ORIGINAL ARTICLE

Thyroid gland volume of schoolchildren in the North of Iran: Comparison with other studies

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Background: Few studies have shown the limitation of the World Health Organization (WHO)/ International Council for the Control of Iodine Deficiency (ICCIDD)-adopted thyroid gland volume references as universal normative values for thyroid gland volume. So we decided to measure thyroid gland volume by sonography in schoolchildren in Rasht, Gilan Province, Iran — Rasht is a metropolitan city on the Caspian Sea coast — and compare them to WHO normative values. **Materials and Methods:** In a cross-sectional study, 2,522 schoolchildren, aged 6-13 years, in Rasht, Gilan Province, Iran were selected by multistage random sampling. Data were collected on their age, sex, weight, height, body surface area (BSA), and thyroid gland size by palpation and sonography. The terminal phalange of thumb finger volume was calculated with the same formula used in sonography, for the thyroid gland in 1,085 of these cases. **Results:** Goiter prevalence was 64% (1613 cases) by palpation, 76.1% (1228 subjects) grade I and 23.9% (385 cases) grade II. The mean thyroid gland volume in girls was more than boys (3.67 ± 1.89 mL vs 3.41 ± 1.58 mL, $P < 0.0001$). According to the 1997 WHO thyroid gland volume reference, none of the children had goiter based on BSA and age even in those with grade II goiters (23.9%). In contrast, the median thyroid gland volume in our cases was larger than the 2004 WHO reference. The best single predictor of thyroid gland volume was age ($R^2 = 0.391$, $P < 0.0001$) followed by BSA ($R^2 = 0.151$, $P < 0.0001$). There was also a significant difference between thyroid gland and finger volume in all grades of goiter and grade II goiters (3 ± 1.4 mL vs 9.59 ± 2.4 mL; $P < 0.0001$. 4.3 ± 1.4 mL vs 9.3 ± 2.5 mL; $P < 0.0001$). **Conclusion:** The WHO standards for thyroid gland volume by sonography may underestimate or overestimate the goiter prevalence in many areas and populations. Finger volume was much larger than thyroid gland volume in even visible goiters.

Key words: Goiter, schoolchildren, sonography, thyroid gland volume, ultrasonography

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INTRODUCTION

Inspection and palpation have traditionally been used to classify goiter. In severe or moderate iodine deficiency, thyroid gland palpation provides a reliable method for goiter assessment but in areas of mild to moderate iodine deficiency disorders (IDDs), the sensitivity and specificity of palpation are poor[1-3] and measurement of thyroid gland volume by ultrasound is preferable.[4-6] Although, thyroid gland palpation is less reliable in children than in adults, goiter prevalence in children is mainly used to estimate iodine deficiency in the general population because of their easy recruitment and representativeness of the different social classes.[7,8] Correct interpretation of ultrasonography also relies on the availability of standardized reference criteria from populations whose iodine status is known to be adequate, i.e., where average intake is ≥150 μg/day and median urinary iodine is >100 μg/L. Since thyroid gland size varies by age and body height and weight,[1] derivation of normative values intended for universal application needs to be based on both these variables. In 1997, the World Health Organization (WHO)/International Council for the Control of Iodine Deficiency (ICCIDD)-adopted thyroid gland volume ultrasonography results from European schoolchildren as the international reference for goiter.[1] Few studies have shown the limitation of the recommended references as universal normative

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values for thyroid gland volume, suggesting that these references are too high.[9,10] Exploiting the WHO criteria may underestimate or overestimate the prevalence of goiter; so WHO recommends that normal values for each region be estimated separately, given the variability as a consequence of geographic, racial, and nutritional differences.[11] In 2000 the WHO/ICCIDD workshop updated references and corrected the systematic differences found between studies.[12] It was suggested that residual effects of iodine deficiency in the recent past of some European countries might explain this diversity and interpretation of the ultrasonic thyroid gland volume measurements that require a valid reference form iodine sufficient populations. WHO/Nutrition Health and Development Iodine Deficiency Study conducted a survey on the measurement of thyroid gland volume by sonography in an international sample of children living in different regions of the globe, living in areas of long-term iodine sufficiency.[13] This study reported that the thyroid gland volumes of subjects were 20% smaller than the 1997 reference values.[1] In this survey we measured thyroid gland volume by sonography in schoolchildren of Rasht (capital city of Gilan Province in the north of Iran, on the Caspian Sea coast) for the determination of regional criteria and their comparison with the normative values reported by WHO, a Tehranian schoolchildren study[14] and other countries' data.[9,10] We also appraised the WHO definition for goiter in physical examination. According to the WHO criteria, a thyroid gland whose lateral lobes have a volume greater than the terminal phalanges of the thumbs of the person examined will be considered as goiterous in physical examination.[15]

MATERIALS AND METHODS

In a cross-sectional, observational study, schoolchildren attending the primary and intermediate schools in Rasht, the capital city of Gilan Province, Iran, located on the Caspian Sea coast, were selected by multistage stratified random sampling from 82 primary schools of 55 areas in Rasht (100 clusters). The study population consisted of 2,522 schoolchildren with age ranging from 6 years to 13 years. Information on their birth date, sex, weight, and height, thyroid gland size (by palpation and ultrasonography) was collected. Age was extrapolated from the identification documents.

Body weight was measured by the nearest 0.1 kg using a balance weighing scale (Richter, Richter, Birmingham, England). Standing height was measured by the nearest 0.1 cm using Seca height scale (SECA beam balanced scale, Birmingham, England). Body surface area (BSA) (m2) was calculated according to the formula: (weight $^{0.425}$ × height $^{0.725}$ × 71.84) × 10-4.

Palpation of thyroid gland was performed by an endocrinologist and thyroid gland size was scored according to the updated WHO criteria (grades I to III).[16] Thyroid gland sonography was performed for all the subjects by a single expert radiologist using a portable ultrasound machine (Philips SDR 1200, Amsterdam, Holland) with a 5-MHz transducer. Thyroid gland volume was calculated in milliliters (mL) according to the formula: Width × length × thickness × 0.000479 for each lobe. Thyroid gland volume was considered as a sum of the two lobes' volumes (the volume of the isthmus was not included). Thyroid gland volumes above the 97th percentile according to the WHO/ICCIDD by age and BSA were accepted as goiter.[1,17]

Due to previous recent studies, urine iodine concentration of Gilan schoolchildren was found to be compatible with WHO standards; Gilan is an iodine sufficient area.[17,18]

The volume of the terminal phalange of the thumb of the subject being examined was calculated with the same formula used in sonography of the thyroid gland in 1,088 of these cases. Terminal phalange volume was also measured by a calibrated tube in water in 93 of these cases. The mean measured and calculated finger volumes were compared to each other and the thyroid gland volume was calculated by sonography.

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 17 (IBM, New York, US). The logarithmic transformation was used to normalize the distribution of thyroid gland volume. The Kolmogrov-Smirnov test was used to assess the normality of data before linear regression. The data were presented as median and ranges, or mean ± standard deviation (SD). Chi-square and *t*-test were applied to evaluate the correlation among qualitative and quantitative variables, respectively, and Kappa test and Bland-Altman plot were used for assessment of the agreement between the findings in sonography and physical examination. Differences between paired data were examined using the paired *t*-test. Correlations between variables were evaluated using Pearson's test and independent sample *t*-test. Stepwise regression was used for data regression analysis. A *P* value of less than 0.05 was determined as significant.

RESULTS

A total number of 2,522 schoolchildren aged 6-13 years were enrolled in the study. The mean age of the subjects was 9.86 ± 2.33 years. There were 1,239 (49.1%) boys and 1,283 (50.9%) girls. The mean of height, weight, and BSA was 138.37 ± 14.33 cm, 35.54 ± 12.51 kg, and 1.6 ± 0.24 sq.m, respectively. The prevalence of goiter on physical examination was 64% (1,613 subjects). In total, 23.1% of the subjects had grade II (visible) goiters and 76.1% had grade I goiter. The prevalence of goiter was significantly higher in girls than boys (33.1% vs 30.6%,

$P < 0.01$). The prevalence of goiter on applying sonography was found in 71 cases (2.76%, 1.46% female and 1.3% male).

The median and 97th percentile for thyroid gland volumes were 3.67 ± 1.89 mL and 7.19 ± 1.95 mL in girls versus 3.41 ± 1.58 mL and 5.8 ± 1.3 mL in boys. The thyroid gland volume in girls was significantly higher than in boys ($P < 0.001$ and $P < 0.007$, respectively). As a whole, the frequency of goiter was lower in the 6-years age group and it increased with age in both sexes ($r = 0.312$, $P < 0.01$). There was a significant correlation between thyroid gland volume and age in all the age groups. ($r = 0.463$, $P = 0.0001$). The 97th thyroid gland volume percentile of schoolchildren in Rasht, Gilan Province, Iran in the various age groups was smaller than that of the 1997 WHO reference[1] and larger than the 2004 WHO[13] reference. WHO-recommended reference also did not have normative values for children with BSA less than 0.8 m². Goiter frequency, the median, and the 97th thyroid gland volume percentile for sex and age group are described in Table 1. Using BSA-specific criteria, the median thyroid gland volume in Rasht schoolchildren was 32% smaller than the iodine-sufficient European children from whom the WHO/ICCIDD reference data were first derived[1] but larger than the new 2004 WHO reference.[13] Goiter frequency, the mean, median, and 97th thyroid gland volume percentile based on BSA are described in Table 2.

The R^2 values for different predictors of natural log (In) of thyroid gland volume were determined for Rasht schoolchildren. Age and BSA were the best predictors of thyroid gland volume ($R^2 = 0.391$ and 0.151, respectively; $P < 0.0001$) [Table 3].

The mean calculated and measured volume of the terminal phalanges of the thumb of the subjects were significantly different (9.59 ± 2.4 mL and 11.52 ± 2.45 mL, respectively; $P < 0.0001$). So we considered the calculated volume to compare with the thyroid volume reported by sonography. As a whole, there was no agreement between the mean of thyroid gland volume and the terminal phalange of the thumb in any clinical grades of goiter. There was a significant difference between the volume of the terminal phalange of the thumb and thyroid gland even in grade II goiters ($P < 0.0001$). The mean of the calculated thyroid gland volume and terminal phalange by the grading of goiter in physical examination is depicted in Table 4.

DISCUSSION

The Iran plateau is located on the iodine deficiency belt. The first efforts for iodized salt were launched by Dr. Azizi *et al*. in 1988; so after 7 years more than 95% of the Iranian population consumed iodized salt.[19] Guilan Province had the highest rate of iodine consumption among the other provinces in a national survey in 1996, with urine iodine of 652 ± 327 μg/L, which was significantly highest in the country.[17] The present study was conducted 15 years after iodination of salt and seven years after effective IDD control program and consumption of iodized salt.

In our study, the prevalence of goiter in the schoolchildren of Rasht, Gilan Province, Iran was 64% on physical examination; grade I and grade II (visible) goiters were 76.1% and 23, 1%, respectively. This finding was compatible with a previous study in Rasht, Gilan Province, Iran reporting goiter prevalence of 72%[17] and also Tehran (Tehran Province, Iran) study findings of a 42% prevalence of goiter 3 years after the public consumption of iodized salt.[14] Our study is in sharp contrast to another one conducted in Rasht Gilan Province, Iran in 2001, indicating a rate of 11.3%.[18] This discrepancy might have been due to missing some small goiters,

Table 1: The goiter frequency, the age-specific median, and 97th percentile thyroid gland volume for both sexes

Age (years)	No.	Sex	Median (mL)	Total	97th percentile (mL)	Total	Goiter frequency (*n*)	Total
6	190	Boys	2.11	1.93	3.75	5.02	1	4
		Girls	2.4		5.4		3	
7	280	Boys	2.34	2.19	4.62	4.75	4	8
		Girls	2.4		4.94		4	
8	333	Boys	2.76	2.68	4.83	5.37	6	10
		Girls	2.91		5.63		4	
9	315	Boys	3.38	3.24	5.79	5.78	4	9
		Girls	3.27		5.83		5	
10	324	Boys	3.55	3.37	6.75	7.04	4	9
		Girls	3.56		7.88		5	
11	351	Boys	3.82	3.68	7.03	7.84	5	10
		Girls	4.03		8.82		5	
12	319	Boys	4.01	4.16	6.73	8.62	4	9
		Girls	4.75		9.69		5	
13	410	Boys	4.35	4.4	7.32	8.82	6	12
		Girls	4.99		9.36		6	

Table 2: Goiter frequency, the BSA-specific mean, median, and 97th percentile thyroid gland volume

BSA	No.	Median (mL)	97th percentile (mL)	Mean	Goiter frequency (*n*)
0.65-0.74	13	1.61	4.36	1.02	1
0.75-0.84	196	2.1	4.66	2.26	8
0.85-0.94	336	2.44	4.97	2.66	2
0.95-1.04	411	2.7	5.6	3.05	16
1.05-1.14	354	3.24	5.81	3.3	12
1.15-1.24	318	3.78	7.25	3.82	7
1.25-1.34	308	3.92	8.3	4.1	10
1.35-1.44	243	4.04	8.1	4.35	7
1.45-1.54	158	4.02	9.68	4.52	4
1.55-1.64	88	4.11	10.1	4.55	2
1.65-1.74	59	4.8	11.6	5	1
1.75-1.84	32	4.35	7.87	4.24	0
1.85-1.7	8	4.5	14	5.6	1

BSA = Body surface area

Table 3: The relation of various factors with thyroid gland volume in schoolchildren

Predictor	Ln thyroid gland volume R^2	*P* value
Ln age	0.391	<0.001
Ln BSA	0.151	<0.001
Ln height	0.146	>0.05
Ln weight	0.128	>0.05

BSA = Body surface area, Ln = Natural log

Table 4: The mean ± SD of thyroid gland and finger volumes (calculated by sonography) by grade

Thyroid grade	Thyroid vol. (mL)	Finger vol. (mL)
Io	2.2±1.26	9.5±2.5
Ia	3.1±1.4	9.7±2.4
Ib	3.1±1	9.7±2.1
II	4.3±1.4	9.3±2.5
total	3±1.4	9.5±2.4

WHO thyroid grading, I to II

considering that the interobserver variation for detecting grade 0 to bordering grade 2 goiters can be as high as 40% in physical examination.[1] In our survey the prevalence of visible goiters were significantly lower than the small ones, which was consistent with others reporting a decrease of large goiters after consumption of iodized salt.[19-21] It has been shown that the thyroid gland 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 had larger thyroid volumes than children from iodine sufficient areas even 10 years after intervention.[22] Actually there is a lag period lasting from months to years before the thyroid gland size decrement after iodine repletion.[23-25] In our study the prevalence of goiter, consistent with a recent report in Gilan, Iran[18] was significantly more in girls than boys in all ages but is in contrast with an earlier report in this province, indicating the same prevalence of goiter in both the sexes.[17]

In our study the median and 97th percentile thyroid gland volume in girls was significantly more than boys. This trend was especially more considerable with increasing age in girls. The rationale might be that borderline iodine deficiency affects girls more than boys. This data is in contrast to some studies[14,21,26,27] reporting a comparable thyroid gland volume in both sexes of all ages and in accordance with others reporting larger goiters in girls than boys with no significant difference in thyroid gland volume between both sexes at the age of 7-8 years and larger volume in girls from the age of 9 years onward.[1,18,28] In contrast, in Wiersinga's study[29] the earlier onset of puberty in girls rendered their thyroid gland volume larger than boys at the age of 12 ± 13 years but boys had a larger thyroid gland volume at the age of 14 years. In the study of Moradi *et al*., thyroid gland volume in boys was reported to be significantly higher than girls.[30]

In accordance with some studies[9,14,21] the prevalence of goiter on applying sonography was considerably lower than the physical examination and there was a considerable disagreement between these two methods in the present study (2.76% vs 64%). Aghini-Lombardi *et al*. evaluated the prevalence of goiter in the schoolchildren in the area of East Tuscany. They showed goiter prevalence of 17% using ultrasonography and 10% using traditional palpation.[22] In contrast, Toromanovic *et al*. studied 480 schoolchildren in Tuzla Canton of Bosnia and found goiter prevalence of 13.5% by palpation and 12.9% by ultrasonography using WHO data. This study emphasized the importance of physical examination of the thyroid gland even in mild iodine deficiency areas.[31] The results of our study confirmed previous observations[4,32] of the inadequacy of palpation for the assessment of thyroid gland enlargement in children.

Using BSA-specific criteria, the median thyroid gland volume in Rasht schoolchildren was 32% smaller than the iodine-sufficient European children from whom the WHO/ICCIDD reference data were first derived[1] but larger than the new 2004 WHO reference.[13] The median thyroid gland volume of our children up to age 10 years was comparable to a Tehran study[14] in 2001 but 17% smaller onward. In contrast our cases had a thyroid gland volume of 14% larger than that of the Tehran study in 2007.[21] The rationale could be that Tehranian schoolchildren had lived all their lives in an iodine sufficient area as against our cases who had spent some part of their lives in iodine insufficiency. The thyroid gland volume of the children in our study was moderately smaller than those reported in the study of Vitti *et al*.,[32] and much smaller than the study of Klima *et al*.[33], moderately larger than the study of Gutekunst *et al*.,[4] and comparable to the studies of Foo *et al*.,[9] Xu *et al*.,[10] and Ivarsson *et al*.[34]

Other investigators have also reported a disparity between their findings and those of recently adopted WHO/ICCIDD references. Azizi *et al*.[21] in a study conducted on schoolchildren of Tehran, Tehran Province, Iran who had spent all of their lives in this iodine sufficient area, reported smaller thyroid glands than the new recommended international references. Bakshi *et al*. studied thyroid gland volume in normal children in Delhi, India. Goiter prevalence was 24.3% on clinical assessment. Urinary iodine levels were in the range of mild to moderate deficiency in 61% of the children. None of the children met the WHO recommended sonographic criteria for goiter when WHO age-specific norms were used for comparison. On applying BSA-specific norms, only two children were classified as having goiter.[35] Filipsson Nystrom *et al*. reported that thyroid gland volumes were significantly higher in Swedish schoolchildren than in the international reference study although iodine intake was considered to be optimal in Sweden.[36] In a study on Japanese schoolchildren in Tokyo where iodine deficiency has never existed, a total of 654 subjects aged 6-12 years were enrolled to set up a normative thyroid gland volume. Regardless of gender the computed median and 97th percentile thyroid gland volumes based on age or BSA in Japanese children were generally lower than the corresponding values recently reported in iodine-sufficient areas and these values were slightly higher (5-13%) than those in the WHO/ICCIDD international reference.[37] Szybiński *et al*. conducted a study in a group of 642 children aged 6-12 years living in the Polish seaside area with a proven history of best iodine supply. The normative thyroid gland volume was lower than the 1997 WHO normative values but higher than the 2004 reference currently adopted by WHO.[38] Hess *et al*. conducted a study in a representative national sample of 600 Swiss children aged 6-12 years. Application of the WHO/ICCIDD thyroid gland volume references to the Swiss children resulted in a prevalence of 0% goiter. Upper limits of normal (97th percentile) thyroid gland volume from Swiss children using BSA, sex, and age were similar to those reported in iodine-sufficient children in the USA but were 20-56% lower than the corresponding WHO/ICCIDD references.[39] In a Philippian study, the median thyroid gland volumes of schoolchildren investigated were generally lower compared to th einternational reference data by age group but not by BSA.[40] Gonzalez, *et al*. studied 591 children in Colombia and reported that the normal thyroid gland volume of the subjects was smaller than the WHO reference value.[11] A study in Nigeria demonstrated that thyroid gland volume in schoolchildren was significantly smaller than the 1997 WHO reference but very similar to similar environments.[27] In agreement with our findings, all of these studies indicate that for assessing thyroid gland volume, a population-specific reference rather than a universal one is required. The comparison between the median thyroid gland volume in our study and some other ones is depicted in Table 5 and Figure 1.

Many factors are involved for the discrepancy of the ultrasonic thyroid gland volume reported by different studies. Interequipment variability, iodine status of the community, genetic and racial factors,[41] and high interobserver variations[32] should all be taken into account. Considering all of these data, the WHO standards for thyroid gland volume by ultrasonography tend to underestimate or overestimate goiter prevalence in many areas and a population-specific reference for thyroid gland volume is needed.

In the present study, age and BSA were the best predictors of thyroid gland volume in both sexes. There was no significant difference in the prevalence of goiter based on age versus BSA. So it is more practical to use a reference based on age rather than BSA. This is in argument with the study in European schoolchildren.[42] Some studies report that thyroid gland volume correlated better with height, weight, and BSA[14,27,36,43] but we could not find a significant relation between height and weight and thyroid gland volume. Some other investigators demonstrate that age, height, weight, and BSA are all predictors of thyroid gland volume in schoolchildren.[26,37,40,44-47] In contrast to our findings, a German study showed that thyroid gland volume was independent of age in children aged 8-12 years.[48]

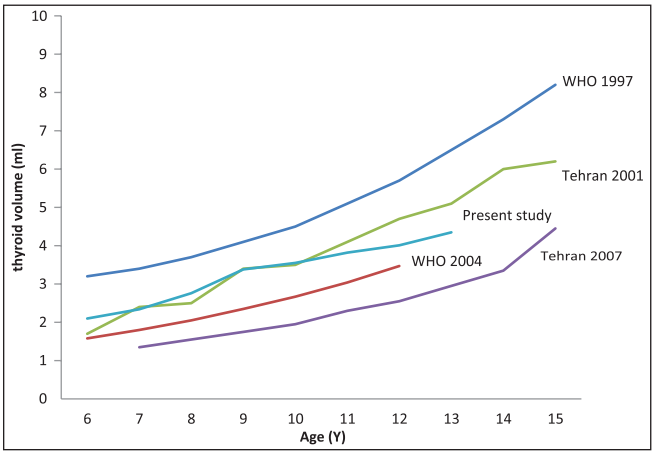

Figure 1: The median of thyroid volume (mL) in different studies

Table 5: The median of thyroid gland volume (mL) in different studies

Age (years)	WHO 1997	WHO 2004	Tehran 2001	Tehran 2007	Gutekunst study	Present study
6	3.2	1.58	1.7		1.5	2.1
7	3.4	1.8	2.4	1.35	1.8	2.34
8	3.7	2.05	2.5	1.55	2	2.76
9	4.1	2.35	3.4	1.75	2.4	3.38
10	4.5	2.67	3.5	1.95	2.8	3.55
11	5.1	3.04	4.1	2.3	3.1	3.82
12	5.7	3.47	4.7	2.55	3.7	4.01
13	6.5		5.1	2.95	4.2	4.35
14	7.3		6	3.35	5	
15	8.2		6.2	4.45	5.8	

In the present survey, we were unable to find any agreement between the mean of thyroid gland volume and the terminal phalange of the thumb in any clinical grade of goiter. There was a significant difference between the volume of the terminal phalange of the thumb and thyroid gland even in grade II goiters and the thyroid gland volume was significantly smaller than the terminal phalanx of the thumb; so the WHO criteria for goiter definition in physical examination should be revised.

CONCLUSION

The WHO standards for thyroid gland volume by sonography may underestimate or overestimate goiter prevalence in many areas and populations. Finger volume was much larger than thyroid gland volume in even visible goiters.

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Conflicts of interest
There are no conflicts of interest.

AUTHOR'S CONTRIBUTION

SK contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. MVM contributed in the conception of the work, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

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