 39% in boys	1993	50% of households consumed iodized salt
	1996	MUI	205 µg/l		
Sari	1989	TGR	60% in girls and 57% in boys	1990	Beginning of distribution of iodized salt
				1993	44% of households consumed iodized salt
	1996	TGR	48% in girls and 50% in boys		
	1996	MUI	180 µg/l		
Rasht	1989	TGR	86% in girls and 83% in boys	1990	Beginning of distribution of iodized salt
				1993	48% of households consumed iodized salt
	1996	TGR	72% in girls and 68% in boys		
	1996	MUI	390 µg/l		
Ilam	1989	TGR	94% in girls and 95% in boys	1991	Beginning of distribution of iodized salt
				1993	40% of households consumed iodized salt
	1990	MUI	19 µg/l		
	1996	TGR	85% in girls and 78% in boys		
	1996	MUI	420 µg/l		

* 1984, 1989 and 1996 data have been derived from references no. 20, 23 ads 35, respectively; the rest of the information was taken from unpublished sporadic surveys. † TGR: total goiter rate; MUI: median urinary iodine.

dized salt in 700-1000 g bags for household use in 1994, the percentage of iodized salt consumption by the household increased to a mean of 75 and 90% by 1995 and 1996, respectively. Therefore, at the time of this study, in 1996, 90% of the household had been consuming iodized salt for at least one year.

Quality assurance of iodized salt

From the outset of the salt iodization program, 40 gm of potassium iodate is added to each kg of salt. There exists a systematic approach with written objectives and detailed description of programs of monitoring at production, storage, distribution and consumption levels (21). Salt producers in each work shift take three samples of iodized salt from the production line and test it for iodine content and homogeneity. The results registered from all factories showed between 15 and 55 ppm in 97% of the cases. Officers of the provincial Food Safety Department visit each production unit regularly.

Monitoring of iodized salt is performed at the distribution level on a monthly basis in each province. Sampling of iodized salt is performed so that all available brand names of salt in every region are sampled and tested at least once each month. Table 2 shows the results of quality testing of samples obtained at retailers in four provinces, two years prior to this study. Mean iodine content of salt was 35±9 ppm and 97% of the salt samples contained 15-55 ppm iodide.

Table 2 - *Iodide content of iodized salt in four cities obtained at retailers during the 2 yr prior to population study.*

Name of the city	Yr	Salt samples (no.)	Content of the salt		
			Mean±SD (ppm)	>55 ppm (%)	<15 ppm (%)
Sari	1994	81	33±9	0	6.0
	1995	30	34±8	0	3.3
Tehran	1994	71	37±8	0	1.3
	1995	98	38±9	4.2	2.1
Rasht	1994	69	35±9	0	1.9
	1995	39	37±10	3.1	3.4
Ilam	1994	72	30±9	0	5.6
	1995	53	31±7	0	1.9

Field surveys

In Tehran, Sari, Rasht and Ilam, 4381, 543, 596 and 528 people were evaluated, respectively. As seen in Table 3, the percentage of individuals with goiter increased with age, and larger goiters were present in older subjects. The rate of iodide consumption one year before the study was the same for all age groups.

Serum thyroid hormones: results of serum T_4, T_3 and TSH concentrations and urinary iodine content in three age groups in four cities are shown in Table 3. Mean FT_4I, FT_3I and TSH concentration were within normal range in the three age groups. There was no statistical difference in serum FT_4I and urinary iodine concentrations between the four cities and between various age groups. FT_3I was higher in 6-18 yr olds as compared to other age groups.

The numbers of cases with thyroid derangement are shown in Table 4. Only 0.75% of population studied had serum TSH of ≤0.1 mU/l. The prevalence of overt and subclinical hyperthyroidism was 0.34 and 0.41%, respectively. One point fifty-eight per cent of the population had TSH values above 5.0 mU/l; 1.2% in the 19-40-yr-old age group, and 1.95% in >40-yr-old subjects. The prevalence of subclinical and overt hypothyroidism was 1.07 and 0.51%, respectively.

Thyroid antibodies: mean anti TPO and anti Tg titers in the age groups of 19-40 and >40 yr were 67.4±31.5 and 88.3±63.5, and 56.7±74.7 and 67.7±105.0 IU/ml, respectively. The percentage of subjects having anti Tg and anti TPO above 100 IU/ml was 9.8 and 18.0% in the age group of 19-40 and 17.6 and 25.6% in >40-yr-old subjects, respectively.

Table 3 - *Serum T_4, T_3 and TSH concentration and median urinary iodine content in three age groups in populations of four cities.*

Variables	Age groups (yr)		
	6-18 (no.=2982)	19-40 (no.=1611)	>40 (no.=1455)
Mean age (yr)	12.1±3.6	29.3±6.5	54.1±10.3
Total goiter rate (%)	57	62	68
Percentage of visible goiter (grade 2)	18	23	34
Median urinary iodine (µg/l)	188	197	190
FT_4I	7.9±1.5	7.8±1.8	7.4±1.5
FT_3I	173±39*	134±35	124±34
Serum TSH (mU/l)	1.6±1.0	1.1±1.0	1.1±1.0

*$p<0.001$, as compared to other age groups.

Table 4 - *Number of cases with thyroid derangement among 6048 subjects studied in four cities.*

Thyroid derangement	Known by history	Newly discovered	Total
Thyrotoxicosis			
Clinical	6 (0.09%)	15 (0.25%)	21 (0.34%)
Subclinical	–	25 (0.41%)	25 (0.41%)
Hypothyroidism			
Clinical	11 (0.18%)	20 (0.33%)	31 (0.51%)
Subclinical	–	65 (1.07%)	65 (1.07%)

DISCUSSION

The findings of the present study do not show any occurrence of IIH in the Iranian population, one year after 75% of the population had been consuming iodized salt.

A small but important rise in the occurrence of thyrotoxicosis has been reported in several endemics. Sharp rises in hospital admissions and surgical thyroidectomies between 1924 and 1928 in the United States (7, 9-11) had no epidemiological controls. It is noteworthy to mention that the initial concentration of iodine in salt in many parts of the United States was very high, 0.02%, and was quickly reduced to 0.01%. Tasmania is referred to as the country that has, by far, presented the best documented epidemic of IIH (12, 13). The country was affected by modest to moderate endemic goiter. In 1963, iodide supplementation resulted in mean urinary iodine excretion of 173 to 264 µg per 24 h (14). A rise in the number of patients with hyperthyroidism presenting to the clinics and hospitals for a few years after iodine supplementation was reported; the diagnosis was based on clinical assessment, PBI, ^{131}I uptake and T_3 resin uptake. Most of the patients were in the older age groups and had nodular goiter (12).

In Switzerland the salt iodization program at 3.75 ppm iodine caused a rise of mean urinary iodine from 20 to 55-60 µg daily; only five cases of thyrotoxicosis in a population of 300,000 were seen. In 1980, when the level of salt iodine was increased to 15 ppm, urinary excretion of iodine rose to 90-150 µg/g creatinine and it was suggested that a rise of 10% in hyperthyroidism had occurred in the next two years with a subsequent fall (25). Again there is no population survey on thyrotoxicosis, relying mainly on empiric observations.

Following reports of occurrence of IIH in two African countries (5, 6), ICCIDD, WHO and UNICEF in a partnership study evaluated the outcome of iodized salt consumption in seven African countries. The report indicates that in Zimbabwe and the Democratic Republic of Congo, people were exposed to iodine

excess due mostly to poor monitoring of the quality of iodized salt (26). Again, an increase in cases of IIH was reported by physicians and no population study on the prevalence of IIH and systematic determination of thyroid hormones in blood samples, collected from a representative sample of the population, was available. Similar observations have been reported from Zaire, when iodized salt (1 to 840 ppm, with 25% of samples >50 ppm) was introduced into the Kivu region and caused hyperthyroidism in many subjects (5).

Several reports of IIH have appeared from other regions of the world in literature available today. A critical review of these reports indicates the following:

1. Introduction of iodinated salt at a level exceeding WHO recommendation of 20-40 ppm; such as Chile (27) and the African countries (5, 6, 26).
2. Clinical or biochemical thyrotoxicosis following iodized oil administration or excess iodine intake, such as the Brazil (28), Argentina (29), Nepal (30), Ecuador (31), Malaysia (32), Iran (33, 34), Sudan (35).
3. Increased cases of hyperthyroidism following consumption of iodized salt (in bread or household salt) reported from clinics and hospitals, such as with Netherlands (36), Austria (37), Spain (38).
4. Experimental IIH or exposure to iodine containing medications, in particular amiodarone (39).

Many prophylactic programs with salt iodization at various levels and with iodized oil in varying amounts have not demonstrated increase in incidence of thyrotoxicosis (40-43). In the present study, at least 50% of the population had consumed iodized salt only for two years and 25% for one year prior to this study. It has been shown that the majority of cases of IIH occur 1-2 years following iodine supplementation in iodine deficient populations. Although there are no data regarding the rates of thyroid dysfunction before salt iodization began in Tehran, in 1985 an epidemiologic survey in Shahriar, a town 35 km southwest of Tehran conducted on 1323 members of 300 families had shown prevalence of thyroid hormone deficiency and excess of 2.3 and 3.7%, respectively (16). The distribution of people were 44, 29 and 27% for age groups of 6-18, 19-40 and >40 yr, not significantly different from that of the current report. In the present study, the frequency of both thyroid deficiency and excess is so low that if there had been an increase, the extent of the increase would most likely have been very small.

Autoimmune thyroid disorders are less prevalent in iodine deficient than in iodine sufficient regions (44, 45). Iodine supplementation may increase the frequency of lymphoid infiltrate of the thyroid and serum thyroid antibody levels (46, 47). In the present study, the rate of positive anti Tg and anti TPO is comparable to other studies (48-50). In 1985, in a previous study in Shahriar, a city near Tehran, we had reported that the prevalence of thyroid antibodies was very low, 4.0% anti-Tg and 3.2% anti-microsomal; however, hemaglutination test was used for the determination of the titer of thyroid antibodies (16). To date no systematic epidemiologic study has been performed on the occurrence of IIH in an iodine-deficient population that had consumed iodized salt at the recommended level of 20-40 ppm. Therefore, the findings of the present study, which was designed to explore the occurrence of hyperthyroidism in an iodine-deficient population with recent onset of iodized salt consumption, may reiterate that IIH is rare in a well-executed IDD control program and the enormous benefits that correction of iodine deficiency has in preventing brain damage, ensuring child survival and learning and improving the quality, may be worth the risk of the rare occurrence of IIH. Careful management of any prophylactic health program is the key to its ultimate success, and the IDD control program is no exception.

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REFERENCES

1. Coindet JF. Decouvete'd un remede contrele goiter. Ann Chim Et Phys 1820, 15: 49.
2. Hetzel BS. Iodine-induced thyrotoxicosis (jodbasedow). In: Stanbury JB, Hetzel BS eds. Endemic Goiter and Endemic Cretinism. New York: Wiley. 1980, 562.
3. Fradkin JE, Wolff J. Iodide-induced thyrotoxicosis. Medicine 1983, 62: 1-20.
4. Pennington JA. A review of iodine toxicity reports. J Am Diet Assoc 1990, 90: 1571-81.
5. Bourdoux PP, Ermans AM, Mukalay A, et al. Iodine-induced thyrotoxicosis in Kivu, Zaire [Letter]. Lancet 1996, 347: 552-3.
6. Todd CH, Allain T, Gomo AZ, et al. Increase in thyrotoxicosis associated with iodine supplements in Zimbabwe [letter]. Lancet 1995, 346: 1563-4.
7. Stanbury JB, Ermans AE, Bourdoux P, et al. Iodine-induced hyperthyroidism: occurrence and epidemiology. Thyroid 1998, 8: 83-100.

8. WHO. Recommended iodine levels in salt and guidelines for monitoring their adequacy and effectiveness. WHO, Division of Nutrition, Geneva, 1997.
9. Kohn LA. The Midwestern American "epidemic" of iodine-induced hyperthyroidism in the 1920s. Bull N Y Acad Med 1976, 52: 770-81.
10. McClure RD. Thyroid surgery as affected by the generalized use of iodized salt in an endemic goiter region preventive surgery. Ann Surg 1934, 100: 924-7.
11. Hartsock CL. Abuse of iodine, especially of iodized salt, in the prevention of goiter. Ann Intern Med 1927, 1: 24-8.
12. Connolly RJ, Vidor GI, Stewart JC. Increase in thyrotoxicosis in endemic goiter area after iodation of bread. Lancet 1970, 1: 500-2.
13. Vidor G, Stewart JC, Wall JR, et al. Pathogenesis of iodine-induced thyrotoxicosis: Studies in northern Tasmania. J Clin Endocrinol Metab 1973, 31: 901-9.
14. Connolly RJ. An increase in thyrotoxicosis in southern Tasmania after an increase in dietary iodine. Med J Austral 1971, 1: 1268-71.
15. Emami A, Shahbazi H, Sabzevari M, et al. Goiter in Iran. Am J Clin Nutr 1969, 22: 1584-8.
16. Azizi F, Kimiagar M, Bastani J, Navai L, Ghazanfari F. Evaluation of goiter in Shahriar. J Beheshti Med Sch 1985, 9: 75-80.
17. Azizi F, Kimiagar M, Navai L, Navarabadi M, Mostafavi H. Goiter in Tehran and suburbs. Recent progress in thyroidology. Proceedings of the Third Asia and Oceania Thyroid Association Meeting (Vichayanart, A. et al. eds.). Dec. 4-6, 1986, p.50.
18. Kimiagar M, Azizi F, Mavai L, Yassai M, Nafarabadi M. Survey of iodine deficiency in a rural area near Tehran: Association of food intake and endemic goiter. Eur J Clin Nutr 1990, 44: 12-22.
19. Azizi F, Kimiagar M, Nafarabadi M, Yassai M. Current status of iodine deficiency disorders in the Islamic Republic of Iran. EMR. Health Serv J 1990, 8: 23-7.
20. Azizi F, Sheikholeslam R, Hedayati M, et al. Sustainable control of iodine deficiency in Iran: beneficial results of the implementation of the mandatory law on salt iodization. J Endocrinol Invest 2002, 25: 409-13.
21. Azizi F. Assessment, monitoring and evaluation of iodine deficiency disorders in the Middle East and Eastern Mediterranean Region. Sara. Publ Tehran 2002.
22. Roti E, Degli Uberti E. Iodine excess and hyperthyroidism. Thyroid 2001, 11: 493-500.
23. WHO/UNICEF/ICCIDD. Assessment of the iodine deficiency disorders and monitoring their elemination. Report of consultation, May. 4-6 WHO/NHD/01.1, Geneva, 2001.
24. Dunn JT, Crutchfield ME, Gutekunst R, Dunn AN. Methods for measuring iodine in urine. Geneva, ICC/IDD/UNICEF/WHO publication. 1993.
25. Baltisberger BL, Minder CE, Burgi H. Decrease in incidence of toxic nodular goiter in a region of Switzerland after full correction of mild iodine deficiency. Eur J Endocrinol 1995, 132: 546-9.
26. Delange F, de Benoist B, Alnwick D. Risks of iodine-induced hyperthyroidism after correction of iodine deficiency by iodized salt. Thyroid 1999, 9: 545-56.
27. Zanzi I, Bradford I, Cordova J. Aspectos epidemiologicos del hypertiroidismo en Chile. Rev Med Chile 1973, 100: 1055-63.
28. Martins C, Lima N, Knobel M, Medeiros-Neto H. Natural course of iodine-induced thyrotoxicosis (jodbasedow) in endemic goiter area: A 5 year follow-up. J Endocrinol Invest 1989, 12: 239-44.
29. Wanatable T, Moran D, El Tamera E, et al. Iodized oil in the prophylaxis of endemic goiter in Argentina. In: Dunn JT, Mederios G eds. Endemic goiter and cretinism: continuing threats to world health. PAHO Scientific Publication No. 292, PAHO Washington, DC, 1974, p. 231.
30. Croxon MS, Gluckman PD, Ibbertson HK. The acute thyroidal response to iodized oil in severe endemic goiter. J Clin Endocrinol Metab 1976, 42: 926-30.
31. Kevany J, Fierro-Benitez R, Pretell EA, Stanbury JB. Prophylaxis and treatmet of endemic goiter with iodized oil in rural Ecuador and Peru. Am J Clin Nutr 1969, 22: 1597-607.
32. Maberly GF, Corcoran JM, Eastman CJ. The effect of iodized oil on goiter size, thyroid function and the development of the jod basedow phenomenon. Clin Endocrinol 1982, 17: 253-9.
33. Azizi F, Kimiagar M, Ghazi AA, Nafarabadi M. The effects of iodized oil injection in eu- and hypothyroid iodine deficient girls. J Endocrinol Invest 1997; 20: 18-23.
34. Azizi F, Daftarian N. Side-effects of iodized oil administration in patients with simple goiter. J Endocrinol Invest 2000, 23: 301-5.
35. Elnager B, Eltom M, Karlsson FA, et al. The effects of different doses of oral iodized oil on goiter size, urinary iodine, and thyroid-related hormones. J Clin Endocrinol Metab 1995, 80: 891-7.
36. Van Leeuwen E. Een vorm van genuine hyperthyreose (M. Basedow zonder exophthalmus) na gebruik van gejodeerd brood. Ned Tijdschr Geneeskd 1954, 98: 81-9.
37. Mostbeck A, Galvan G, Bauer P, et al. The incidence of hyperthyroidism in Austria from 1987 to 1995 before and after an increase in salt iodization in 1990. Eur J Nucl Med 1998, 25: 367-74.
38. Galofre JC, Fernandez-Calvet L, Rios M, Garcia-Mayor RV. Increased incidence of thyrotoxicosis after iodine supplementation in an iodine sufficient area. J Endocrinol Invest 1994, 17: 23-7.
39. Surks MI, Sievert R. Drugs and thyroid function. N Engl J Med 1995, 333: 1688-94.
40. Lazarus JH, Parkes AB, N'Diaye JR, et al. Endemic goiter in Senegal-Thyroid function, etiological factors and treatment with oral iodized oil. Acta Endocrinol 1992, 126: 149-54.
41. Pharoah PO, Connolly KJ. A controlled trial of iodinated oil for the prevention of endemic cretinism: a long-term follow-up. Int J Epidemiol 1987, 16: 68-73.
42. Phillips DI, Osmond C. Iodine supplementation with oral or intramuscular iodized oil. A two-year follow-up of a comparative trial. Int J Epidemiol 1989, 18: 907-10.

43. Ranganathan S, Reddy V. Human requirements of iodine & safe use of iodized salt. Indian J Med Res 1995, 102: 227-32.

44. Weetman AP, McGregor AM. Autoimmune thyroid disease: further development in our understanding. Endocr Rev 1994, 15: 788.

45. Dayan CM, Daniels GH. Chronic autoimmune thyroiditis. N Engl J Med 1996, 335: 99-107.

46. Boukis MA, Koutras DA, Souvatzoylou A. Thyroid hormone and immunologic studies in endemic goiter. J Clin Endocr Metab 1983, 57: 859-62.

47. Kahaly G, Dienes HP, Beyer J, Hommel H. Randomized double-blind, placebo-controlled trial of low dose iodine in endemic goiter. J Clin Endocrinol Metab 1997, 82: 4049-53.

48. Prentice LM, Phillips DI, Sarsero D, et al. Geographical distribution of subclinical autoimmune thyroid disease in Britain: a study using highly sensitive direct assays for autoantibodies to thyroglobulin and thyroid peroxidase. Acta Endocrinol 1990, 123: 493-8.

49. Roti E, Gardini E, Minelli R, et al. Prevalence of anti-thyroid peroxidase antibodies in serum in the elderly: comparison with other rests for anti-thyroidies. Clin Chem 1992, 38: 88-92.

50. Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 2002, 87: 489-99.