Thyroid volumes in schoolchildren of Tehran: Comparison with European schoolchildren

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ABSTRACT. Since the normative values of thyroid volume ultrasonography results from European schoolchildren were endorsed by the World Health Organization (WHO), few studies have addressed the limitation of the recommended references as universal normative values for thyroid volume. Our objective was to describe thyroid volume measured by ultrasonography in Tehranian schoolchildren and compare them with the WHO normative values. Cross-sectional studies were performed in 2016 schoolchildren, aged 6-15 yr, in Tehran 10 yr after distribution of iodized salt. Data were collected on age, sex, weight, height, thyroid size by palpation and ultrasonography, and urinary iodine. Age/sex and body surface area (BSA) upper limits (97th percentile) of thyroid volume were derived. The goiter prevalence was 42% by palpation, 31% grade 1 and 11% grade 2. Median urinary iodine was 21.2 µg/dl. The 97th percentiles were comparable in girls and boys of all ages. Applying the WHO thyroid volume references to the Tehranian children, they did not show any enlarged thyroid based on BSA and on age, even in 11% of children with grade 2 (visible) goiter. In the Tehranian children, the best predictors of thyroid volume were BSA, height and weight. Using linear regression, the 97th percentile of thyroid volume from Tehranian children were lower than the corresponding references from the WHO normative values. The results indicate that a thyroid volume reference based on weight alone would perform as well as the one based on BSA. In addition, until the adoption of a new applicable international reference for thyroid volume, the use of local reference in the screening of children for thyroid enlargement is recommended.

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INTRODUCTION

For decades, thyroid size has been evaluated by palpation and a region is considered endemic if more than 5% of the population have thyroid enlargement or goiter (1, 2). Accordingly, several classifications of goiter stages have been used in field surveys of endemic goiter (3, 4). Although it is easily performed with minimal cost, goiter staging by palpation has low sensitivity and specificity (5). Thyroid ultrasonography is therefore performed for the reliable quantitative measurement of thyroid size (6, 7). Correct interpretation of ultrasonography in goiter surveys depends on the availability of a valid reference. Firstly, the normative values proposed by Gutekunst *et al*. were used (8). However, following the collaborative study of thyroid volume in 7599 schoolchildren, aged 6-11 yr, in European countries by Delange *et al*. (9), the findings were recommended by the World Health Organization (WHO) and the International Council for Control of Iodine Deficiency Disorders (ICCIDD) for use as an international reference for thyroid volume in children (10). Since then, few studies have questioned the pertinence of the European norms in other populations, particularly those in developing countries (11, 12).

In this paper, we examined the thyroid volume of 6-15-yr-old schoolchildren in Tehran. Iodine deficiency existed as hyperendemic goiter (13) and impairment of physical and intellectual development in Iran (14, 15). Efforts to implement universal salt iodination began in 1989 and the percentage of the population consuming iodized salt gradually increased reaching more than 50% and 95% by 1994 and 1996, respectively (16). Urinary concentration of iodine in the Tehran population was optimum in 1996 (17). Therefore, for at least 3 yr prior to this study, almost all Tehranian children have received adequate amount of iodine (18). The objective of

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Table 1 - *Median and 97th percentile (P97) thyroid volumes (ml) by age in Tehranian schoolchildren.*

Age (yr)	Median	P97
6*	1.8	3.3
7	2.3	3.2
8	2.5	3.6
9	3.4	5.3
10	3.5	6.1
11	4.0	6.2
12	4.2	7.7
13	4.8	7.3
14	5.1	9.1
15	5.8	10.8

*There were 200 to 206 schoolchildren in each age group.

this study was to describe thyroid volumes measured by ultrasonography in Tehran and compare them with the WHO references (8-10) and findings of other investigators (11, 12).

SUBJECTS AND METHODS

The subjects were schoolchildren attending grades 1 to 9, in primary and intermediary schools in Tehran City. Two-thousand and sixteen schoolchildren aged 6 to 15 yr were selected by multiple stage random sampling from all schools in Tehran. The ages of the children were calculated from the dates of birth reported in the school register and the date of survey. There were 200 to 206 children in each age group. Information on sex, height, weight, goiter by palpation, thyroid volume estimated by ultrasonography and urine samples for urinary iodine measurement were collected.

Table 2 - *Relation of several factors with thyroid volume in Tehranian schoolchildren (no.=1186).*

Predictors	Thyroid volume (R^2)	Ln thyroid volume (R^2)
BSA (m^2)	0.64*	0.68
Ln BSA	0.61	0.69
Weight (kg)	0.64	0.65
Ln weight	0.61	0.68
Height (cm)	0.59	0.68
Ln height	0.58	0.68
Age (months)	0.54	0.62

*p<0.001 for all predictors. BSA: body surface area; ln: natural log.

Table 3 - *Median and 97th percentiles (P97) of thyroid volumes (ml) by body surface area (BSA) in Tehranian schoolchildren.*

BSA (m^2)	No.	Median	P97*
0.6	31	1.5	-
0.7	85	1.7	-
0.8	175	2.0	3.1
0.9	185	2.4	4.0
1.0	229	3.0	4.0
1.1	209	3.3	6.0
1.2	253	4.0	6.2
1.3	212	4.3	7.9
1.4	145	5.2	8.6
1.5	97	5.3	-
1.6	89	7.1	-
1.7	43	7.2	-
1.8	24	7.5	-

*P97 was calculated for numbers >100.

Palpation: Thyroid was palpated by an endocrinologist and graded according to the WHO classification (2).

Anthropometry: Standing height was measured to the nearest 0.1 cm using standing height scale. Body weight was measured by the nearest 0.1 kg using a SECA beam balanced scale. Body surface area (BAS, m^2) was calculated by the formula: weight $(kg)^{0.425}$ 71.84 10^{-4} (19).

Thyroid volume: Ultrasound volume was measured according to Brunn *et al.* (20) using Aloka SSD-500 (Tokyo, Japan) portable ultrasound unit with a standard 5.0 MHz transducer. The volume of each lobe was calculated by the formula: length • width • thickness (mm)• 0.000479 and the result was expressed as ml. The thyroid volume was the sum of the volumes of both lobes (isthmus was not included). Thyroid glands were classified into normal or enlarged using thyroid volume-for-age and thyroid volume-for-BSA (8, 10). Volumes ≤97th percentile were considered as normal and those >97th percentile as goitreous.

Urinary iodine: Casual urine samples were collected, packed and transported to the Endocrine Research Centre on the same day. Urinary iodine analysis was performed using a modified acid-digestion method, based on the catalytic effect of iodine on the reaction between cerium IV and arsenic III (Sandell-Kolthoff Reaction) (21).

Statistical methods: Statistical analyses were performed using SPSS Version 9-for Windows. The log-

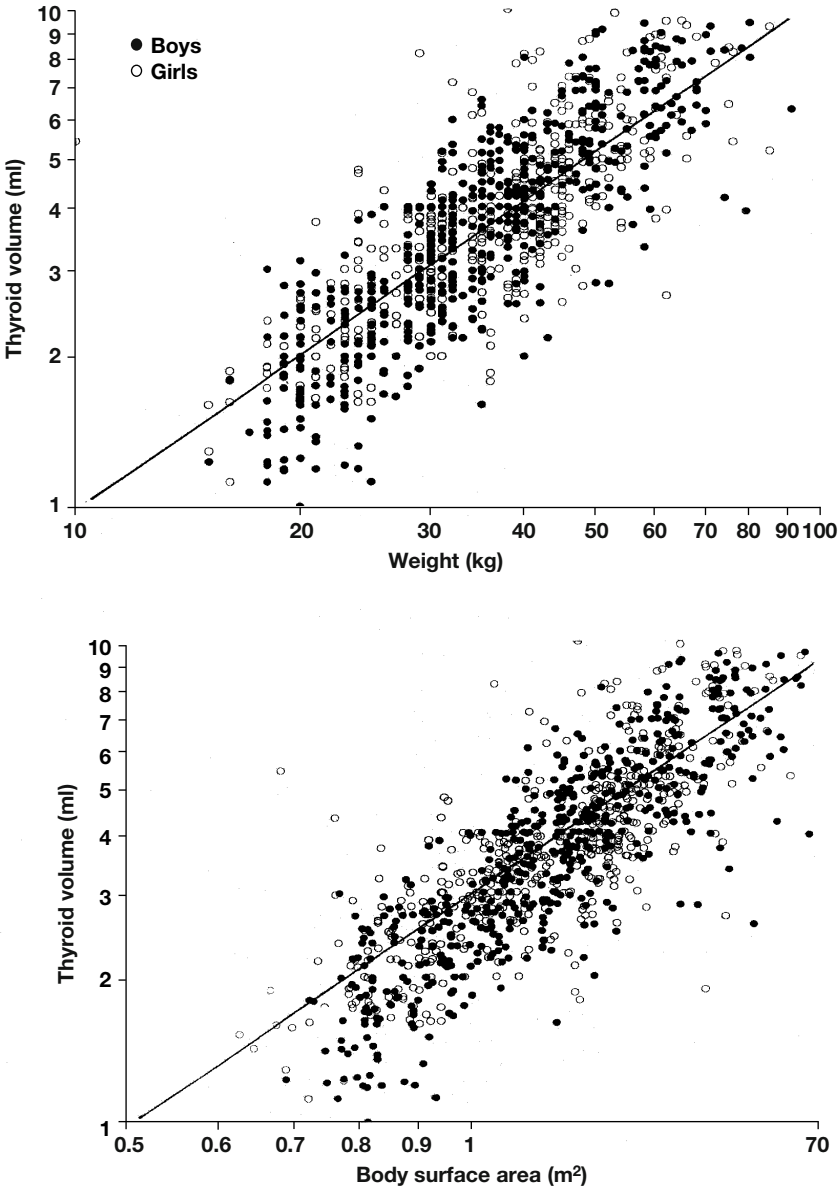

Fig. 1 - *Scatter plots of thyroid volume vs body surface area and weight.*

arithmic transformation was used to normalize the distribution of thyroid volume. Kolmogrov-Smirnov test was applied to check normality before linear regression was done (22). Correlation and multiple regression analyses were used to examine for association between thyroid volume and age, sex and the measured or calculated anthropometric measurements. The 97th percentile thyroid volume for each age or other grouping was taken as the upper limit of normality for the grouping. Curves of median and 97th percentile thyroid volumes against age and the anthropometric measurements were constructed and smoothed using SPSS software. The 1994 WHO/UNICEF/ICCIDD (2) criteria were used to classify the severity of iodine deficiency disorders, and the National Center for Health Statistics (NCHS) growth reference (23) was used for comparison of anthropometric data.

RESULTS

There were 1007 girls and 1009 boys in the study. *Thyroid palpation:* In total, 11% had grade 2 (visible) and 31% had grade 1 goiter. The prevalence of

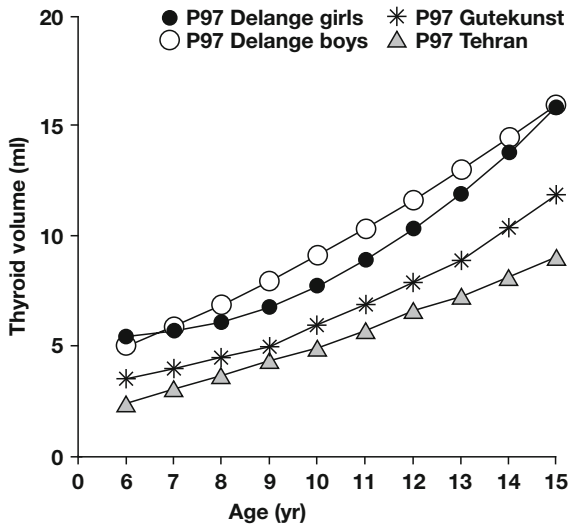

Fig. 2 - *Comparison of the World Health Organization references with 97th percentiles of thyroid volume from the Tehran schoolchildren by age.*

goiter in boys and girls was: grade 1, 29% and 31%; and grade 2, 8% and 13%, respectively.

Anthropometry: Tehranian children were, on average, shorter and smaller than NCHS growth reference.

Urinary iodine: Median of urinary iodine was 21.2 in all, 20.6 in girls and 21.8 µg/dl in boys; 92% had urinary iodine >10 µg/dl and 2.8% had urinary iodine <50 µg/dl.

Thyroid volume: The 97th percentiles in all ages were comparable between females and males. Median and 97th percentiles for thyroid volumes for Tehranian children aged 6-15 yr are shown in Table 1. The 97th percentile of Tehranian children in various age groups did not exceed that of the WHO thyroid volume reference (10). The WHO-recommended reference did not have normative values for 6% of Tehranian children with BSA<0.8 m^2. When the Gutekunst reference (8) was applied to Tehranian children, the prevalence of enlarged goiter was 6%. In each age group, thyroid volume increased significantly with age ($p<0.001$ for both sexes). The R^2 values for different predictors of thyroid volume and the natural log (ln) of thyroid volume were determined for Tehranian schoolchildren (Table 2). The ln of thyroid volume was analyzed because of skewness; after the transformation, the ln of thyroid volume was found to be normally distributed. BSA, weight and height were the best predictors of the thyroid volume, followed by age ($p<0.001$).

The median and upper limits of thyroid volumes by BSA are presented in Table 3. Again, there was no significant difference in upper limit of thyroid volumes between boys and girls. Sixty-eight schoolchildren, 13 boys and 55 girls (6% of total), had BSA<0.8 m^2. References for 97th, 50th and 3rd percentiles of normality were derived from Tehranian children. Scatter plots for BSA and weight lines are shown in Figure 1. About 6% of individuals have thyroid volumes beyond the 3rd percentile for each predictor.

Comparisons of 97th percentile of two thyroid volume references and that of Tehranian schoolchildren are shown in Figure 2. The 97th percentiles from Tehranian children are lower than those of European children (9) and slightly lower than Gutekunst values (8).

Table 4 - *Average median (P50) and upper limit of normal (P97) reported for thyroid volumes (ml) measured by ultrasonography in iodine-repleted school-age boys as a function of age.*

	Median (P50)				Upper limit of normal (P97)				
Age (yr)	1*	2**	3°	4°°	1*	2**	3°°	4°°	5#
6	3.2	1.5	-	1.7	5.4	3.5	-	2.4	-
7	3.4	1.8	2.1	2.4	5.7	4.0	4.1	3.1	4.5
8	3.7	2.0	2.4	2.5	6.1	4.5	4.5	3.7	5.0
9	4.1	2.4	2.8	3.4	6.8	5.0	5.0	4.5	6.0
10	4.5	2.8	3.1	3.5	7.8	6.0	5.7	5.8	6.5
11	5.1	3.1	-	4.1	9.0	7.0	-	6.2	7.0
12	5.7	3.7	-	4.7	10.4	8.0	-	6.7	8.0
13	6.5	4.2	-	5.1	12.0	9.0	-	7.4	-
14	7.3	5.0	-	6.0	13.9	10.5	-	9.1	-
15	8.2	5.8	-	6.2	16.0	12.0	-	9.2	-

*WHO/ICCIDD (10); **Gutekunst *et al.* (8); °Foo *et al.* (11); °°Azizi *et al.* (present paper); #Xu *et al.* (12)

DISCUSSION

In this study we evaluated the goiter prevalence by palpation and thyroid volume by sonography in schoolchildren of Tehran and compared the results to previously published data. We found that Tehranian children have significantly smaller thyroids than the WHO references. Therefore, despite high prevalence of grade 1 and 2 goiter, the thyroid volume of Tehranian schoolchildren remained within normal range of European children (9).

Previous studies of goiter prevalence in Tehran were based on thyroid palpation. In 1985, there was a high prevalence of goiter (13); however, with effective iodine deficiency disorder control program (16) and consumption of iodized salt, goiter prevalence decreased (16-18). It is of interest to note that, 10 yr after distribution of iodized salt and 3 yr after universal salt consumption in Tehran, 42% of schoolchildren have goiter. It has been shown that thyroid size in children exposed to iodine deficiency in the first years of life might fail to regress completely following consumption of iodized salt, and children born prior to iodine prophylaxis still 10 yr after intervention had larger thyroid volume than children from iodine-sufficient area (24). However, since sonography is the gold standard for determination of thyroid volume, the results of palpation in the present study should be considered as unreliable findings.

The thyroid volumes of the children in our study are much smaller than those reported by Vitti *et al*. (25) and Delange *et al*. (9). The median thyroid volumes of the children in Tehran are approximately 20-25% smaller than the mean thyroid volumes of Italian (25) and 25-30% smaller than European (9) children. Our findings appear comparable with those reported by Gutekunst *et al*. (26), Ivarsson *et al*. (27), Liesenkotter *et al*. (28), Xu *et al*. (12) and Foo *et al*. (11). Table 4 compares findings of this paper with some of the above-mentioned studies.

Many factors might account for the discrepancy between data obtained from investigations of thyroid volume by ultrasonography in various parts of the world. Although different ultrasound equipment and possible role of genetic factors have been suggested (29), the most important factors of disparity appear to be the inter-observer variation (25) and the status of iodine consumption in the different regions of the world. It has been proposed (11, 12) and agreed (30) that the findings from European children (9) are not appropriate to be used as an international reference for general use. The larger thyroids in European children study may have resulted from residual effects of iodine deficiency disorders in the recent past in some European countries or, less likely, from the consumption of goitrogen. In addition, the exact measurement of each dimension of thyroid lobes has not been accurately defined and inter- and intra-observer variations need further consideration.

Based on the present study, no important differences were found in the prevalence of goiter based on weight *versus* BSA. Therefore, it is simpler to use a reference based on weight rather than BSA. This was not the case with the study in European schoolchildren (9). We found no difference in 97th percentile of thyroid volumes between males and females. This is in agreement with other studies in iodine-sufficient regions (8, 25, 27, 31) but not with the European study (9), since iodine deficiency existed in some European countries and borderline iodine deficiency affects girls more than boys.

The inapplicability of the WHO/ICCIDD reference for thyroid volume to the Tehranian population is apparent. The findings of this paper and of other reports (11, 12) suggest the need for population-specific references even for BSA-adjusted thyroid volumes, as suggested by Foo *et al*. (11). At the beginning of the new millennium, major efforts should be focused on the adaptation of an applicable international reference for thyroid volume taking into consideration many variables, including sex, BSA, history of iodine deficiency, length of time of iodine sufficiency, goitrogen, genetic factors, equipment and inter-observer differences.

Until then, a local reference should be sought for the proper evaluation of thyroid volume.

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