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Differences between subjects with sufficient and deficient urinary iodine in an area of iodine sufficiency

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ABSTRACT. ***Background:*** **Iran has long been recognized as a country of iodine sufficiency; however, recent studies show that the proportion of subjects with insufficient urinary iodine is gradually increasing in Tehran capital city.** ***Aim:*** **The aim of this study was to evaluate differences between individuals with sufficient and deficient urinary iodine in Tehran.** ***Material and methods:*** **In this cross-sectional study, 639 Tehranian adult subjects, aged ≥19 yr (242 males, 397 females), were enroled through randomized cluster sampling. A 24-h urine sample was collected for measurement of urinary iodine, sodium and creatinine concentrations using the digestion method, flame photometry and autoanalizer assay, respectively. Salt intake was estimated and iodine content of household salt was measured by titration.** ***Results:*** **Medians (interquartile range) of 24-h urinary iodine concentrations in subjects with sufficient and deficient urinary iodine were 163.0 (126.0-235.0) and 44.0 (26.0-67.0) μg/l, *p*<0.001, respectively. Salt with iodine content of >20 parts per million was consumed by 77.4 and 38.3% of subjects with sufficient and deficient urinary iodine, respectively (*p*<0.001). Median daily salt intake in subjects with sufficient urinary iodine was significantly higher than in those with deficient urinary iodine (8.1 *vs* 7.3 g, *p*<0.001). No significant differences in the mentioned variables were observed between males and females. Fifty and 30% of subjects with insufficient and sufficient urinary iodine had <7 yr education, respectively (*p*<0.001).** ***Conclusions:*** **Iodine content of salt, the amount of salt intake and education levels differ greatly between subjects with sufficient and deficient urinary iodine in Tehran.**
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INTRODUCTION

Iodine deficiency has been recognized as the one of four leading causes of nutritional deficiency in the world, causing a wide spectrum of iodine deficiency disorders (IDD) from spontaneous abortion, still birth, congenital anomaly and prenatal mortality in fetus to impaired mental function, decreased educability, reduced work productivity, goiter and hypothyroidism in adults (1, 2). Based on the 2007 World Health Organization (WHO) report, there is insufficient iodine intake in 52.4% Europeans, 47.2% Eastern-Mediterraneans, 42.5% Africans and 30.0% South-East Asians (3).

By WHO definition, a median urinary iodine concentration (UIC)≥100 μg/l in men and non-pregnant women denotes iodine sufficiency. With this criteria, at least 50% of population still have UIC<100 μg/l, i.e. they are iodine deficient. For instance, in Poland and Romania with median UIC of 103 and 101 μg/l, 47.2 and 46.9% of the population had insufficient urinary iodine, respectively (4); whereas, in The Netherlands and Slovakia with median UIC of 154 and 183 μg/l, only 37.5 and 15% of subjects had deficient urinary iodine, respectively (4).

The Islamic Republic of Iran was known as an area of iodine deficiency (5, 6).Production and nationwide consumption of iodized saltbegan in 1990 and became mandatory for household consumption by 1994. Since then, national surveys conducted every 5 yr have shown sustainable elimination of IDD in schoolchildren (7, 8). However, a 2010 study demonstrated that adult inhabitants of Tehran city suffered from mild iodine deficiency (9).

Data from several studies reveal that causes of iodine deficiency vary in different countries, including environmental disturbances (heavy rain in Ecuador and war in Bosnia), changes in governmental policies (Brazil and former Union of Soviet Socialist Republics), failure of monitoring of salt iodization (Guatemala and Haiti), changes in dietary iodine intake through reduction in iodine content of foodstuffs and increased use of non-iodized salt (Australia and New Zealand), and decreased daily salt consumption (Switzerland and Austria) (10).

Multiple issues influence dietary iodine status and information on factors associated with deficient urinary iodine is helpful in sustainable elimination of iodine deficiency in all age groups. Hence, the aim of this study was to evaluate differences between subjects with sufficient and deficient urinary iodine in Tehran.

MATERIALS AND METHODS

Subjects

In a 2009 cross-sectional study conducted in Tehran, the capital city of Iran, 8 of Tehran's 22 districts, from different areas (i.e. the south, west, east and north), were randomly selected. In each

Key-words: Urinary iodine concentration, salt intake, iodized salt, Tehran.

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district, a health center was randomly assigned. From each health center, of those subjects who had a documented medical history, 85 non-pregnant and non-lactating adults (age ≥19 yr) in five clusters were randomly chosen. During home visits, the purpose and methodology of the study were clarified. Out of a total of 680 subjects initially selected to participate in this study, 7 subjects refused to collaborate and 34 were excluded due to incomplete urine samples. Hence, 639 adults remained for the current analysis. Informed consent was obtained from each participant. Personal information, personal history of thyroid diseases and hypertension, consumption of medications (including levothyroxine and antithyroid drugs), and iodine-containing supplements were obtained and documented using an interviewer administered questionnaire.

Salt sample collection

During the home visit, two tablespoons (approximately 30 g) of household salt samples were collected. The samples were kept in lightproof and closed plastic cans and labeled with the code of each participant.

Urine collection

At the first home visit, written instructions and a labeled 2.5-l plastic container were given to each participant, who was asked to collect all urine passed during a 24-h period, beginning on Friday (a weekend day in Iran) starting from the second morning urine and ending with the first urine passed the following morning.
At the second visit, on the following Saturday, all samples were collected and sent to the iodine laboratory of the Endocrine Research Center (ERC), the reference laboratory of the Eastern Mediterranean region; total volume was measured and urine was transferred into screw-top labeled plastic vials. The aliquots were kept frozen until iodine, sodium and creatinine measurements.

Salt intake estimation

Salt intake was estimated by 24-h urinary sodium excretion (1 g salt equals to 17.1 mmol sodium) (11-13).

Laboratory measurements

Iodine concentration of salt samples was determined using the iodometric titration method with 1 part per million (ppm) sensitivity and 1% coefficient of variation (14). The obtained values were shown in ppm. Iodine concentration in urine samples was analyzed using the Sandell-Kolthoff (acid-digestion) reaction (15) and results were expressed as μg of iodine per liter of urine. The intra- and inter-assay coefficients of variation were 9.6 and 10.4%, respectively, and the sensitivity was 2 μg/l. Completion of 24-h urine sample collection was confirmed with creatinine concentration. Urine samples with creatinine levels <500 mg/day were considered incomplete. Urinary creatinine was measured by the kinetic Jaffé method (creatinine colorimetric kit, Pars Azmoun, Tehran, Iran). The assays were run with an autoanalizer (Vitalab, Selectra-2, The Netherlands). The assay sensitivity and coefficient of variation were 0.2 mg/dl and 2.1%, respectively. Sodium excretion in 24-h urine collections was analyzed by emission flame photometry (Corning 480, NY, USA).

Definition of terms

According to WHO/International Council for the Control of Iodine Deficiency Disorders (ICCIDD)/United Nations Children's Fund (UNICEF) criteria, median UIC<100 and UIC≥100 μg/l represented deficient and sufficient urinary iodine (3).

Statistical analyses

Frequency distribution (%) and median [interquartile range (IQR)] were computed according to qualitative and continuous numerical variables. Non-parametric and categorical variables were compared by Mann-Whitney test. Univariate and multiple logistic regressions were used to identify influence factor(s) associated with UIC<100 μg/l. Statistical analyses were done using the SPSS for windows (version 15.0, 2006, SPSS Inc., Chicago, IL, USA), *p*<0.05 being considered as significant.

RESULTS

Three hundred and ninety-seven (62.1%) females (mean age 42.2±12.7 yr) and 242 (37.9%) males (mean age 44.1±13.7 yr) completed this study. Overall, 408 (63.8%) participants (mean age 43.6±13.2 yr) and 231 (36.2%) participants (mean age 41.7±12.8 yr) had urinary iodine levels < and ≥100 μg/l, respectively. Fifty percent of subjects with insufficient urinary iodine had <7 yr of education; this low literacy level was also observed in approximately 30% of subjects with sufficient urinary iodine (*p*<0.001). Basic characteristics of participants with sufficient and deficient urinary iodine in Tehran are shown in Table 1. A significant difference in personal history of hyperthyroidism and hypertension between two categories was observed.
Based on WHO/ICCIDD/UNICEF classifications, frequency distribution of individuals with UIC ranges of 100-199, 200-299, and >300 μg/l were 68.8, 22.5, and 8.7%, in the sufficient group, respectively. In the deficient urinary iodine group, the proportion of participants with UIC<20, 20-49, and 50-99 μg/l were 17.8, 40.5, and 41.7%, respectively. Table 2 shows median (IQR) 24-h UIC in males and females of the two groups in Tehran. Median (IQR) 24-h UIC in subjects with sufficient urinary iodine was 163.0 (126.5-234.8) μg/l, whereas, it was 44.0 (26.3-67.0) μg/l in subjects with insufficient urinary iodine. In the sufficient group, median (IQR) 24-h UIC in males and females were 173.0 (129.0-253.0) and 155.0 (125.0-211.0) μg/l, respectively; in males and females of the deficient group these values were 43.0 (26.0-66.0) and 45.2 (27.0-67.0) μg/l, respectively.
Salt with iodine content of >20 ppm was found in 77.4 and 38.3% of subjects with sufficient and deficient urinary iodine, respectively. Median (IQR) salt iodine was 26.9 (20.1-37.0) *vs* 11.6 (2.1-27.5) ppm in participants with sufficient *vs* those with deficient urinary iodine. Median (IQR) salt iodine was 29.6 (20.1-37.0) *vs* 10.6 (2.1-

Table 1 - *Frequency distribution of basic characteristics of participants with urinary iodine concentration (UIC)<100 and ≥100 μg/l in Tehran.*

	UIC		
	<100 μg/l no. (%)	≥100 μg/l no. (%)	*p*
Goiter	12 (2.9)	4 (1.7)	0.347
Hyperthyroidism	0 (0.0)	5 (2.2)	0.003
Hypothyroidism	24 (5.9)	9 (3.9)	0.276
Hypertension	57 (14.0)	20 (8.7)	0.047
Use of iodine containing supplement	6 (1.5)	5 (2.2)	0.517

Table 2 - *Median (interquartile range) of urinary iodine concentration (UIC), iodine content of salt, salt intake and iodine intake in individuals with UIC<100 and ≥100 μg/l in Tehran by gender.*

	UIC			*p*
	<100 μg/l (no.=408)	≥ 100 μg/l (no.=231)	Total	
24-h UIC (μg/l)				<0.001
Male	43.0 (26.0-66.0)	173.0 (129.0-253.0)	72.9 (37.0-138.0)	
Female	45.2 (27.0-67.0)	155.0 (125.0-211.0)	70.0 (33.2-128.3)	
Iodine content of salt (ppm)				<0.001
Male	13.7 (2.1-27.5)	30.7 (21.2-38.1)	21.2 (3.2-31.7)	
Female	10.6 (2.1-27.5)	29.6 (20.1-37.0)	20.1 (3.2-31.7)	
Salt intake (g/day)				0.007
Male	7.4 (5.5-9.7)	8.2 (5.7-12.0)	7.7 (5.5-10.2)	
Female	7.2 (5.4-9.6)	8.0 (6.1-10.6)	7.6 (5.7-9.8)	
Iodine intake (μg/day)				<0.001
Male	74.3 (16.6-189.4)	234.9 (121.4-344.7)	134.6 (24.5-255.6)	
Female	65.5 (14.8-185.3)	223.3 (126.5-341.3)	131.2 (24.5-238.5)	

ppm: part per million. Mann-Whitney U test shows no significant difference in 24-h UIC, iodine content of salt, salt intake and iodine intake between the two genders.

27.5) ppm in females with sufficient vs. females with insufficient urinary iodine; whereas, it was 30.7 (21.2-38.1) vs. 13.7 (2.1-27.5) ppm in males with sufficient *vs* males with insufficient urinary iodine.

Median of daily salt intake in subjects with sufficient urinary iodine was significantly higher than subjects with deficient urinary iodine (8.1 *vs* 7.3 g; *p*=0.001). Medians (IQR) of daily salt intake were 8.2 (5.7-12.0) *vs* 8.0 (6.1-10.6), and 7.4 (5.5-9.7) *vs* 7.2 (5.4-9.6) g in men *vs* women, in subjects with sufficient and deficient urinary iodine, respectively.

With respect to the amount of salt intake and iodine content of salt, daily iodine intakes >150 μg (recommended dietary allowance) were 68.8 and 33.1% in those with sufficient and deficient UIC, respectively. Median of daily iodine intake in adults with sufficient urinary iodine was significantly higher than those with insufficient urinary iodine (229.6 *vs* 68.6 μg; *p*<0.001).

There was a statistically significant difference in 24-h UIC and iodine content of salt between the two groups (*p*<0.001). No significant differences were observed in 24-h UIC, iodine content of salt, salt intake and iodine intake between the two genders.

Statistically significant correlations were observed be-

Table 3 - *Identification of factor(s) associated with urinary iodine concentration (UIC)<100 μg/l by univariate logistic regression.*

	UIC<100 μg/l no. (%)	UI≥100 μg/l no. (%)	Unadjusted odds ratio	95% CI	*p*
Sex					
Male	153 (37.5)	89 (38.5)	1.00	Reference	
Female	255 (62.5)	142 (61.5)	1.04	0.74-1.45	0.791
Age (yr)					
19-24	39 (9.6)	22 (9.5)	1.00	Reference	
25-34	68 (16.7)	46 (19.9)	0.83	0.43-1.58	0.581
35-49	157 (38.5)	104 (45.0)	0.85	0.47-1.51	0.583
≥50	144 (35.3)	59 (25.5)	1.37	0.75-2.51	0.302
Education level					
University	59 (14.5)	56 (24.2)	1.00	Reference	
Secondary	151 (37.0)	95 (41.1)	1.50	0.96-2.35	0.075
Primary	164 (40.2)	73 (31.6)	2.13	1.34-3.37	0.001
Illiterate	33 (8.1)	7 (3.0)	4.47	1.83-10.93	0.001
Iodine content of salt (ppm)					
Q4 (≥31.7)	62 (15.2)	91 (39.4)	1.00	Reference	
Q3 (21.2-31.7)	82 (20.1)	73 (31.6)	1.64	1.05-2.58	0.034
Q2 (3.2-21.2)	107 (26.2)	42 (18.2)	3.73	2.31-6.05	<0.001
Q1 (≤3.2)	157 (38.5)	25 (10.8)	9.21	5.41-15.68	<0.001
Salt intake (g/day)					
Q4 (≥9.9)	89 (21.8)	69 (29.9)	1.00	Reference	
Q3 (7.7-9.9)	96 (23.5)	58 (25.1)	1.28	0.81-2.01	0.284
Q2 (5.6-7.7)	112 (27.5)	52 (22.5)	1.67	1.05-2.63	0.022
Q1 (≤5.6)	111 (27.2)	52 (22.5)	1.65	1.05-2.60	0.030
Hypertension					
No	351 (86.0)	211 (91.3)	1.00	Reference	
Yes	57 (14.0)	20 (8.7)	1.71	1.00-2.93	0.050

CI: confidence interval; Q: quartile; ppm: part per million.

Table 4 - *Identification of factor(s) associated with urinary iodine concentration (UIC)<100 μg/l by multiple logistic regression.*

	Adjusted odds ratio	95% CI	*p*
Education level			
University	1.00	Reference	
Secondary	1.26	0.77-2.05	0.344
Primary	1.26	0.75-2.10	0.377
Illiterate	2.58	0.99-6.71	0.052
Salt iodine (ppm)			
Q4 (≥31.7)	1.00	Reference	
Q3 (21.2-31.7)	1.58	0.99-2.53	0.054
Q2 (3.2-21.2)	3.70	2.25-6.10	<0.001
Q1 (≤3.2)	9.00	5.15-15.72	<0.001
Salt intake (g/day)			
Q4 (≥9.9)	1.00	Reference	
Q3 (7.7-9.9)	1.34	0.81-2.21	0.240
Q2 (5.6-7.7)	1.78	1.08-2.93	0.024
Q1 (≤5.6)	1.76	1.07-2.90	0.026
Hypertension			
No	1.00	Reference	
Yes	1.92	1.07-3.44	0.027

CI: confidence interval; Q: quartile.7

tween iodine content of salt, salt intake and dietary iodine intake, and with 24-h UIC values (r=0.46, *p*<0.001, r=0.12, *p*=0.001, r=0.45, *p*<0.001, respectively). The results of univariate and multiple logistic regressions are shown in Tables 3 and 4. In the multivariate adjusted model, lower iodine content of salt and salt intake quartiles increased risk of UIC<100 μg/l as compared to higher quartiles. Risk of UIC<100 μg/l in hypertensive subjects was 1.92 fold greater than in normotensive subjects (95% confidence interval, 4.35-15.23). Participants with <7 yr of education were more vulnerable to UIC<100 μg/l than those with higher literacy levels.

DISCUSSION

This cross sectional study indicated that subjects with deficient urinary iodine consumed less daily salt and that their salts were inadequate in iodine. Therefore, they had lower dietary iodine intake as compared to those with sufficient urinary iodine. Based on WHO/ICCIDD/UNICEF guidelines, the criteria for sustainable elimination of IDD require less than 50 and 20% of men and non-pregnant women have UIC levels <100 and 50 μg/l, respectively, and over 90% consumption of adequately iodized salt as well (3). Previous comprehensive national surveys on monitoring of iodine nutrition indicated an upward trend in the number of subjects with deficient urinary iodine in Tehran. Percentage of UIC<100 μg/l in Tehran was 10.6 in 1996, 17.6 in 2001 and close to 50 in an unpublished 2007 report, respectively (7, 8); a recent study revealed that increase in UIC<100 μg/l was due to use of inadequate iodized salt (9). The present results demonstrated that median UIC in females was 45.2 μg/l in the insufficient urinary iodine group, a matter of great concern, especially in women of childbearing age, considering the critical role of iodine in fetal neurologic development. An ineffective salt iodization program may result in iodine deficiency in women of childbearing age specifically, and in adult populations generally (16). Similar to countries with recurrence of iodine deficiency due to lack of the required level of iodine content of salt, such as Azerbaijan, Kazakhstan, Kyrgyzstan, Guatemala, Thailand and Haiti, the present study reaffirms that the iodine content of salt has a strong influence on dietary iodine status (17-20). Low iodine content of salt among subjects with insufficient urinary iodine may have been resulted from lack or low level of knowledge and awareness regarding importance of iodine, poor preservation conditions (e.g. exposure to light, humidity and uncovered containers) (21), or food cooking processes (22) and washing habits in households.

Furthermore, in countries where iodized salt is the only main dietary iodine source, several studies have indicated that both increases and decreases in daily salt intake can affect dietary iodine status. Stimec et al. have shown that sufficiency in iodine intakes among Slovenian adolescents is attributed to excessive salt intake (23). However, the current WHO recommendation of a maximum daily salt intake of 5 g may be accompanied by increased risk of UIC<100 μg/l, unless the concentration iodine in salt is increased (24). Some other regions worldwide have experienced iodine deficiency due to low salt intake, despite sufficiency in iodine content of salt (25-28). In the present study UIC<100 μg/l was observed more in subjects who consumed daily salt amounts, close to recent WHO recommendations, whereas previous studies from Iran reported daily salt intakes above the recommended value, indicating that over these 10 yr (2000 to 2010) median daily salt intake has decreased from 10 to 7 g, and has been accompanied by an increased percentage of UIC<100 μg/l (9, 29, 30).

The reasons for reduction in salt intake have been ascribed to recommendations for prevention and control of hypertension and cardiovascular diseases, cultural issues, mass medical education, decrease in use of convenience foods and changes in dietary habits. Our data showed that hypertensive subjects with restricted salt intake were vulnerable to UIC<100 μg/l. It has been confirmed that in hypertensive women, dietary salt restriction and iodine deficiency had a positive association (31). Reduction in salt intake, due to high prevalence of cardiovascular disease, has been reported in a previous survey in Iran, even though we found no other study confirming the prevalence of iodine deficiency (32).

The current study showed that subjects with deficient urinary iodine were more prevalent among those with low levels of education. Data from several studies indicated that knowledge and awareness regarding iodine are among the most important components for successful advocacy of iodine deficiency. Despite serious efforts in elimination of iodine deficiency in some countries, interventional programs have been unsuccessful, due to the lack and or low levels of public awareness (33). Failure in public awareness and education has resulted in iodine deficiency in India, Senegal, Island, Ethiopia, and South Africa (33-36). In addition, in Australia, previously considered an iodine sufficient area, iodine deficiency has recurred, partly due to lack of strategies on improvement of public awareness (37, 38).

The WHO/ICCIDD/UNICEF recommended that iodine nutrition status in populations is primarily measured by

UIC which reflects recent iodine intakes with day-to-day variation (39). Considering this limitation, current studies proposed that an additional suitable indicator i.e. serum thyroglobulin (Tg), a thyroid-specific protein with little daily variation and a precursor in synthesis of thyroid hormone, be used in conjunction with UIC in evaluation of iodine nutritional status (40, 41). This was reaffirmed by a 2009 Danish study showing that despite the median UIC being marginally low (according to WHO criteria), serum Tg showed that the salt iodization program was successful and confirmed sufficiency in iodine intake in Denmark (42).

The present study does have a few limitations. Firstly, a single 24-h urine sample was obtained which is a poor indicator of habitual iodine intake, due to variation in daily dietary iodine intake. Secondly, the cross-sectional design of this study cannot establish causality relationships. In conclusion, despite Iran is being recognized as an Iodine deficiency disorders-free country, a large gap is observed between subjects with sufficient and deficient urinary iodine levels in Tehran, which may be attributed to iodine content of salt, amount of salt intake and the education levels of subjects. These findings emphasize further detailed monitoring of iodine content of salt combined with monitoring of salt intake, in addition to community awareness on adequate iodine nutrition. Furthermore, it seems that estimation of nutritional iodine sufficiency based on merely median urinary iodine may not be as precise a criterion as believed, and 50% of the population, in such areas considered "iodine sufficient", may exhibit some degrees of iodine deficiency, hence emphasizing the need to re-evaluate current WHO criteria for sufficiency of iodine nutrition.

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