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Sustainability of a well-monitored salt iodization program in Iran: Marked reduction in goiter prevalence and eventual normalization of urinary iodine concentrations without alteration in iodine content of salt

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ABSTRACT. ***Objective:*** **Two yr after legislation of salt iodization of 40 parts per million (ppm) in 1994, goiter was still endemic and urinary iodine concentration (UIC) remained elevated in many provinces of Iran. Goiter prevalence and UIC were compared 2 and 7 yr after sustained consumption of uniformly iodized salt by Iranian households.** ***Methods:*** **Schoolchildren (7-10 yr) of all provinces were randomly selected by cluster sampling from December 2000 to June 2001. Goiter rate, UIC, and household salt iodine values were compared to those in 1996. Factory salt iodine was also compared in 2001 *vs* 1996. Ultrasonographically determined thyroid volumes of 7-10 yr old children were compared in 2001 *vs* 1999.** ***Results:*** **In 2001 (no.=33600) *vs* 1996 (no.=36178), total, grade 1, and grade 2 goiter rates were 13.9 *vs* 53.8%, 11.0 *vs* 44.8%, and 2.9 *vs* 9.0%, respectively (p<0.0001). Weighted total goiter rate was 9.8% in 2001. Median (range) UIC in 2001 (no.=3329) was 165 (18-499) μg/l and in 1996 (no.=2917) was 205 (10-2300) μg/l (p<0.0001). In 2001 *vs* 1996, mean±SD for iodine salt content was 32.7±10.1 *vs* 33.0±10.2 ppm (p=0.68) in households and was 33.2±13.4 and 33.8±13.2 ppm (p=0.57) in factories, respectively. Among 7-10 yr old children in 2001 (no.=400) *vs* 1999 (no.=396), only 7-yr-old children in 2001 (the only group with probably no history of iodine deficiency) showed significant smaller thyroid volumes by ultrasonography compared to those in 1999.** ***Conclusions:*** **After 7 yr of optimized iodized-salt supplementation in Iran, adequate UIC values and marked reduction in goiter rate have been achieved.**
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INTRODUCTION

In the last decade, iodine deficiency has been recognized as the leading cause of preventable brain damage worldwide (1, 2). Although the importance of adequate iodine intake is obvious (3, 4), and outstanding efforts from international agencies had resulted in the worldwide pledge of achieving iodine sufficiency by the year 2005, there are still many regions even in most industrialized countries of the world that are suffering from iodine deficiency (4-6). Although one of the most common ways of achieving this goal was through universal salt iodization, less than 100 countries had iodized salt legislation by 1998 (7, 8). Recently, it has been reported that approximately one-third of the world population is still suffering from low iodine intake (9).

Once the criteria of iodine repletion have been achieved (8), the sustainability of iodine sufficiency would then be the major concern. One of the major causes of failure in iodine deficiency elimination programs is the sense of complacency toward maintenance of adequate iodine intakes in a population (10). Recurrence of iodine deficiency has been reported shortly after discontinuation of salt iodization and also following lapse of annual monitoring of iodine status in an area with successful elimination of iodine deficiency (11, 12). Thus, strategies

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worldwide have to prepare societies for regular monitoring programs in order to control their iodine status and implement appropriate interventions once iodine deficiency recurs (6, 8).
The prevalence of goiter in various provinces of Iran was between 10-60% in 1968 (13). However, no preventive measures for the control of iodine deficiency were undertaken. Local studies in the 1980s and a large survey in 1990 revealed that goiter prevalence was much higher than previously reported, as goiter rate was greater than 60% in the majority of the provinces in Iran. A nationwide survey of goiter in 1989 showed that goiter existed in schoolchildren in most provinces at a rate of 30% to 80% and it was estimated that 20 million people were at risk of iodine deficiency (14). Scattered measurement of urinary iodine concentration (UIC) in various parts of the country had also shown mild to severe iodine deficiency. The Minister of Health and Medical Education set up the Iranian National Committee for Control of iodine deficiency disorders (IDD) in 1989. The production and distribution of iodized salt with 40 mg potassium iodide per kg of sodium chloride began and the education of policy makers, health personnel, and public was started in 1990. However, a rapid survey of iodized salt consumption showed that less than 50% of the population consumed iodized salt in 1993 with mean UIC of 50 to 82 μg/l in spot locations. Therefore, the first law requiring mandatory iodination of all salts for household use was passed in 1994. Multiple rapid surveys on iodized salt consumption demonstrated that more than 90% of households consume iodized salt. An early assessment in 1996 showed that goiter remained endemic despite adequate iodine intake by Iranian schoolchildren (15). It was assumed that goiter endemicity was largely due to residual goiters from the iodine deficiency era and that goiter rate would decrease as the program continued. Due to the continuous risk of recurrence of iodine deficiency in a previously iodine-deficient area (12), an every-5-yr surveillance program on sustainability of iodine sufficiency in Iran by the assessment of goiter prevalence and measurement of UIC has been conducted since 1996. In this study the indicators of the second (i.e., 2001) *vs* first (i.e., 1996) national monitoring program of sustainability of iodine deficiency control in Iran were compared.

MATERIALS AND METHODS

General considerations

Five separate groups of samples were randomly and cross-sectionally selected and assessed. The first 3 groups were selected in 2001:

- Group #1: schoolchildren for goiter prevalence and UIC,
- Group #2: household table salt samples (these samples were selected from different households recruited for the group #1)
- Group #3: salt samples from iodized salt producing factories for measurement of iodine values.

Of the above-mentioned variables, goiter rates of the first national study in 1996 have been reported earlier (15), and therefore we reported only goiter rates of 2001 in detail and showed the differences of goiter rates in 2001 *vs* 1996 by figures. However, data on UIC and household and factory salt iodine contents in 2001 *vs* 1996 are reported and compared minutely in this study.

- Groups #4 and 5: In Iran, ultrasonographic assessment of thyroid volume in a large population of schoolchildren was first performed in 1999 (16). However, the recruited children probably had a past history of iodine deficiency (16). In the present study, we also compared ultrasonographically-determined thyroid volumes of schoolchildren in 1999 (group #4) *vs* 2001 (group #5) to assess the effect of 2 yr of iodine supplementation on thyroid volumes (16-18).

Clinical goiter assessment and urinary iodine concentration (group #1)

This cross-sectional study was conducted on Iranian schoolchildren aged 7-10 yr. The data on households collected in the 1996 countrywide poll were made available by the Deputy of Health of the Ministry of Health and Medical Education (MHME); provincial territories were redefined and there are now 28 (instead of 26) provinces in Iran since 1997 (Fig. 1); Golestan and Ghazvin, the two new provinces, were previously part of Zanjan and Mazandaran provinces (15).
To estimate goiter prevalence in each province, we employed the sample size formula presented previously using the maximum amount of variance by considering p=q=0.5 (19, 20). Accordingly, 596 samples needed to be collected from rural and 596 from urban regions of each province (i.e., 33,376 children for the whole country) to have an estimate on goiter prevalence with an error of 5% and a design effect of 1.55.
Cluster random sampling was used for the enrollment of the subjects (21). Using household data, ages of the children were calculated from the recorded birth dates. In each province, 20 codes of the households of 10 female and 10 male children were randomly selected and by direct questioning their school addresses were obtained. Of each subject's school, 3 clusters, each containing 20 randomly selected schoolchildren according to the child's code in the school, were selected. Thus, 60 clusters containing 1200 (600 rural and 600 urban) schoolchildren were enrolled from each province, resulting in 33,600 subjects as the total sample size of the present study.
Children were examined at schools in the morning, and thyroid size was assessed using the palpation method and classified into grades 0-2 according to the classification of World Health Organization (WHO)/United Nations Children's Fund (UNICEF)/International Council for the Control of Iodine Deficiency (ICCIDD). All efforts were made to ensure the presence of all students at the time of clinical examination (8).
To reduce interobserver differences in goiter assessment by the palpation method (22), 10 general practitioners were recruited and trained under supervision of an experienced endocrinologist of the study prior to initiation of the program. Each physician had to determine goiter grades in 60 schoolchildren. Kappa co-

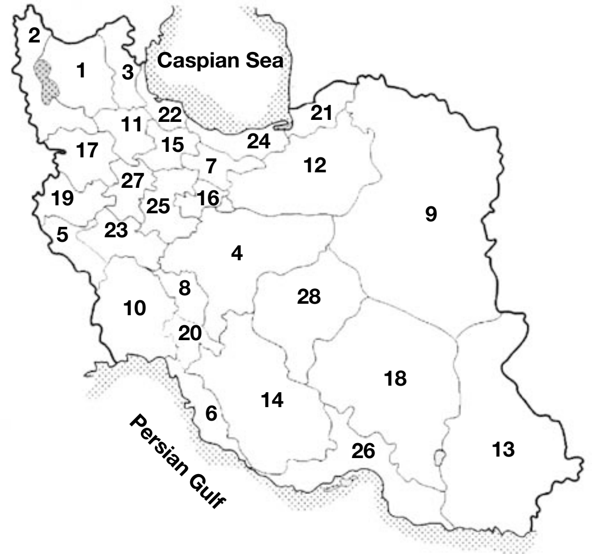

Fig. 1 - *Twenty-eight provinces of Iran. 1: East-Azarbaijan, 2: West Azarbaijan, 3: Ardabil, 4: Isfahan, 5: Ilam, 6: Boushehr, 7: Tehran, 8: Charmahal-Bakhtiari, 9: Khorasan, 10: Khousestan, 11: Zanjan, 12: Semnan, 13: Sistan-Balouchestan, 14: Fars, 15: Ghazvin, 16: Ghom, 17: Kordestan, 18: Kerman, 19: Kermanshah, 20: Kohkiloyeh-Boyerahmad, 21: Golestan, 22: Guilan, 23: Lorestan, 24: Mazandaran, 25: Markazi, 26: Hormozgan, 27: Hamedan, 28: Yazd.*

efficient of agreement was calculated for validation, based on obtained results from each physician and those of the endocrinologist. Only 8 examiners who had the highest kappa (the minimum value of 0.70) for detection of goiter grades 1 and 2 were employed (data not shown).

One-tenth of the children enrolled for goiter assessment were randomly selected for UIC measurement. Thus, 120 (equal numbers of rural and urban) urine samples from each province (i.e., 3360 totally) were expected to be obtained in the study; finally, 3329 samples were collected. Spot urine samples (10 ml) were collected between 08:00 and 11:00 am during the time of children's attendance at schools. Urine samples were transferred on ice to the laboratory of the Endocrine Research Center (ERC) in screw-top plastic bottles and kept frozen at –20 C until the time of iodine measurement at the end of the study (8). The study was approved by the Human Research Review Committee of the MHME and oral consent was obtained from household guardians (mostly fathers), where required.

Household salt iodine measurement (group #2)

A total number of 412 (equal numbers of rural and urban) households were selected for qualitative and quantitative assessments of table salt iodine using their national codes. Qualitative assessment was performed on site by health workers using rapid (field) test kits and 10 g of the table salt were transferred to the laboratory for food and drug control of the health center in each province for quantitative iodine measurement.

Iodized salt at factory level (group #3)

At the time of the study, there were 124 iodized salt producing factories in the country, distributed in 11 provinces throughout the country (Fig. 1; provinces # 1, 2, 4, 9, 11, 12, 14, 16, 17, 23, and 27). Three samples (2 from different parts of the warehouse and 1 from the production department of the entire iodized salt production process) were to be collected from each factory. Taking into account missing samples, a total of 297 factory salt samples were collected and sent to the Laboratory for Food and Drug Control of the health center in each province for quantitative iodine measurement.

Thyroid volume by ultrasound (groups #4 and 5)

In order to assess possible changes in ultrasonographic thyroid volume normative values, we enrolled 396 Tehranian schoolchildren aged 7-10 yr in 1999 (group #4) and 400 age-, sex-, weight-, height-, and city-matched children (equal number of each sex) in 2001 (group #5). The latter were not those recruited earlier for the clinical goiter evaluation. Thyroid volume was the sum of the volume of each lobe (isthmus not included). The volume of each lobe was measured using Width (cm)×Depth (cm)×Length(cm)×0.479 formula (23). To prevent inter-observer variations, ultrasonographies were performed by a trained examiner (24).

Laboratory and ultrasound measurements

All UIC values were assayed by two trained technicians at the ERC laboratory using acid digestion method (25). Median UIC<100 μg/l was representative of iodine deficiency. Mild, moderate, and severe iodine deficiency were considered if median UIC was 50-99, 20-49, and <20 μg/l, respectively. Median UIC of 100-199, 200-299, and ≥300 μg/l were considered as adequate, more than adequate, and excessive, respectively (1, 8). Intra-assay coefficient of variation (CV) of UIC measurement method for concentrations of 3.5, 15, and 38 μg/l were 11.2%, 8.2%, and 9.4%, and inter-assay CV values for the same concentrations were 12.5%, 8.9%, 10.3%, respectively.

For qualitative salt iodine measurement, rapid test kits were used (26). Quantitative salt iodine measurements were performed by iodometric titration assay (27) and values were shown in parts per million (ppm). The titration method has been standardized by the ERC and approved by the MHME for uniform measurement of salt iodine in the laboratories for food and drug control of the health center of each province. Inter-examiners' differences in various provinces have been shown to be negligible for the titrimetric method of determining salt iodine content (data not shown). Data regarding rapid salt and titration assays were finally sent to and analyzed at the ERC in Tehran.

A portable ultrasound-machine (Aloka SSD 500, Tokyo, Japan) with a 7.5 MHz linear transducer was employed for thyroid imaging, with the subjects sitting upright on a straight-backed chair with their necks slightly extended. Ninety-seventh percentile (P97) for thyroid volumes was considered the upper normal limit (18). Standing height was measured to the nearest mm using a standing height scale and body weight was measured with a SECA beam balanced weighing-scale to the nearest 100 g.

Statistical analyses

Because investigators employed similar goiter detection and classification and UIC measurement methods in 1996 and 2001, their data were compared between the two studies. Categorical variables were compared by chi-squared test and continuous variables by Student's *t*, analysis of variance (ANOVA), Mann-

Whitney, and Kruskal-Wallis ANOVA tests, depending on normality of their distributions.

The sample size calculated for goiter prevalence was the same for all provinces; however, total population and household frequencies differed widely among them. Using the same sample size for more and less populated provinces may result in under- or overestimation of goiter rate in those areas. Thus, total goiter rate (TGR), which is estimated by the frequency of goitrous-divided by total schoolchildren in a region (here, a province), was also multiplied by the proportion of household frequency "weight" in that region to the total household frequencies in the country using the formula presented previously (19, 20). We reported goiter prevalence as TGR and also weighted total goiter rate (TGR_w).

Body surface area (BSA) was measured using the formula of BSA (m^2)=($W_{(kg)}^{0.425} \times H_{(cm)}^{0.725}$)×0.007184 (28), where W is body weight in kg and H is height in cm. Body mass index (BMI) was also calculated by the formula of BMI (kg/m^2)=$W_{(kg)}/H_{(m^2)}$, where W is body weight in kg and H is height in m. Correlations between continuous numerical variables were assessed by Spearman's Rank and Pearson coefficients. SPSS 9.05 software package (SPSS, Inc., Chicago, IL) was used for the statistical analyses and $p<0.05$ was considered as significant.

RESULTS

Goiter rates

In 2001, goiter rate data were collected in 33,600 schoolchildren with a mean age of 8.7±1.0 yr. Total, grade 1, and grade 2 goiters were present in 4670 (13.9%), 3686 (11%), and 984 (2.9%) children in 2001. These goiter rates were significantly lower than the corresponding rates of 53.8, 44.8, and 9% among 36178 schoolchildren in the 1996 study ($p<0.0001$). In 2001, weighted total, grade 1, and grade 2 goiter rates were 9.8, 8.0, 1.8%, respectively. Prevalence of total, grade 1, and grade 2 goiters in 2001 and 1996 by provinces are shown in Figure 2 A-C. Boushehr, Charmahal-Bakhtiari, Sistan-Balouchestan, Ghom, Kordestan, and Kermanshah were provinces with grade 2 goiter rates greater than 5%. Goiter was present in 1970 (11.8%) urban and in 2700 (16.0%) rural children [odds ratio 1.4, 95% confidence interval (95% CI) 1.35-1.53, $p<0.0001$]. Of 16,721 females 2160 (12.9%) and of 16,879 males 2510 (14.9%) were goitrous (odds ratio 1.18, 95% CI 1.11-1.25, $p<0.0001$).

UIC values in 2001 vs *1996*

A total of 3329 urine samples were assayed in 2001 and 2917 samples in 1996. Median (range) UIC and 95% CI for the mean were 165 (18-499) and 183-190 µg/l in 2001 *vs* 205 (10-2300) and 286-307 µg/l in 1996, respectively ($p<0.0001$). Central tendency measures of UIC by provinces in 2001 and 1996 are shown in Table 1.

In 2001, median (range) UIC in urban areas (no.=1667) was 160 (20-499) µg/l and in rural areas (no.=1662) was 170 (18-488) µg/l ($p=0.16$). It was 230 (10-2300) µg/l in urban (no.=976) *vs* 205 (10-2300) µg/l in rural (no.=1924) areas in 1996 ($p=0.047$).

Median (range) UIC in 1676 males was 170 (20-488) µg/l and in 1653 females it was 160 (18-499) µg/l in 2001 ($p=0.18$). Median (range) UIC in 1504 males was 205 (10-2300) µg/l and in 1388 females it was 224 (10-2300) µg/l in 1996 ($p=0.96$).

UIC<100 and ≥100 µg/l were present in 655 (19.7%) and 2674 (80.3%) children in 2001 and were present in 413 (14.2%) and 2504 (85.8%) children in 1996, respectively ($p<0.0001$).

Excluding UIC<100 µg/l, values 100-299, 300-500, and >500 µg/l were present in 2083 (62.6%) and 591 (17.8%) and 0 (0%) in 2001 while corresponding values were 1617 (55.4%), 496 (17%), and 391 (13.4%) in 1996, respectively ($p<0.0001$).

In 2001, goiter (grade 1 and 2) was present in 14.4% of 655 children with UIC<100 µg/l, in 14.3% of 1520 children with UIC of 100-199 µg/l, and in 14.9% of 1154 subjects with UIC≥200 µg/l ($p=0.89$). In 1996, goiter was present in 50.6% of 362 children with UIC<100 µg/l, in 58.8% of 656 children with UIC of 100-199 µg/l, and in 63.3% of 1206 subjects with UIC≥200 µg/l ($p<0.0001$).

Qualitative and quantitative salt iodine measurement

Qualitative assays showed that all 412 household table salt samples were iodinated. Quantitative assays of 410 household salt samples (2 samples not available for titration) showed that mean±SD (95% CI) and median (range) iodine content in 2001 were 32.7±10.1 (31.8-33.7) and 32.8 (2-75) ppm and of 395 samples in 1996 were 33.0±10.2 (32.0-34.0) and 32.8 (5-79) ppm, respectively ($p=0.68$). Frequency distributions of household table salts with iodine contents of <20, 20-40, and >40 ppm were 34 (8.3%), 294 (71.7%), and 82 (20.0%) in 2001 *vs* 31 (7.8%), 284 (71.9%), and 80 (20.3%) in 1996, respectively ($p=0.97$).

Mean±SD (95% CI) and median (range) iodine content of 297 factory salt samples in 2001 were 33.2±13.4 (31.7-34.7) and 32.8 (6-84) ppm and of 278 samples in 1996 were 33.8±13.2 (32.2-35.3) and 33.9 (8-91) ppm, respectively ($p=0.57$). Frequency distributions of factory salts with iodine contents of <20, 20-40, and >40 ppm were 51 (17.2%), 162 (54.5%), and 84 (28.3%) in 2001 and were 44 (15.8%), 152 (54.7%), and 82 (29.5%) in 1996, respectively ($p=0.89$).

Household and factory salts had similar median iodine contents in 2001 ($p=0.57$) and in 1996 ($p=0.31$).

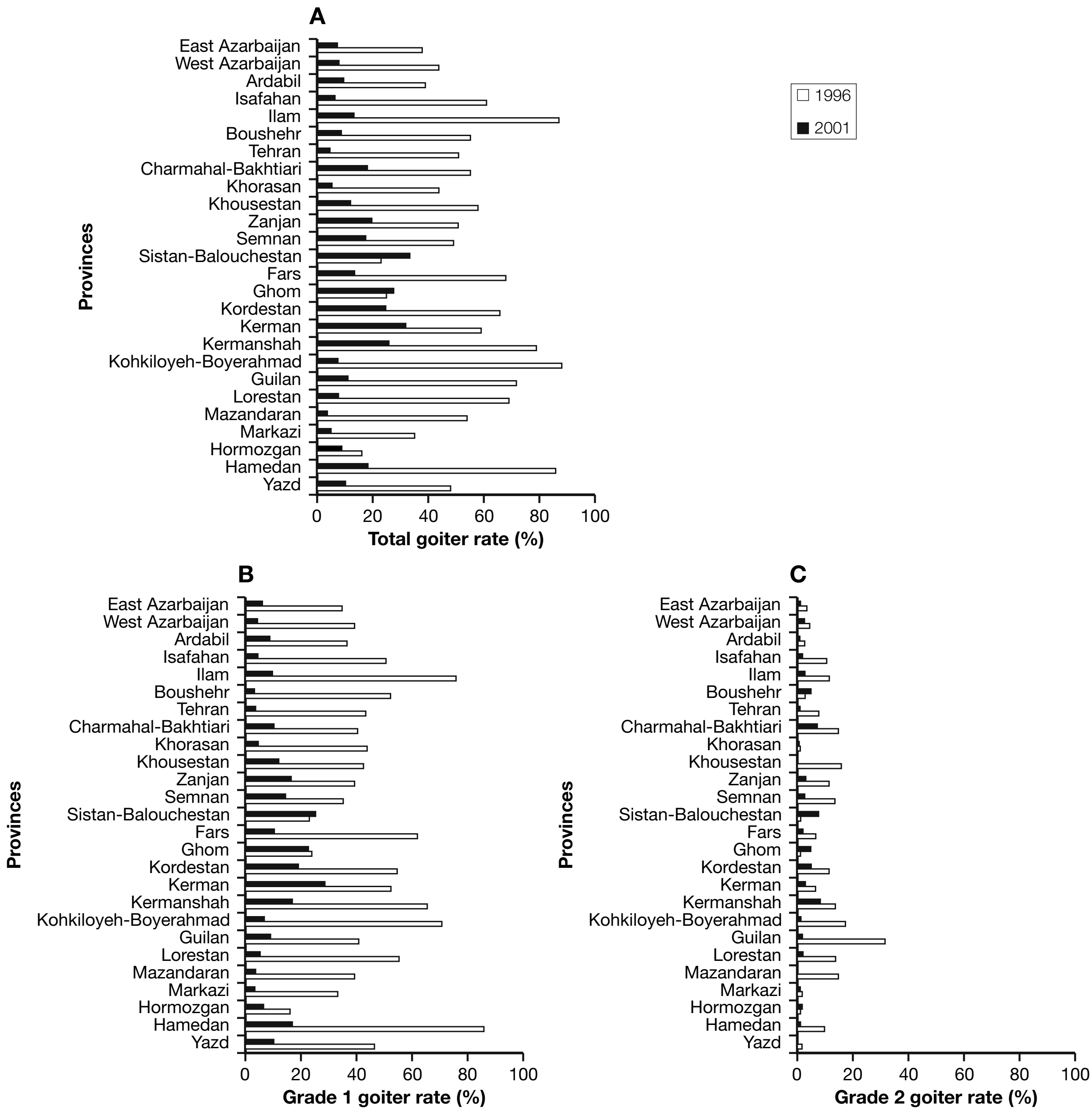

Fig. 2 - *Goiter rates in schoolchildren in 2001. A) Total goiter rates of 24 provinces in 2001 were significantly lower than those of the same provinces in 1996 (p<0.0001). Ghom showed no significant difference between 2 studies (p=0.10). Sistan-Balouchestan was the only province that showed higher goiter prevalence in 2001 as compared to 1996, i.e., 33.4% and 23.5%, respectively (p=0.002). No comparisons were made for total goiter rate in Ghazvin and Golestan because these provinces were governed by Zanjan and Mazandaran in 1996. B) Grade 1 goiter rates of 24 provinces in the present study were significantly lower than those of the same provinces in 1996 (p<0.0001). Ghom showed no significant difference between 2 studies (p=0.855). Sistan-Balouchestan was the only province that showed higher grade 1 goiter rate in 2001 as compared to 1996 (p=0.002). No comparisons were made for grade 1 goiter in Ghazvin and Golestan because these provinces were governed by Zanjan and Mazandaran in 1996. C) Grade 2 goiter rates of 20 provinces in the present study were significantly lower than those of the same provinces in 1996 (p<0.0001). There were no significant differences in grade 2 goiter prevalence in the 2 studies in Boushehr (p=0.46), Khorasan (p=0.18), Markazi (p=0.13), and Hormozgan (p=0.097) provinces. Conversely, grade 2 goiter was 8.3% in 2001 vs 1.1% in 1996 in Sistan-Balouchestan and was 5.3% in 2001 vs 1.2% in 1996 in Ghom (p<0.0001). No comparisons were made for the rate of grade 2 goiter in Ghazvin and Golestan because these provinces were governed by Zanjan and Mazandaran in 1996.*

Table 1 - *Urinary iodine concentrations among various provinces in 2001* vs *1996**.

No.	Province	Year	Mean±SD	Median	Range	95%CI[a]	*p*[b]
1	East Azarbaijan	1996	346±310	310	20-1250	291-402	<0.0001
		2001	155±72	160	20-400	141-168	
2	West Azarbaijan	1996	148±119	130	10-500	126-171	0.044
		2001	165±89	140	20-406	149-181	
3	Ardabil	1996	427±465	370	25-2300	343-512	<0.0001
		2001	189±96	185	20-405	171-206	
4	Isfahan	1996	214±173	190	10-794	182-246	<0.0001
		2001	137±91	120	20-423	121-154	
5	Ilam	1996	617±454	620	25-1930	533-701	<0.0001
		2001	179±98	157	20-405	162-197	
6	Boushehr	1996	229±203	230	25-1150	193-266	<0.0001
		2001	163±112	140	20-400	143-183	
7	Tehran	1996	219±86	232	15-404	204-235	0.354
		2001	209±106	190	20-410	189-228	
8	Charmahal-Bakhtiari	1996	254±138	240	39-500	228-279	0.001
		2001	193±108	170	18-463	173-213	
9	Khorasan	1996	248±114	246	25-610	226-269	<0.0001
		2001	168±108	130	20-454	148-187	
10	Khousestan	1996	333±284	275	25-1370	279-387	<0.0001
		2001	171±87	160	21-437	155-187	
11	Zanjan	1996	503±398	500	25-2300	412-594	<0.0001
		2001	208±101	180	20-410	190-226	
12	Semnan	1996	361±356	300	25-1600	297-425	<0.0001
		2001	161±109	130	20-405	142-181	
13	Sistan-Balouchestan	1996	229±84	230	27-610	214-244	0.559
		2001	227±116	190	20-408	206-248	
14	Fars	1996	319±291	280	25-1300	266-372	0.672
		2001	234±108	220	20-402	214-253	
15	Ghazvin[c]	1996	-	-	-	-	-
		2001	228±115	200	20-400	207-248	
16	Ghom	1996	184±124	190	10-636	162-207	0.781
		2001	174±97	160	20-400	157-192	
17	Kordestan	1996	280±152	258	10-510	252-307	<0.0001
		2001	195±122	160	20-456	172-218	
18	Kerman	1996	288±300	250	25-1650	234-343	0.001
		2001	180±100	150	20-429	162-198	
19	Kermanshah	1996	196±115	190	24-586	175-217	0.284
		2001	210±109	180	37-417	190-230	
20	Kohkiloyeh-Boyerahmad	1996	230±104	231	24-510	212-249	0.002
		2001	189±94	180	40-400	172-206	
21	Golestan[c]	1996	-	-	-	-	-
		2001	154±88	140	20-390	138-170	
22	Guilan	1996	651±328	650	45-1800	592-710	<0.0001
		2001	189±93	170	20-410	172-206	
23	Lorestan	1996	236±160	230	10-500	207-265	0.336
		2001	201±106	170	30-488	182-220	
24	Mazandaran	1996	178±135	170	10-510	153-202	0.196
		2001	190±104	165	20-483	171-209	
25	Markazi	1996	164±131	161	25-910	140-188	0.018
		2001	191±108	170	20-452	172-211	
26	Hormozgan	1996	588±420	580	20-1500	250-286	<0.0001
		2001	181±108	160	20-400	161-200	
27	Hamedan	1996	268±720	275	10-405	487-688	<0.0001
		2001	189±116	150	20-499	168-211	
28	Yazd	1996	170±418	170	25-245	162-178	0.269
		2001	194±88	170	25-409	178-210	

*From each province between 66-121 samples of urine were collected. All urinary iodine concentrations are presented in µg/l. [a]95% confidence interval. [b]Compared by Mann-Whitney U test. [c]Ghazvin and Golestan, previously governed by Zanjan and Mazandaran respectively, have been recognized as new provinces since 1997.

Thyroid volume by ultrasonography

Mean±SD and median (range) of height, weight, BSA, and BMI of children were 134±7.7 and 133 (117-159) cm, 28.3±6.8 and 27 (18-57) kg, 1.03±0.14 and 1.01 (0.77-1.54) m^2, and 15.7±2.6 and 15.0 (11.6-31.3) kg/m^2 in 1999 *vs* 134±7.8 and 133 (116-159.5) cm, 28.5±6.9 and 27 (15-58) kg, 1.03±0.14 and 1.01 (0.72-1.53) m^2, 15.8±2.6 and 15.1 (10.8-31.4) kg/m^2 in 2001, respectively (all had p values >0.50).

There was a significant correlation between thyroid volume and height (r=0.62, p<0.0001), weight (r=0.64, p<0.0001), BSA (r=0.66, p<0.0001), and BMI (r=0.42, p<0.0001) in 1999 and also of height (r=0.62, p<0.0001), weight (r=0.65, p<0.0001), BSA (r=0.68, p<0.0001), and BMI (r=0.41, p<0.0001) in 2001. Median (P50) and P97 of thyroid volumes of children by age and sex are shown in Table 2 and by BSA in Table 3. Only 7-yr-old children in 2001 showed significantly smaller thyroid volumes compared to those in 1999.

Ultrasonographic thyroid volumes vs *an international reference range*

Using P97 of a suggested international reference range (29) as the upper limit of normal thyroid volumes in 7-10 yr children, goiter was present in 2001 *vs* 1999 in 11.1% *vs* 12.4% of 9-10-yr old (p=0.87) and in 3.1% *vs* 7.7% of 7-8-yr old (p=0.068) Tehranian children, respectively. In general, goiter was present in 6.95% (26 of 374) in 2001 and 10% (36 of 360) children in Tehran in 1999.

DISCUSSION

In the second national report on monitoring of iodine deficiency control in Iran conducted in 2001, goiter rate was significantly decreased in the majority of provinces compared to 1996. With no alteration in the salt iodine contents, UIC, once elevated in 17 provinces in 1996, has been normalized in almost all provinces in 2001. These are important novel findings demonstrating that despite sustainable salt iodization program, normalization of iodine deficiency parameters may require a long time.

Because goiter represents maladaptation of thyroid to iodine deficiency (30, 31), the reduction of goiter rate to less than 5% of the schoolchildren population indicates the successful elimination of IDD as a major public health problem (8). Comparison between 2001 and 1996 studies revealed a significant reduction of 74.2%, 75.5%, and 67.8% in the total, grade 1, and grade 2 goiter rates by the observation/palpation method, respectively. This finding was supported by ultrasonographic thyroid volume in Tehran as compared to an international reference range (although data regarding Tehran cannot be generalized to other provinces). However, TGR by observation/palpation method was 13.9% in the whole country and goiter rate by ultrasonography method was approximately 7% in Tehran in 2001. This means that after 7 yr of iodized salt supplementation, the goiter prevalence is still greater than 5% of schoolchildren.

Salt iodine content was similarly within optimal range of 20-40 ppm in 2001 and 1996 and, therefore, could not be responsible for the persistence of elevated goiter rate. One explanation could be the lag period between reduction of thyroid size after immediate normalization of UIC. Our experience, as previous studies (15, 32, 33) supports the discrepancy between the correction of UIC and normalization of goiter rate immediately after salt iodization. However, by comparison of goiter rates in 1996 and 2001 it seems that the rate is declining toward values of less than 5% of schoolchildren (Fig. 2 A-C). Another explanation is the higher sen-

Table 2 - *Median (P50) and 97th percentile (P97) thyroid volumes by age and sex in 1999 and 2001.*

Yr	Age (yr)	No.[a]	Total[b] P50	Total[b] P97	Total[b] Mean±SD	Male P50	Male P97	Male Mean±SD[c]	Female P50	Female P97	Female Mean±SD[c]
1999	7	100	2.50	3.48	2.51±0.53[e]	2.47	3.41	2.47±0.49[f]	2.50	3.54	2.55±0.57
	8	96	2.51	3.90	2.55±0.73	2.50	3.90	2.41±0.78	2.59	3.99	2.68±0.66
	9	100	3.50	5.50	3.59±0.86	3.35	5.51	3.55±0.83	3.52	5.53	3.64±0.89
	10	100	3.52	6.01	3.48±0.95	3.52[d]	6.22	3.42±0.97	3.55[d]	6.71	3.55±0.94
2001	7	100	2.29	3.47	2.34±0.53	2.22	3.15	2.25±0.46[f]	2.34	3.51	2.44±0.58
	8	100	2.45	3.60	2.42±0.69	2.41	3.52	2.28±0.72	2.45	3.68	2.55±0.64
	9	100	3.34	5.29	3.46±0.85	3.10[d]	5.34	3.41±0.83	3.36[d]	5.39	3.50±0.88
	10	100	3.30	6.02	3.21±0.94	3.42	5.77	3.40±0.88	3.49	6.06	3.46±0.79

[a]There were 50 boys and girls in each age group (except for 46 8-yr-old boys in 1999). [b]Values of thyroid volume are presented in ml. [c]No significant difference was seen between males and females of any age group in 1999 and in 2001 (p>0.053). [d]Because of non-Gaussian distribution of thyroid volumes, medians were compared using Mann-Whitney U test (p>0.405). [e]Mean thyroid volume of 7-yr children was significantly lower in 2001 as compared to 1999 (p=0.032). [f]Mean thyroid volume of 7-yr males was significantly lower in 2001 as compared to 1999 (p=0.027).

Table 3 - *Median (P50) and 97th percentile (P97) thyroid volumes by body surface area (BSA) in 1999 and 2001**.

Yr	BSA (m^2)	No.	Mean±SD[a]	P50	P97
1999	0.9	70	2.4±0.6	2.4	3.4
	1.0	145	2.9±0.7	2.8	4.0
	1.1	90	3.4±0.8	3.5	5.3
	1.2	40	3.7±0.6	3.7	5.3
2001	0.9	79	2.2±0.7	2.2	3.2
	1.0	140	2.7±0.7	2.7	4.0
	1.1	88	3.3±0.8	3.3	5.1
	1.2	45	3.6±0.6	3.5[b]	4.9

*BSA values <0.9 and >1.2 m^2 were not included. [a]Mean thyroid volumes of all BSA groups were compared in 1999 *vs* 2001 using Student's t-test ($p \geq 0.08$). [b]Median thyroid volumes of those with BSA of 1.2 were compared in 1999 *vs* 2001 using Mann-Whitney U test ($p=0.21$).

sitivity but lower specificity of the 1994 *vs* 1960 WHO criteria for goiter assessment by the palpation method (34); it is therefore conceivable that our goiter rate could be overestimated.

Boushehr, Ghom, Sistan-Balouchestan, Charmahal-Bakhtiari, Kordestan, and Kermanshah had high grade 2 goiter rates in our study (Fig. 2-C), but their median UIC values were 140-190 µg/l.

Also, goiter was significantly higher in boys than in girls and in rural *vs* urban areas. Because of the insignificant differences of UIC between females/males and urban/rural areas, assessments of other goitrogens, e.g., nutritional habits, deficiencies of selenium (35, 36), iron (37, 38), and vitamin A (39), and endocrine disruptors (40-43) might be useful in detecting the underlying causes of these different goiter rates between males/females and rural/urban areas.

Iodine supplementation to a region with chronic iodine-deficiency, specifically if accompanied by excessive amounts of iodine intake, may provoke a reduction in salt iodine content because of possible risk of thyroid pathologies (6, 44-47). As a general rule, gradual increase of iodine intake toward the optimal levels and maintenance within the recommended range using regular monitoring programs would obviously be the most logical approach. Two years after enactment of the law on mandatory salt iodization (i.e. 1996), UIC values were still higher than the WHO/UNICEF/ICCIDD optimal levels in many provinces of Iran (Table 1). To handle this, one approach could be to reduce salt iodine contents, which were within the optimal range of 20-40 ppm at that time. We might, therefore, have lower exposures to excessive iodine, but here, people with already borderline-low (but adequate) iodine intake would be shifted to an iodine-deficient state. This condition is particularly important in pregnant and lactating women whose low iodine intake could be accompanied by detrimental outcomes in vulnerable populations such as neonates, infants, and young children (1, 48). Another approach could be to maintain the optimal salt iodine contents and to wait and observe changes in UIC, if any, during a specified time period. After 7 yr of national salt iodization, an optimal median UIC level was obtained among schoolchildren without any change in salt iodine content. The risk of iodine-induced hyperthyroidism would be reduced as the frequency distribution of UIC>200 µg/l decreased from 64.3% in 1996 to 14.9% in 2001. A population-based study conducted in 4 cities of Iran had previously shown that iodine-induced hyperthyrpoidism was not increased in our country (49). Because iodine content of salts remanied unchanged, we are unaware as to whether the reduction in UIC values from 1996 to 2001 in our study was due to a dietary change in schoolchildren (e.g., increase in consumption of meals cooked by microwave resulting in lower iodine intake) or some other environmental factors (e.g., poor preservation condition of salts from the factory to the consumer levels). Results of the next Iranian national monitoring program would provide information on whether there is a *decrescendo* pattern of UIC values in our country or not. A similar downward trend was primarily observed between National Health and Nutrition Examination Survey (NHANES) I and III; however, median urine iodine finally stabilized at adequate UIC levels on further follow ups (50).

Although assessment of thyroid size by ultrasonography is recommended in the field surveys (8), defining normal values for school-aged children has not been without difficulties and application of the local *vs* international reference ranges in the field surveys is still a matter of controversy (18, 29). Thyroid volumes were assessed in Tehranian schoolchildren in 1999. However, the recruited subjects were those who had been living for some years prior to the mandatory law on salt iodization in Iran and might probably have had positive histories of iodine deficiency during their early childhood (16). Therefore, upper limits reported for thyroid volume normal values might be overestimated. The present study showed that thyroid volumes were significantly smaller only in 7-yr-old children, probably because they might have had no history of iodine deficiency since the 1994 legislation of salt iodization in Iran. In general, P97 values in females in 2001 were smaller than those in 1999 but they do not reach statistical significance in any age group (Table 2). We are unaware whether earlier pre-pubertal hormonal changes in girls than boys might attenuate the effect of iodine supplementation on thyroid volume reduction, resulting in the different behavior in goiter rate documented between 7-yr-old boys and girls (Table 2).

It would therefore be worthwhile designing the next national program of monitoring of iodine deficiency control, with a view to determining not only a national thyroid volume reference range of children with no history of iodine deficiency but also integrating ultrasonography in the context of determination of goiter rates for the assessment of a more precise goiter prevalence in Iran.

In conclusion, the well-monitored salt iodization program in Iran has ultimately resulted in optimization of UIC, despite transient elevation of UIC early in the program, and has drastically decreased the goiter rate, although the latter effect appeared some years after normalization of UIC. For adults and older individuals, it may take even longer to achieve the effect of salt iodization. This study emphasizes the importance of having patience when evaluating the effect of salt iodization programs. Finally, preparing a local reference range for sonographically determined thyroid volumes requires enrollment of children with no previous history of iodine deficiency.

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