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Smaller Thyroid Gland Volume with High Urinary Iodine Excretion in Japanese Schoolchildren: Normative Reference Values in an Iodine-Sufficient Area and Comparison with the WHO/ICCIDD Reference

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Iodine deficiency disorders (IDDs) are serious global public health problems and approximately 2 billion people are at risk of IDD complications. Urine iodine and thyroid size by ultrasound in school-age children are important indicators for assessing IDD in a population. Interpretation of sonographically measured thyroid volume requires valid reference criteria from iodine-sufficient populations, and in 2003 WHO (World Health Organization)/ICCIDD (International Council for the Control of Iodine Deficiency Disorders) proposed new international reference values for thyroid volume in children aged 6–12 years. To establish a normative reference of thyroid volume and characterize the current status of iodine nutrition in Japanese schoolchildren in Tokyo, where iodine deficiency has never existed, a total of 654 subjects aged 6–12 years (317 girls and 337 boys) in three primary schools were enrolled in the study in 2002. Thyroid volume was determined by using the standardized method recommended by WHO/ICCIDD and the iodine concentration in spot urine samples and the anthropometric measurements were evaluated. Thyroid volume was positively correlated with the children's age, height, weight, or BSA. Regardless of gender the computed median and 97th percentile thyroid volumes based on age or BSA in Japanese children were generally lower than the corresponding values recently reported in iodine-sufficient areas, although these values were slightly higher (5–13%) than those in the 2003 WHO/ICCIDD international reference. The computed median value of urinary iodine concentration was 281.6 μg/L (303.7 μg/gCre) and extremely high values exceeding 1,000 μg/L were found in 16% of the subjects. The present study clearly indicated a high iodine intake in Japanese schoolchildren and also established reference values for thyroid volume that might be applicable to countries in the Far East as a population-specific local reference.

Introduction

Iodine deficiency has serious effects on the physical and mental development of children and is recognized as a major global public health problem. According to current WHO (World Health Organization) and ICCIDD (International Council for Control of Iodine Deficiency Disorders) data based on representative urinary iodine values (<100 μg/L), 3,034 of 6,080 million people, or people in 84 of 159 countries, are iodine deficient, suggesting that approximately 2 billion people, including 285 million school-age children, live in countries with significant iodine deficiency and are at risk of its complications (1,2).

The proportion of children with an enlarged thyroid measured by ultrasound and the urinary iodine (UI) concentration in school-age children are important indicators to assess the severity of iodine deficiency in a population. Thyroid volumes greater than the 97th percentile are considered to be abnormally enlarged thyroids and are used as normal reference cutoff points. The interpretation of thyroid volume requires valid reference criteria from iodine-sufficient populations. The sex- and body surface area (BSA)-specific references for thyroid volume in children aged 6–15 years were proposed by WHO (World Health Organization)/ICCIDD in 1997 based on data from European children living in an iodine-sufficient area (3) and used as an international reference.

However, WHO/ICCIDD provisionally updated this reference in 2001 (4) because several reports from other iodine-sufficient countries suggested that these criteria might be too high (5–10). In addition, the applicability of this updated reference value to populations other than those in European countries, particularly those in the developing countries, has

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not been established. Therefore WHO/ICCIDD recently conducted thyroid volume studies in 6–12-yearr-old schoolchildren by ultrasound using a validated technique from the long-standing iodine-sufficient areas of six countries on each continent to establish an international reference for general use (11). Samples from all six sites were pooled and combined and new international reference values for thyroid volume by ultrasound were proposed (12).

It is well known that Japan is a non-goitrous country due to the high dietary iodine intake of the Japanese. However, few recent data on UI excretion and thyroid volume in Japanese schoolchildren are available. The purpose of this study is to assess the current status of iodine nutrition and to establish reference ranges for thyroid volume by ultrasound in Japanese schoolchildren in Tokyo.

Materials and Methods

Subjects

In October–November 2002, schoolchildren aged 6–12 years in grades 1–6 were recruited from 3 of 21 elementary schools in Meguro-ku, Tokyo, Japan. Schools and classrooms were all randomly selected by drawing lots. The three schools are situated within a distance of 1.2 to 3.5 km of each other. After obtaining permission to participate in the study from the school principals, the parents of the children to be examined were asked to give their written consent in advance. Our epidemiological study was designed and performed according to the surveillance methods for IDD prevalence recommended by WHO/UNICEF (United Nations Children's Fund)/ICCIDD (13,14). The study was approved by the Ethics Committee of Toho University and conducted with the approval and collaboration of the Meguro City Board of Education.

Body weight and height were measured using the standardized method of UNICEF. After measuring their height and weight, an ultrasonographic examination to estimate thyroid volume was carried out on the children sitting upright with the neck extended. In case of abnormality in the sonographic examination of the thyroid, the parents of the children received a written note describing the abnormal results of the examination. The parents were provided with iodine-free plastic test tubes and paper cups. Casual urine samples were obtained in the children's homes at a relatively late hour, between 8 pm and 12 midnight before the survey and then stored in the refrigerator. The collected urine samples were kept frozen at -30° until they were analyzed for iodine and creatinine concentrations.

Short stature was defined as a height below the mean-2.5SD on the growth curves of Japanese children reported in 2001 by the Japanese Ministry of Education, Culture, Sports, Science and Technology. Total body surface area was calculated using the following formula (15): $\mathrm{BSA}\ (\mathrm{m}^2) = \mathrm{W}\ (\mathrm{kg})^{0.425} \times \mathrm{H}(\mathrm{cm})^{0.725} \times 71.84 \times 10^{-4}$.

Thyroid ultrasonography was performed by three experienced examiners (YF, NS, and TT) using a real-time sector scanner (Aloka SSD-500, Tokyo, Japan) with a 7.5-MHz, 40-mm linear transducer. In preparation for this study the authors invited two experts from WHO/ICCIDD, Michael Zimmermann (MZ) and Sonja Hess, and had a meeting on thyroid ultrasound technique for standardization of the method to unify the criteria to be used. The standardized method that we adopted is as follows: For each thyroid lobe, the maximum perpendicular anteroposterior (AP) and mediolateral (ML) dimensions were measured on a transverse image of the largest diameter, without including the isthmus. The maximum craniocaudal (CC) diameter of each lobe was then measured on a longitudinal image with the thyroid capsule excluded. The volume of each lobe was calculated, using the formula: $\mathrm{V}\ (\mathrm{ml}) = \mathrm{width} \times \mathrm{length} \times \mathrm{thickness}\ (\mathrm{cm}) \times 0.479$ (16). The total thyroid volume was the sum of both lobes and the isthmus volume was not included.

The intra- and inter-observer variations were calculated according to the method described by Zimmermann *et al.* (17). To estimate inter-observer variability between MZ from WHO/ICCIDD and us (YF and TT), 10 schoolchildren were randomly selected and the thyroid volume was measured in each child by all three examiners (MZ, YF, and TT). Duplicated and repeated measurements were performed with the examiners unaware of the results of the previous measurements. The mean inter-observer variations between MZ and us were 11.1% (MZ vs. TT) and 12.1% (MZ vs. YF). Another 30 children were recruited to assess variability among the three examiners (YF, NS and TT) and the mean intra- and inter-observer errors were 2.4–9.2% and 5.8–22.5%, respectively.

The thyroid volumes in Japanese schoolchildren were compared with two WHO/ICCIDD reference values proposed in 2001 (4) and 2003 (12), respectively. Thyroid enlargement was defined using the upper limit of normal thyroid volume (percentile 97; P97) in these reference values.

Schoolchildren adjusted for age and sex were divided into two groups according to urinary iodine excretion, *e.g.,* those with high iodine excretion ($\mathrm{UI} > 300\ \mu\mathrm{g/L}$) and those with relatively normal excretion ($\mathrm{UI} \geq 300\ \mu\mathrm{g/L}$), and their thyroid volumes, body weight, height, and BSA were compared between the two groups.

Assays

Iodine concentrations in urine were determined by the newly-developed ammonium persulfate digestion on microplate (APDM) method (18). The analytical sensitivity of this assay was $1.39 \mu\mathrm{g/dL}$ and the intra-assay and inter-assay coefficients of variation were 4.8–5.9% and less than 15%, respectively. The creatinine concentration in urine was estimated by colorimetric enzymatic assay. All urine samples were assayed in duplicate. Renal iodine excretion was expressed relative to creatinine excretion (μg iodine per g creatinine) or as a concentration in μg iodine per 1000 ml of urine (μg/L) for better comparison of the iodine deficiency status with the WHO-defined deficiency grades. Since WHO guidelines for IDD status use μg/L for cutoff points in IDD surveillance, we gave SI units (μmol/L) in parentheses. (For conversion to S.I. units: $1\ \mu\mathrm{g/dL} = 0.079\ \mu\mathrm{mol/L}$)

Statistics

The results were presented as mean, SD, SEM, median, range, or percentile. The thyroid volume and urinary iodine concentration in each age and BSA groups, separately for girls and boys, were distributed asymmetrically and skewed towards high values. Their logarithmically transformed values were therefore used to normalize the distribution. The nor-

Table 1. Characteristics of the subjects

N	Age (years)	Weight (kg)	Height (cm)	BSA (m^2)	Boys : Girls ratio
37	6.8 (0.1)	22.8 (4.9)	118.9 (5.9)	0.87 (0.11)	1.06
112	7.5 (0.3)	24.1 (4.3)	121.9 (5.4)	0.90 (0.09)	1.04
112	8.5 (0.3)	26.9 (5.2)	127.5 (6.0)	0.98 (0.10)	0.90
116	9.5 (0.3)	31.7 (6.6)	134.6 (6.0)	1.09 (0.12)	1.19
100	10.5 (0.3)	35.7 (7.7)	140.7 (6.1)	1.18 (0.13)	1.22
116	11.5 (0.3)	38.9 (7.2)	146.2 (8.3)	1.26 (0.14)	1.19
61	12.3 (0.2)	45.4 (12.2)	152.1 (7.7)	1.38 (0.18)	0.79

Mean (SD).

mality of the transformed data was tested using the Kolmogorov–Smirnov test. Means and standard deviations of logarithm of the thyroid volume were then used as parameters to fit a normal distribution, and the 97th and 50th percentiles (P97 and median) were calculated based on the standard normal distribution by transforming back to the linear scale. Differences between paired data or groups were examined using one-way analysis of variance (ANOVA) and Tukey's multiple comparison test. Simple linear regression analysis was used to search for correlations between thyroid volume and its determinants. The level of significance was defined as a p-value less than 0.05. Data processing and statistical analysis were carried out using GraphPad Prism 4.0 from GraphPad Software Inc. (San Diego, CA, U.S.A.).

WHO/UNICEF/ICCIDD-recommended criteria have been used to classify a population's severity of IDD based on schoolchildren (13,14). The epidemiological criteria for assessing iodine nutrition are based on median UI and are as follows: mild deficiency, 50–99 μg/L; moderate deficiency, 20–49 μg/L; severe deficiency, < 20 μg/L. For the prevalence of goiter or thyroid volume > 97th percentile are as follows: mild deficiency, 5.0–19.9%; moderate deficiency, 20.0–29.9%; severe deficiency, > 30%.

Results

The clinical characteristics of the 654 children aged 6–12 years enrolled in the study are shown in Table 1. The study group comprised 337 boys and 317 girls (M:F ratio = 1.06:1). Four boys (0.6% of the total subjects) were classified as being of short stature. At the time of thyroid ultrasonography a solitary small sonolucent lesion typical of a simple cyst was observed in 9 out of 654 (1.4%) children (3 boys and 6 girls). Their thyroid volumes were within the 97th percentile of those in the present study.

Thyroid volume

Thyroid volume varied from 0.8 to 8.5 mL with a mean of 3.3 ± 1.5mL (median: 2.5 mL). The log-transformed thyroid volume was positively correlated with the children's age ($r^2 = 0.32$, $p < 0.0001$), height ($r^2 = 0.36$, $p < 0.0001$), weight ($r^2 = 0.33$, $p < 0.0001$) or BSA ($r^2 = 0.37$, $p < 0.0001$). Mean ± SEM, SD and range of thyroid volume according to age and BSA are presented in Tables 2 and 3, respectively. The mean thyroid volumes increased gradually at age 8 in boys and 9 in girls and then remained stable at ages 11 and 12. The mean thyroid volumes were slightly larger for girls than for boys;

Table 2. Mean (SEM), SD and observed ranges of thyroid volumes (ml) measured by ultrasonography according to age and gender

	Boys				Girls			
Age (years)	N	Mean (SEM)	SD	Range	N	Mean (SEM)	SD	Range
6	19	1.9 (0.34)[a]	1.5	0.8–4.5	18	1.8 (0.38)[f]	1.6	0.8–3.9
7	57	1.9 (0.19)[b]	1.4	1.0–3.5	55	1.9 (0.19)[g]	1.4	1.0–4.3
8	53	2.1 (0.19)[c]	1.4	0.9–5.1	59	2.2 (0.18)[h]	1.4	1.0–5.6
9	63	2.4 (0.18)[d]	1.4	1.0–5.0	53	2.4 (0.18)[i]	1.3	1.1–4.5
10	55	2.7 (0.19)[e]	1.4	1.4–6.5	45	2.9 (0.21)[j]	1.4	1.3–5.9
11	63	3.1 (0.18)	1.4	1.8–8.0	53	3.4 (0.19)	1.4	1.8–8.5
12	27	3.6 (0.25)	1.3	2.2–5.9	34	3.9 (0.22)	1.3	2.6–7.7

[a] *vs.* ages 9 ($p < 0.05$), 10 ($p < 0.01$), 11–12 ($p < 0.001$).
[b] *vs.* ages 9–12 ($p < 0.001$).
[c] *vs.* ages 10 ($p < 0.01$), 11–12 ($p < 0.001$).
[d] *vs.* ages 11 ($p < 0.01$), 12 ($p < 0.001$).
[e] *vs.* age 11 ($p < 0.01$).
[f] *vs.* ages 10–12 ($p < 0.001$).
[g] *vs.* ages 9 ($p < 0.05$), 10–12 ($p < 0.001$).
[h] *vs.* ages 10–12 ($p < 0.001$).
[i] *vs.* ages 10 ($p < 0.05$), 11–12 ($p < 0.001$).
[j] *vs.* age 12 ($p < 0.01$).

Table 3. Mean (SEM), SD and observed ranges of thyroid volumes (ml) measured by ultrasonography according to body surface area (BSA) and gender

	Boys				Girls			
BSA (m^2)	*N*	*Mean (SEM)*	*SD*	*Range*	*N*	*Mean (SEM)*	*SD*	*Range*
0.7	7	1.5 (0.57)[a]	1.5	0.8–2.6	14	1.5 (0.37)[f]	1.4	0.8–2.3
0.8	43	1.8 (0.21)[b]	1.4	0.9–3.5	52	1.9 (0.21)[g]	1.5	1.0–5.6
0.9	67	2.1 (0.16)[c]	1.3	0.9–5.1	60	2.1 (0.18)[h]	1.4	1.1–4.5
1.0	63	2.4 (0.18)[d]	1.4	1.2–8.0	51	2.5 (0.18)[i]	1.3	1.5–4.9
1.1	67	2.6 (0.16)[e]	1.3	1.4–5.5	48	2.9 (0.20)[j]	1.4	1.4–5.8
1.2	40	3.1 (0.16)	1.3	2.1–6.1	29	2.9 (0.24)	1.3	1.4–5.6
1.3	25	3.3 (0.28)	1.4	1.0–4.9	29	3.8 (0.24)	1.3	1.9–6.4
1.4	17	3.7 (0.32)	1.3	2.0–6.5	16	3.9 (0.38)	1.5	1.8–8.5
1.5	7	3.8 (0.49)	1.3	2.9–5.3	15	3.8 (0.34)	1.3	1.9–5.9

[a] *vs.* BSA 1.0 ($p < 0.01$), 1.1–1.5 ($p < 0.001$).
[b] *vs.* BSA 1.–1.5 ($p < 0.001$).
[c] *vs.* BSA 1.1 ($p < 0.01$), 1.2–1.5 ($p < 0.001$).
[d] *vs.* BSA 1.2–1.4 ($p < 0.001$), 1.5 ($p < 0.01$).
[e] *vs.* BSA 1.3 ($p < 0.05$), 1.4 ($p < 0.01$), 1.5 ($p < 0.05$).
[f] *vs.* BSA 0.9 ($p < 0.05$), 1.0–1.5 ($p < 0.001$).
[g] *vs.* BSA 1.0 ($p < 0.01$), 1.1–1.5 ($p < 0.001$).
[h] *vs.* BSA 1.0 ($p < 0.05$), 1.1–1.5 ($p < 0.001$).
[i] *vs.* BSA 1.3-1.5 ($p < 0.001$).
[j] *vs.* BSA 1.3–1.4 ($p < 0.05$).

however, there was no statistically significant difference in mean values between boys and girls in all age groups (Table 2).

The BSA-specific thyroid volumes increased with an increase of BSA and were significantly different at BSAs of 0.8 and 1.1 m^2 in boys and at 0.9, 1.0 and 1.2 m^2 in girls. The sex difference in thyroid volume for BSA was not evident (Table 3).

When the computed P50 (50th percentile, i.e., median) and P97 (97th percentile) thyroid volumes by age or BSA in Japanese schoolchildren were compared with the 2003 WHO/ICCIDD new international reference values (12), the age-specific median volumes in all age groups were on average 5.3% higher than the corresponding values of the WHO/ICCIDD reference, i.e., 5.9% (0–12.7%) and 7.7% (−0.6–21%) in boys and girls, respectively, while P97 volumes except in 9-year-old and 12-year-old children were on average 13.9% (0.3–33.8%) higher than the WHO/ICCIDD cutoff values (Table 4, Figs. 1 and 2).

Our BSA-specific median thyroid volumes in all groups except in the children with a BSA of 1.5 m^2 were 4.5–18.4% (average 10.6%) higher or similar to the WHO/ICCIDD reference values. The BSA-specific P97 volumes in all groups except the boys with a BSA of 1.3 m^2 and the children with BSAs of both 0.7 and 1.5 m^2 were 2.6-26.9% (average 11.1%) higher than the corresponding values of the WHO/ICCIDD reference (Table 5, Figs. 1 and 2).

By applying the P97 of thyroid volume against age or BSA in the new WHO/ICCIDD international reference values (12) the overall prevalence of an enlarged thyroid in Japanese schoolchildren was 5.8% (38/654 children, 16 boys and 22 girls) based on age or 6.5% (43/654 children, 16 boys and 27 girls) based on BSA. When the updated WHO/ICCIDD reference values (4) are applied, the goiter rate decreases to 0.9% (6/654 children, 5 boys and 1 girl) based on age or 2.3% (15/654 children, 8 boys and 7 girls) based on BSA.

Urinary iodine excretion

Iodine concentrations in spot urine samples were highly variable, ranging from 14.9 (1.2 μmol/L) to 30,810 μg/L (2,434 μmol/L) and the median value was 281.6 μg/L

Table 4. Comparison of median and P97 (97th percentile) of thyroid volumes (ml) measured by ultrasonography according to age and gender with the 2003 WHO/ICCIDD new international reference values

	Total		Boys				Girls			
Age (years)	*Median*	*P97*	*Median*	*P97*	*Median**	*P97**	*Median*	*P97*	*Median**	*P97**
6	1.9	3.9	1.8	3.8	1.60	2.91	1.9	3.8	1.57	2.84
7	1.8	3.7	1.8	3.3	1.80	3.29	1.8	4.0	1.81	3.26
8	2.1	4.2	2.1	3.8	2.03	3.71	2.2	4.4	2.08	3.76
9	2.4	4.0	2.5	3.9	2.30	4.19	2.4	3.8	2.40	4.32
10	2.7	5.3	2.7	5.0	2.59	4.73	2.8	5.4	2.76	4.98
11	3.1	6.1	3.1	6.3	2.92	5.34	3.3	5.8	3.17	5.73
12	3.6	6.0	3.5	5.6	3.30	6.03	3.7	6.4	3.65	6.59

*by WHO/ICCIDD (2003).

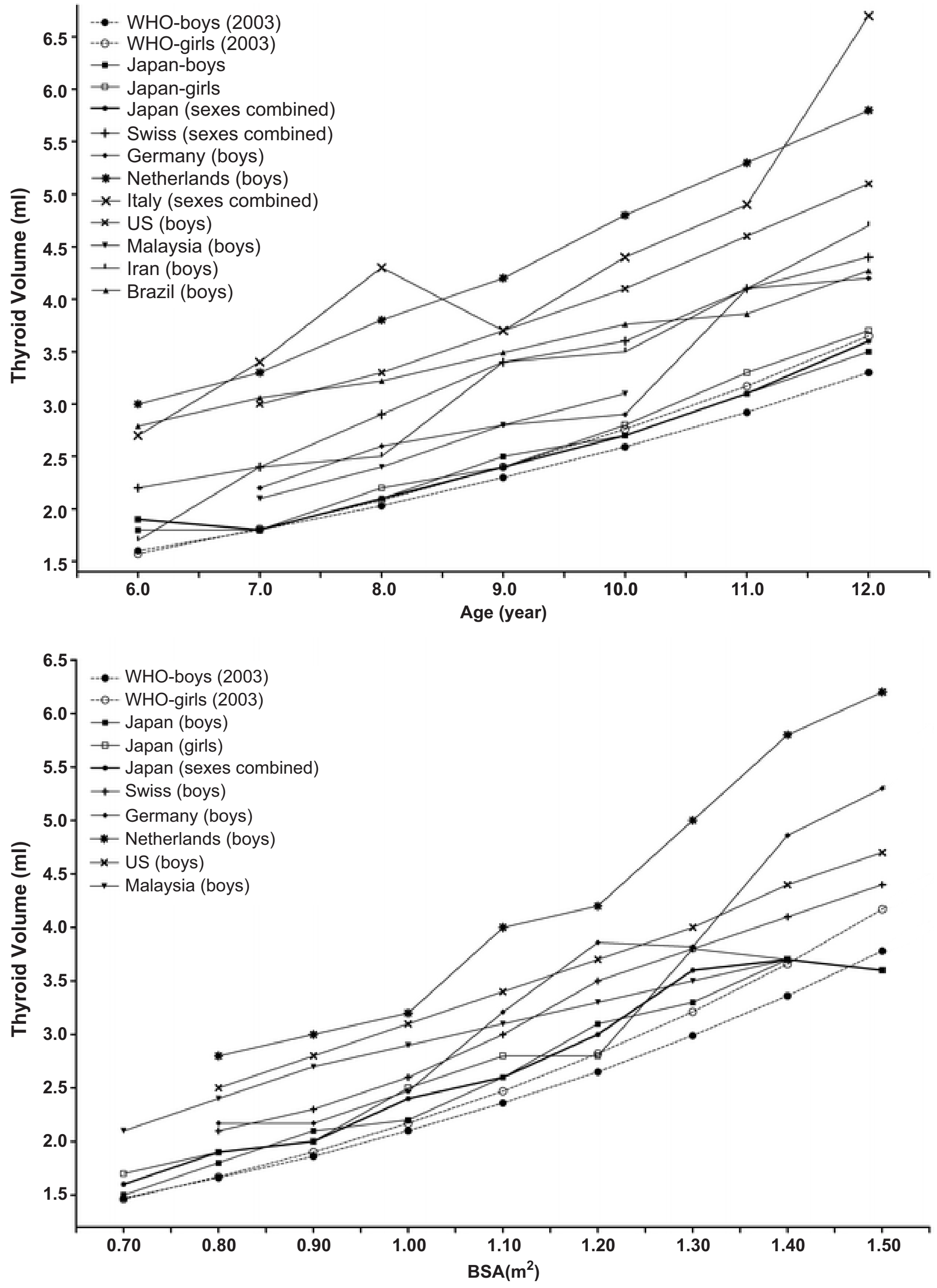

FIG. 1. Comparison of the age- (upper) and BSA-specific (lower) median thyroid volumes recently reported from iodine-sufficient areas in different countries and the 2003 WHO/ICCIDD international reference values with those of the Japanese children in Tokyo. The solid and open marks indicate the values in boys and girls, respectively.

(22.2 μmol/L) (Fig. 3). The rate of the children who excreted iodine that was less than 100 μg/L (7.9 μmol/L) was 6.7% (44/654 children). Extremely high values exceeding 1,000 μg/L (79 μmol/L) were found in 105/654 children (16.1%). When urinary iodine concentrations were expressed as μg I/g creatinine, the median value was 303.7 μg/gCre with the values ranging from 42.7 to 50,616 μg/gCre.

There were no significant correlations of urinary iodine concentration with natural log (ln) thyroid volume, the children's age, height, weight or BSA ($r^2 = 0.00034$–0.0039, $p = 0.11$–0.63). Median UI concentration in boys did not differ from that in girls (277.4 μg/L or 294.1 μg/gCre *vs.* 283.1 μg/L or 317.7 μg/gCre).

Correlation between thyroid volume and urinary iodine concentration

When the children were divided into two groups according to urinary iodine excretion with a cutoff value of 300 μg/L (23.9 μmol/L), no significant differences of mean thyroid volumes was observed between the two groups except in 7- and 8-year-old boys (Fig. 4). The thyroid volume in

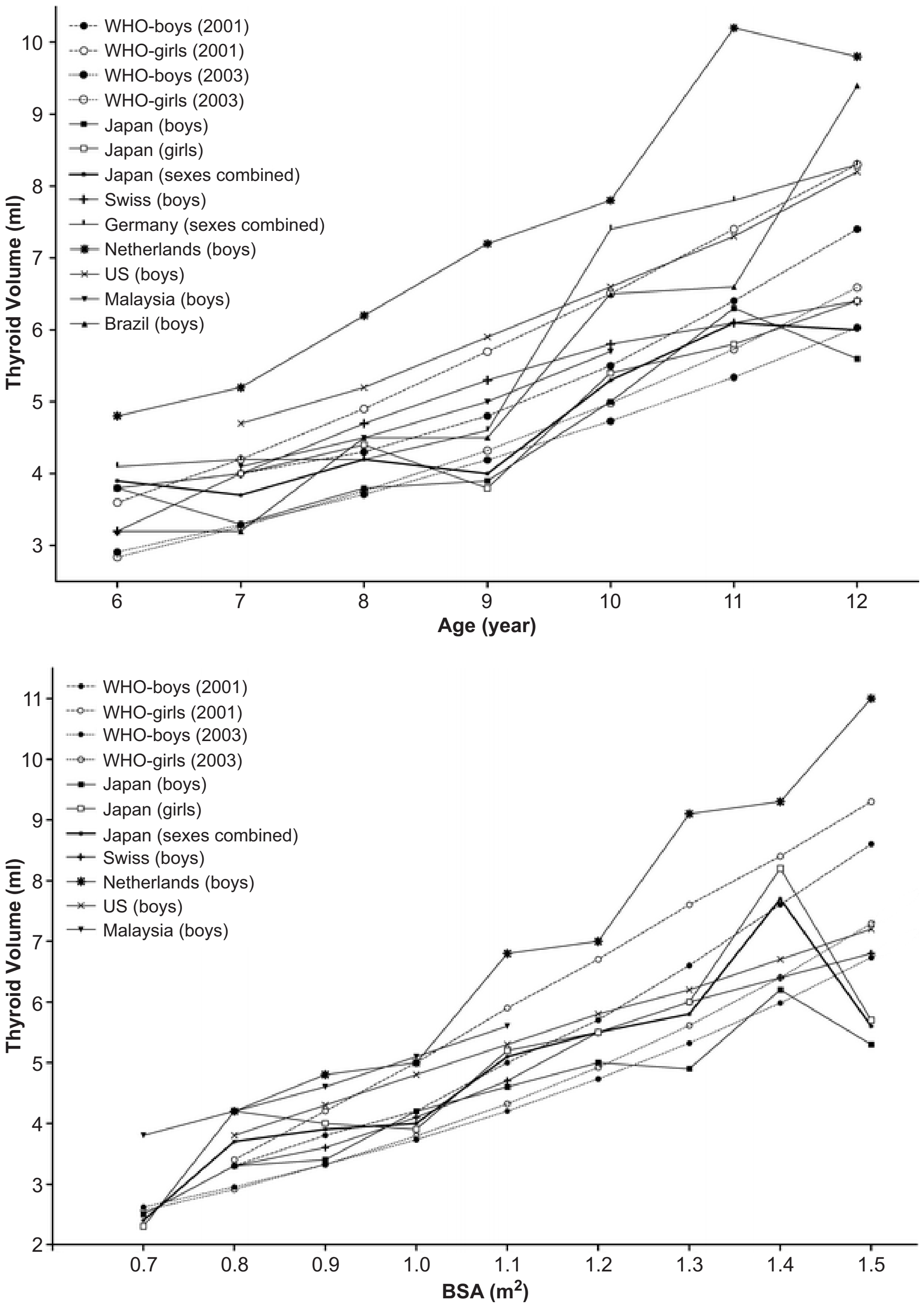

FIG. 2. Comparison of the age- (upper) and BSA-specific (lower) P97 thyroid volumes recently reported from iodine-sufficient areas in different countries and two WHO/ICCIDD reference values (2001 and 2003) with those of the Japanese children in Tokyo. The solid and open marks indicate the values in boys and girls, respectively.

7-year-old boys with normal iodine excretion was smaller than that of those with high iodine excretion (Mean $\pm$ SEM: 1.84 ± 0.09 *vs.*2.19 ± 0.14 mL, $p = 0.03$), while the thyroid volume in 8-year-old boys with normal iodine excretion was larger than that of those with high iodine excretion (Mean $\pm$ SEM: 2.34 ± 0.13 *vs.*1.93 ± 0.12 mL, $p = 0.04$). There were no differences in the mean values of body weight, height or BSA between the two groups except in 8-year-old boys. In this age group, there was no difference in the mean height between the two groups, however, the mean body weight of the children with normal iodine excretion was heavier (Mean $\pm$ SEM: 28.0 ± 0.8 *vs.*25.2 ± 0.8 kg, $p = 0.03$) and the mean BSA was larger (Mean $\pm$ SEM: 1.0 ± 0.01 *vs.*0.94 ± 0.01 m^2, $p = 0.03$) than those in the high iodine excretion group.

Discussion

Our data provides additional information on the thyroid volume of well-nourished schoolchildren living in a long-term iodine-sufficient country. Only a few data on thyroid

TABLE 5. COMPARISON OF MEDIAN AND P97 (97TH PERCENTILE) OF THYROID VOLUMES (ML) MEASURED BY ULTRASONOGRAPHY ACCORDING TO BODY SURFACE AREA (BSA) AND GENDER WITH THE WHO/ICCIDD NEW INTERNATIONAL REFERENCE VALUES

	Total		*Boys*				*Girls*			
BSA (m^2)	*Median*	*P97*	*Median*	*P97*	*Median**	*P97**	*Median*	*P97*	*Median**	*P97**
0.7	1.6	2.4	1.5	2.5	1.47	2.62	1.7	2.3	1.46	2.56
0.8	1.9	3.7	1.8	3.3	1.66	2.95	1.9	4.2	1.67	2.91
0.9	2.0	3.9	2.1	3.4	1.86	3.32	2.0	4.0	1.9	3.32
1.0	2.4	4.0	2.2	4.2	2.10	3.73	2.5	3.9	2.17	3.79
1.1	2.6	5.1	2.6	4.6	2.36	4.2	2.8	5.2	2.47	4.32
1.2	3.0	5.5	3.1	5.0	2.65	4.73	2.8	5.5	2.82	4.92
1.3	3.6	5.8	3.3	4.9	2.99	5.32	3.8	6.0	3.21	5.61
1.4	3.7	7.7	3.7	6.2	3.36	5.98	3.7	8.1	3.66	6.40
1.5	3.6	5.6	3.6	5.3	3.78	6.73	3.6	5.7	4.17	7.29

*by WHO/ICCIDD(2003).

volume by ultrasound in Japanese schoolchildren are available and the published reference is normative values according to the children's height (19). Compared with this height-specific reference, the mean values computed in our study were 58.8% (38.8–65.2%) lower than these reference values in all height groups (data not shown). The difference between the two studies may be accounted for by methodological differences. In his study, a relatively small number of subjects (<300 children) with highly variable age groups (from 8 months to 15 years old) were included. They were examined in a supine position with the neck hyper-extended using either a 5- or 7.5-MHz transducers. This position enabled an increase in the cranio-caudal diameter of the thyroid lobe and the lower-resolution 5-MHz transducer provided images of the thyroid gland that were not as clear as those of the 7.5-MHz transducer. In addition the correction factor of 0.523 instead of 0.479 was used in the elliptical model formula to calculate the thyroid volume.

The positive linear relationship of thyroid volume with age, height, body weight, or BSA observed in our results was consistent with previous reports (19–22) although which parameter is more reliable to assess thyroid volume is still under debate. In most iodine-sufficient areas no difference in thyroid volumes has been reported between girls and boys (19–21) and our results also confirmed this finding.

It is well known that genetic predisposition and environmental factors are involved in the regulation of the thyroid volume (23). In iodine-deficient areas the effect of iodine

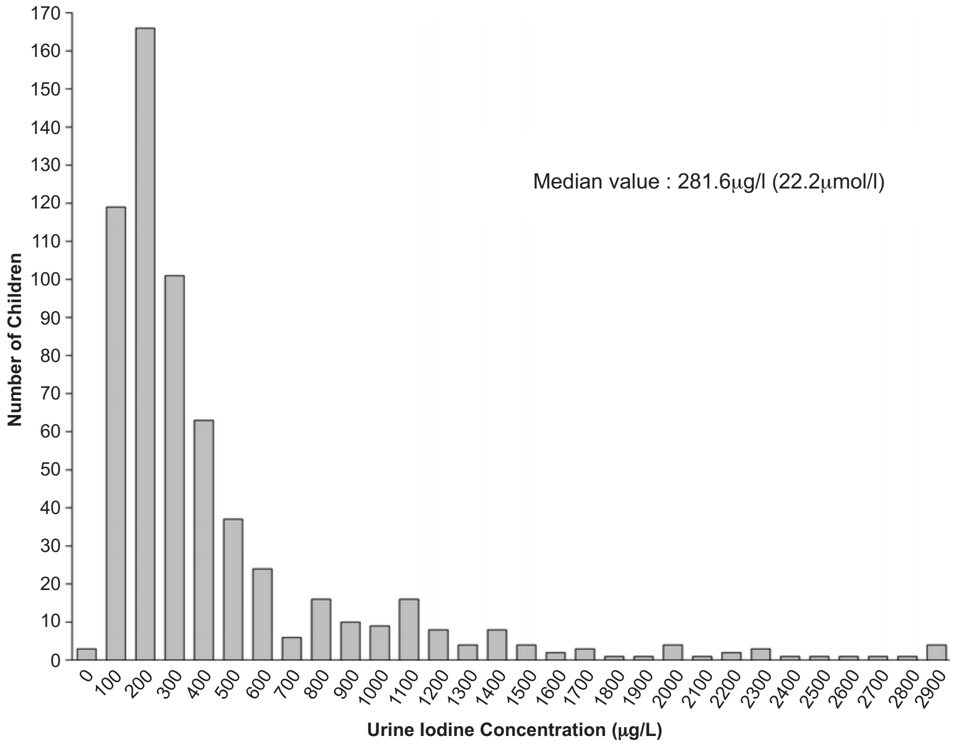

FIG. 3. Frequency histogram of urinary iodine concentration. The median value of urinary iodine concentration is 281.6 μg/L (22.2 μmol/L).

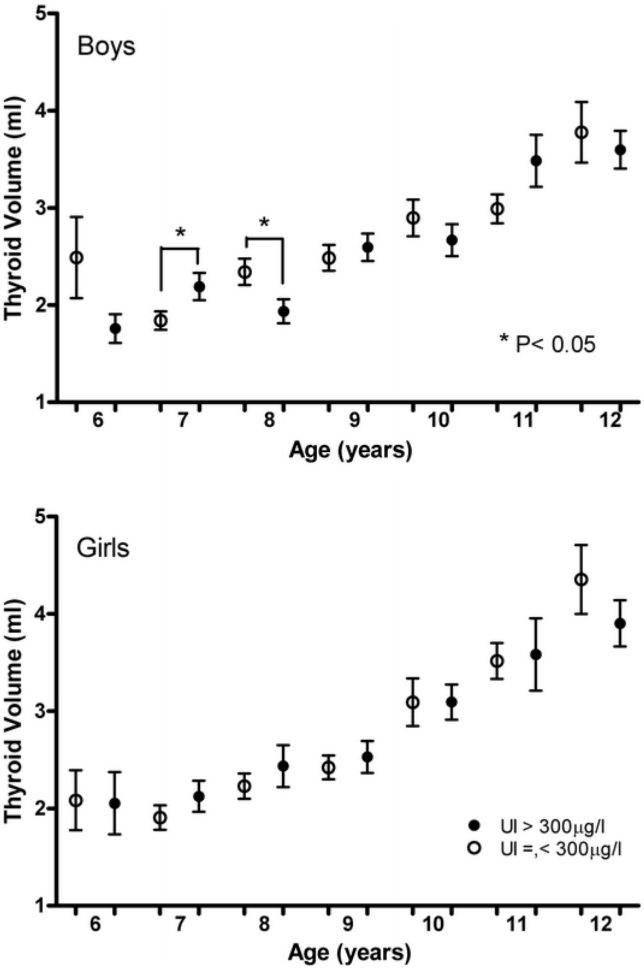

FIG. 4. Thyroid volumes in two groups of children with different iodine intake. Data are expressed as the mean and SEM with whiskers. The open and solid marks indicate the thyroid volumes of the children with normal urinary iodine excretion and those with high iodine excretion (>300 μg/L), respectively. The difference was significant in 7- and 8-year-old boys ($p < 0.05$).

deficiency is the most important determinant, while in an iodine-sufficient area the effects of dietary habits and genetic differences in growth and development on thyroid volume are reported in children (24). In our study the median thyroid volumes based on age and BSA in Japanese children appear to be the lowest among those recently reported in similar studies conducted in iodine-sufficient areas in the Netherlands (24), Switzerland (7,25), Germany (9), Italy (26), the United States (6), Iran (10), Malaysia (5), and central Brazil (27) (Fig. 1).

The median UI value (281.6 μg/L) in our study corresponds exactly to that of the Atlanta metropolitan area in the United States (median UI = 282 μg/L) (6), and is relatively high among those reported from iodine-sufficient areas such as Campania-Southern Italy (median UI = 80 μg/L) (26), Switzerland (median UI = 115 and 150 μg/L) (7, 25), Malaysia (median UI = 132.8 μg/L)(5), the Netherlands (median UI = 154.4 μg/L)(24), Germany (median UI = 183 μg/L)(9), Tehran, Iran (median UI = 212 μg/L)(10), and Zhangwu, China (median UI = 214 μg/L)(28). Although the exact reason is not clear, higher iodine intake may partially account for the smaller thyroids in Japanese schoolchildren.

According to WHO/ICCIDD criteria median urinary iodine concentrations of 100–199 μg/L at the population level indicate adequate iodine intake and optimal nutrition (29,30). A median UI over 300 μg/L in local schoolchildren is regarded as excessive (14). In the present study 45.9% of the Japanese schoolchildren had a high urinary iodine excretion (>300 μg/L). However, except in 7- and 8-year-old boys there were no differences in mean thyroid volumes between the children with high iodine intake and those with normal intake. Although the exact reason for this reverse finding in these two age groups is not clear, the differences in thyroid volume in 8-year-old children may be due to the difference in their body weight. It is therefore suggested that excessive iodine intake has no apparent effect on thyroid size in our schoolchildren. This observation may be related to underlying thyroidal autonomy or genetic susceptibility to excess iodine in the Japanese.

The divergent effects of excess iodine on thyroid function have been reported (31,32). Iodine excess induces either hypothyroidism or hyperthyroidism. The thyroid gland handles excessive quantities of iodine by inhibiting the organification of iodine (acute Wolff–Chaikoff effect) in order to maintain the normal synthesis of thyroid hormone. The Wolff–Chaikoff effect is often of short duration and the escape from the inhibitory effect of large doses of iodine occurs by down-regulation of iodine transport into the thyroid gland. If the so-called "escape" phenomenon does not occur, clinical or subclinical hypothyroidism may develop in normal individuals, newborns and fetuses, in patients with preexisting diseases such as chronic systemic diseases, autoimmune thyroiditis, Graves' diseases, postpartum or subacute thyroiditis and with recombinant interferon-α treatment (31). Conversely, hyperthyroidism caused by excess iodine is frequently observed in euthyroid patients with a previous thyroid disease residing in iodine-insufficient areas (32). This could have occurred usually in later phases of the program of iodine supplementation in an area with iodine deficiency.

Japanese foods in a regular diet have a high iodine content (33,34) and a major dietary source of iodine is seaweed that is served in a large variety of ways under a number of different names, e.g., Kombu (tangle weed, *Laminaria japonica*), Hijiki (*Hizikia fusiformis*), and Wakame (*Undaria pinnatifida*) (35). According to the national nutrition survey carried out from 1975 to 2000 by the Japanese Ministry of Health, Labor and Welfare (36), the daily consumption of seaweed per capita is 4.9 to 6.1 g (average: 5.4 g). Kombu, the most iodine-rich seaweed, contains 1.3 mg of iodine per gram; therefore, the average dietary iodine intake solely from Kombu is 7,000 μg per day.

Since the urinary iodine excretion corresponds to 70 to 80% of the daily iodine intake, subjects with a urinary iodine concentration greater than 5,000 μg could be frequently observed in the Japanese population. Mean urinary iodine excretion in adult Japanese has been reported to be 343.0(113.9–889.8) μg/L (37) or 739–3,286 μg/day with a wide range of variation (90–19,000 μg) (38) and in our study 16% of the schoolchildren excreted a large amount of iodine, greater than 1,000μg/L. In the United States, where iodized salt is used in about 70% of households, the median urinary iodine level in the population (6–74 years of age) is 167.8 μg/L according to the data from NHANES (National Health and Nutrition Examination Survey) 2001–2002 (39).

The recommended dietary allowance (RDA) and tolerable upper intake level (UL) for adults are calculated to be 150 μg/day and 1,100 μg/day, respectively (40). The UL value is based on serum thyrotropin concentration in response to varying levels of ingested iodine (40). In Japan the RDA is identical with that in the United States and the UL is provisionally recommended to be 3 g/day for an adult (41), since at this time there is no sufficient data to determine the optimal iodine intake for the Japanese population. Little is known about the prevalence of thyroid dysfunction that would be related to excess iodine intake in the general population that is chronically exposed to large doses of iodine mainly from dietary sources.

Recently in Japan a transient elevation of thyrotropin was observed in neonates born to mothers who consumed iodine-rich food during pregnancy (34). In addition, an epidemiological study in China suggests that more than adequate or excessive iodine intake may induce hypothyroidism and autoimmune thyroiditis (28). Further surveillance of the incidence of thyroid disorder together with the monitoring of iodine intake is required in the Japanese community to elucidate whether the existence of the status of relatively higher iodine intake than other iodine-sufficient countries can be regarded as a nationwide adverse health consequence.

The upper limit of thyroid volumes (P97) according to age or BSA in Japanese children in our study was generally slightly higher than the 2003 WHO/ICCIDD new international reference but lower than the 2001 WHO/ICCIDD updated reference value and those of Switzerland, Germany, the United States, Netherlands, Malaysia and Brazil reported before 2003 (Fig. 2). The 2001 WHO/ICCIDD updated reference was derived from the 1997 reference by correcting a systematic measurement bias between the examiners. In 1997 WHO and ICCIDD recommended the normative reference values for thyroid volume measured by ultrasound, which were based on a cluster of 3474 children aged 6–15 years born or living in 23 sites in Austria, France, Netherlands and Slovakia where iodine intake was normal as evidenced by mean urinary levels > 100 μg/L (42).

However, these criteria were criticized as being too high for the interpretation of surveillance data (5–10). In a WHO /ICCIDD workshop on thyroid ultrasound held in 2000 it was clearly demonstrated that the differences were accounted for not only by a residual effect of iodine deficiency that existed in many European countries up to the early 1990s, but also by a large systematic measurement bias (+30% volume in all age and BSA groups) between examiners in the 1997 references (17,43). It was also suggested that standardization of the ultrasound technique could increase the precision of thyroid volume measurement in children. The new international reference was compiled with thyroid volume data from 3529 children living in 6 long-term iodine sufficiency areas, i.e., Jona in Switzerland, Manama in Bahrain, Cape Town in South Africa, Lima in Peru, Chelsea, MA in the United States and Asahikawa, Hokkaido in Japan. Although the difference is modest, Japan had both the largest age- and BSA-adjusted thyroid volume among the six countries, while Bahrain and the United States had the smallest age- and BSA-adjusted thyroid volume, respectively (12). They suggest that a population-specific reference in countries with a long-standing iodine sufficiency may be more accurate than a single international reference.

The strength of our research is that the thyroid volume was measured by using a standardized technique proposed by WHO /ICCIDD, while the weakness is the unexpected limited size of some of the groups of children, especially for 6 and 12 years of age, and 0.7, 1.5, 1.6^2 of BSA. The differences in median and P97 thyroid volume between our results and the 2003 WHO/ICCIDD reference were 5.3 and 13.9% for age and 10.6 and 11.1% for BSA, respectively. This could be accounted for by the inter-observer variation between the two studies (11.1–12.1%). Our reference value of thyroid volume in Japanese schoolchildren, together with the new WHO/ICCIDD international reference, might be applicable to countries in the Far East as a population-specific local reference in defining goiter in the context of IDD surveillance.

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