Local versus WHO/International Council for Control of Iodine Deficiency Disorders-recommended thyroid volume reference in the assessment of iodine deficiency disorders

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Abstract

Objective: Iodine deficiency endemicity is defined by the goitre prevalence and the median urinary iodine concentration in a population. Lack of local thyroid volume reference data may bring many health workers to use the European-based WHO/International Council for Control of Iodine Deficiency Disorders (ICCIDD)-recommended reference for the assessment of goitre prevalence in children in different developing countries. The present study was conducted in non-iodine-deficient areas in Malaysia to obtain local children's normative thyroid volume reference data, and to compare their usefulness with those of the WHO/ICCIDD-recommended reference for the assessment of iodine-deficiency disorders (IDD) in Malaysia.

Design and methods: Cross-sectional thyroid ultrasonographic data of 7410 school children (4004 boys, 3406 girls), aged 7–10 years, from non-iodine-deficient areas (urban and rural) in Peninsular Malaysia were collected. Age/sex- and body surface area/sex-specific upper limits (97th percentile) of normal thyroid volume were derived. Thyroid ultrasonographic data of similar-age children from schools located in a mildly iodine-deficient area, a severely iodine-deficient area, and a non-iodine-deficient area were also collected; spot urines were obtained from these children for iodine determination.

Results: The goitre prevalences obtained using the local reference were consistent with the median urinary iodine concentrations in indicating the severity of IDD in the areas studied. In contrast, the results obtained using the WHO/ICCIDD-recommended reference showed lack of congruency with the median urinary iodine concentrations, and grossly underestimated the problem. The local sex-specific reference values at different ages and body surface areas are not a constant proportion of the WHO/ICCIDD-recommended reference. A further limitation of the WHO/ICCIDD-recommended reference is the lack of normative values for children with small body surface areas ($<0.8 \text{ m}^2$) commonly found in the developing countries.

Conclusion: The observations favour the use of a local reference in the screening of children for thyroid enlargement.

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Introduction

Iodine deficiency endemicity is defined by the goitre prevalence and the median urinary iodine concentration in a population. According to the WHO, a region is considered endemic if more than 5% of the population have goitre or thyroid enlargement (1). In the past, thyroid palpation was the standard method for determining thyroid size (2, 3). However, as progress is made towards elimination of iodine deficiency disorders (IDD) worldwide, this procedure has been deemed inadequate for distinguishing mild thyroid enlargement from normal (4). Thyroid ultrasonography, a proven procedure for the quantitative assessment of thyroid size (5–7), is therefore recommended whenever possible (8).

However, evaluation of the ultrasonographic data obtained requires comparison with an appropriate standard or norm, which unfortunately is still lacking.

School children, owing to their easy recruitment, representativeness of different socio-economic classes and high vulnerability to IDD, are considered one of the best target groups for surveillance of IDD. Children aged 8–10 years are particularly recommended (1). Over the past few years, a number of investigators have proposed thyroid volume reference data as standards for assessment of goitre in children (9–11); one of these has recently been recommended by the WHO/International Council for Control of Iodine Deficiency Disorders (ICCIDD) for use as an international reference for thyroid volume in children aged 6–15 years (12). Most of these

data have come from Europe, but have varied considerably in terms of age range, sample size, representativeness, sex stratification (unisex or sex-specific references) and physical anthropometric stratification (height- or body surface area (BSA)-specific references). Their pertinence for the assessment of IDD in other populations, particularly those in the developing countries, is unclear and needs study. In this paper, we examined the thyroid volume of non-iodine-deficient 7- to 10-year-old Malaysian children in relation to age, sex and anthropometric achievement. Appropriate normal reference cut-off points were derived from these data and their usefulness for the assessment of goitre prevalence in iodine-deficient as well as non-iodine-deficient areas in Malaysia was compared with that of the WHO/ICCIDD-recommended reference (12).

Subjects and methods

Subjects

The subjects were children attending school Grades 1–4 in selected primary schools in Peninsular Malaysia. The schools were chosen based on the results of a nationwide survey of school children's iodine status (13). Only those schools ($n=34$) with median urinary iodine concentrations exceeding $100\text{ }\mu\text{g/l}$ were included in this study. These include schools located in the urban as well as the rural areas. The median urinary iodine concentration of these children was $137.6\text{ }\mu\text{g/l}$ (interquartile range (IQR): $114.2\text{--}184.0\text{ }\mu\text{g/l}$); goitrogen intakes, as indicated by the median urinary thiocyanate concentrations, were comparable between the urban and rural children (11.6 mg/l and 10.5 mg/l respectively) (13). In each school, all children attending Grades 1–4 were included in the study. The ages of the children were determined from the dates of birth given in the school register. For comparative and validation purposes, similar-age children from schools located in Baling, a mildly iodine-deficient area in Peninsular Malaysia, Ranau, a severely iodine-deficient area in Sabah, East Malaysia, and Segambut, a non-iodine-deficient area in Kuala Lumpur, the capital of Malaysia, were also studied.

Methods

Urinary iodine concentration Spot urines were collected from the children for iodine determination by catalytic reduction of ceric ion by arsenite salt after digestion with acid (14).

Thyroid volume Thyroid ultrasonography (15) was performed by a single radiologist (AZ in the presence of MN or MTF) using a portable ultrasound machine (Aloka SSD-500, Tokyo, Japan) with a 7.5 MHz transducer. Thyroid volume was calculated according to the formula: width $\times$ length $\times$ thickness $\times 0.479$ for

each lobe. The repeatability and reproducibility of thyroid volume measurements by ultrasonography were assessed in 40 children at the start of the study. AZ measured the children twice while MN measured the same children once. The intra- and inter-measurer errors, as determined from these data, averaged 1.7 ± 2.7 (s.d.) and $3.4 \pm 3.7\%$ respectively. The mean difference between any pairs (within or between measurers) of thyroid volume measurements did not differ significantly (paired t -test). Thyroid size by palpation was scored by one of us (ASA) according to the updated WHO criteria (1).

Body weight, height and surface area Body weight was measured to the nearest 0.1 kg using a SECA beam balance weighing scale. The children were weighed wearing their school uniforms but without shoes, belts or any other items found on them. Height was measured to the nearest 0.1 cm using the SECA height scale. BSA (m^2) was calculated according to the formula: $(\text{weight}^{0.425} \times \text{height}^{0.725} \times 71.84) / 10\,000$.

Statistical analysis The thyroid volume data or, where necessary, their transformed values were tested for normality using the Lilliefors test. Correlation and multiple regression statistics were used to examine for association between thyroid volume and age, sex and the measured or calculated anthropometric measurements. Differences in median thyroid volume between groups were evaluated using the Mann–Whitney test. In accordance with internationally accepted norms, the 97th percentile thyroid volume for each age/sex or other grouping was taken as the upper limit of normal for that grouping. These values were calculated only for those groups whose sample sizes exceeded 200. A sample size of 200 is considered the minimum below which the 97th and other extreme percentile values cannot be estimated with reasonable precision (16). Curves of median and 97th percentile thyroid volumes against age and the selected physical anthropometric achievement were constructed; smoothing of the curves was done using the split-spline technique available in Statistical Analytical System (SAS) software.

Results

All Grade 1–4 children who were in school ($n=7410$) during our visit participated in the study. There were 4004 boys and 3406 girls. The median urinary iodine concentration of the children was $132.8\text{ }\mu\text{g/l}$ (IQR: $108.0\text{--}166.2\text{ }\mu\text{g/l}$). In all age/sex groups, the distributions of thyroid volumes were skewed slightly to the right (skewness: $0.64\text{--}1.13$). The distributions were normalized when the thyroid volume data were transformed logarithmically. In each age/sex group, the volume of the right lobe was, on average, significantly larger than that of the left (Table 1). Sex differentials in median thyroid volume were observed at

Table 1 Mean $\pm$ S.D., median (within brackets) and 97th percentile thyroid volumes by age and sex.

Age (years)	Males					Females				
	<i>n</i>	Right lobe*	Left lobe	Thyroid volume (ml)	97th percentile thyroid volume (ml)	<i>n</i>	Right lobe*	Left lobe	Thyroid volume (ml)	97th Percentile thyroid volume (ml)
7	503	1.3 $\pm$ 0.4 (1.2)	1.0 $\pm$ 0.3 (0.9)	2.3 $\pm$ 0.7 (2.1)	4.1	427	1.3 $\pm$ 0.5 (1.2)	1.0 $\pm$ 0.4 (1.0)	2.3 $\pm$ 0.9 (2.1)	4.2
8	1327	1.5 $\pm$ 0.5 (1.4)	1.0 $\pm$ 0.4 (1.0)	2.5 $\pm$ 0.8 (2.4)	4.5	1099	1.5 $\pm$ 0.5 (1.4)	1.0 $\pm$ 0.4 (1.0)	2.5 $\pm$ 0.8 (2.4)	4.7
9	1318	1.6 $\pm$ 0.4 (1.6)	1.3 $\pm$ 0.4 (1.2)	2.9 $\pm$ 0.8 (2.8) ^a	5.0	1139	1.7 $\pm$ 0.5 (1.6)	1.4 $\pm$ 0.4 (1.3)	3.1 $\pm$ 1.0 (2.9) ^a	5.5
10	856	1.7 $\pm$ 0.4 (1.7)	1.4 $\pm$ 0.4 (1.4)	3.2 $\pm$ 0.9 (3.1) ^b	5.7	741	1.8 $\pm$ 0.5 (1.8)	1.5 $\pm$ 0.4 (1.4)	3.4 $\pm$ 1.0 (3.3) ^b	6.6

Mann–Whitney test: * right lobe vs left lobe for all age/sex groups: $P < 0.0001$; ^a $P < 0.0001$, ^b $P < 0.001$.

ages 9 and 10 years with females having, on average, slightly larger thyroid volume than males (Table 1).

In each sex group, thyroid volume increased significantly with age (males or females: $r = 0.35$, $P < 0.0001$), and was correlated with height (males: $r = 0.38$, $P < 0.0001$; females: $r = 0.43$, $P < 0.0001$), weight (males: $r = 0.36$, $P < 0.0001$; females: $r = 0.42$, $P < 0.0001$), and BSA (males: $r = 0.39$, $P < 0.0001$; females: $r = 0.45$, $P < 0.0001$); the correlation coefficients (r) increased marginally (by 0.01–0.04 point) when the logarithms of thyroid volumes were used. To test whether thyroid volume adjusted for anthropometric achievement and sex was age independent, we analysed the residuals remaining after the regression of thyroid volume (raw or logarithmically transformed values) on sex and BSA. The residuals were significantly correlated with age ($r = 0.23$, $P < 0.0001$).

The 97th percentile thyroid volumes by age/sex group are presented in Table 1, while Table 2 presents the median and 97th percentile thyroid volumes by BSA and sex. The BSA/sex-specific values were not presented

by age because of small group sample sizes. Figures 1 and 2 compare our age/sex-specific and BSA/sex-specific 97th percentile thyroid volume curves with the corresponding WHO/ICCIDD-recommended reference curves. Our age/sex-specific 97th percentile thyroid volumes were approximately 26–32% smaller than the corresponding WHO/ICCIDD-recommended upper limits of normal, while our BSA/sex-specific 97th percentile values were approximately 6–25% smaller. For the BSA/sex-specific values, the magnitude of the difference between the local and the WHO/ICCIDD reference increased with increased BSA.

Seventy-eight (1.1%) children were classified as goitrous by palpation (all clinical grade 1). Of these children, 9 (11.5%) and 11 (14.1%) had normal thyroid volumes by ultrasound based on the above age/sex- and BSA/sex-specific 97th percentile cut-off points respectively. No child had abnormal findings on ultrasound.

The median urinary iodine concentrations of the children in Segambut ($n = 232$), Baling ($n = 89$) and Ranau ($n = 73$) were 128 $\mu\text{g/l}$ (IQR: 102.2–170.8 $\mu\text{g/l}$),

Table 2 Median and 97th percentile thyroid volume by sex and BSA.

BSA (m ²)	Thyroid volume (ml)					
	Boys			Girls		
	<i>n</i>	Median	97th Percentile	<i>n</i>	Median	97th Percentile
0.6	17	2.0	–	19	1.9	–
0.7	313	2.1	3.8	367	2.1	4.0
0.8	1196	2.4	4.2	1070	2.5	4.5
0.9	1319	2.7	4.6	1028	2.8	5.1
1.0	658	2.9	5.1	503	3.1	5.6
1.1	277	3.1	5.6	262	3.3	6.2
1.2	138	3.3	–	91	3.5	–
1.3	63	3.5	–	53	3.9	–
1.4	23	3.7	–	13	4.6	–

Figure 1 Curves of median and 97th percentile thyroid volumes against age; sex specific.

53.5 µg/l (IQR: 32.0–78.6 µg/l) and 10.8 µg/l (IQR: 5.3–20.5 µg/l) respectively. The goitre prevalences, as assessed by palpation and ultrasound using the above local and WHO/ICCIDD-recommended cut-off points are shown in Table 3. In Ranau, 8.2% of subjects (5.6% in Baling) with an abnormal thyroid volume by ultrasound (using local age/sex-specific cut-offs) were judged non-goitrous by palpation, and 4.1% (3.4% in Baling) who were judged goitrous by palpation had normal thyroid volumes by ultrasound. Against ultrasound, palpation had a sensitivity of 81.8 and 54.5% in Ranau and Baling respectively. A thyroid cyst was detected at ultrasound in one visibly goitrous girl from Ranau.

Discussion

The results show that, within the age range 7–10 years, Malaysian children's thyroid volume, under iodine-sufficient conditions, increased with age and was significantly associated with height, body weight, BSA and sex. Among the measured and calculated anthropometric measurements there was little difference in the degrees of their association with thyroid volume.

However, the magnitude of their association suggests that, when assessing children's thyroid size, there may be a need to take the children's anthropometric achievements into account. This may be particularly relevant in impoverished remote communities where IDD and protein-energy malnutrition often coexist. As demonstrated by the results for remote Baling and Ranau, a higher goitre prevalence was obtained when the BSA/sex-specific reference data, instead of the age/sex-specific reference values, were applied. However, regardless of which reference was used, the results obtained were consistent with the median urinary iodine concentrations in indicating the existence of mild and severe iodine deficiency in Baling and Ranau respectively, and the adequate iodine nutritional status of the children in Segambut, thus validating the appropriateness of the above references for the assessment of IDD in Malaysia.

The thyroid volumes of the children in our study appear comparable with those reported by Wacharasin (17) for iodine-sufficient Thai children and Liesenkotter *et al.* (18) for iodine-replete Berlin (German) children. They also appear comparable with those reported by

Figure 2 Curves of median and 97th percentile thyroid volumes against BSA; sex specific.

Gutekunst *et al.* (19) and Ivarsson *et al.* (20) for iodine-sufficient Swedish children of the same age and sex. Our values, however, are much smaller than those reported by Klima *et al.* (21), Vitti *et al.* (9) and Delange *et al.* (11) for other iodine-sufficient European children. For example, the median (sexes combined for comparability of results) thyroid volumes of the children in our study

were approximately 17–22% smaller than the mean thyroid volumes of similar-age Italian children (9), and 30–36% smaller than the age/sex-specific values (extrapolated from graphs) reported by Delange *et al.* (11). These disparities could be attributed to differences in body size or BSA between Malaysian and European children. However, for the same BSA, our upper limits of

Table 3 Prevalence of goitre based on local and WHO/ICCIDD reference data.

Criteria	Goitre prevalence No. (%)		
	Segambut	Baling	Ranau
>97th percentile of local age/sex-specific reference	0 (0)	11 (12.4)	33 (45.2)
>97th percentile of local BSA/sex-specific reference	0 (0)	14 (15.7)	47 (64.4)
>97th percentile of WHO/ICCIDD age/sex-specific reference	0 (0)	2 (2.2)	5 (6.8)
>97th percentile of WHO/ICCIDD BSA/sex-specific reference	—*	—*	—*
Palpation	0 (0)	9 (10.1) ^a	30 (41.1) ^b

* Could not be computed owing to lack of reference values for BSA < 0.8 m².

^a All clinical grade 1; ^b 35.6% grade 1 and 5.5% grade 2.

normal thyroid volume were still smaller (approximately 6–25% smaller) than those reported by Delange *et al.* A possible explanation could be the differential age composition of our two samples. While our sample comprised children aged 7–10 years, the sample of Delange *et al.* was drawn from children aged 6–15 years. As has been shown by the results of the present study, thyroid volume for BSA is not age independent. Thus, with adolescents making up possibly half of their sample, it is not inconceivable that their BSA/sex-specific medians and upper limits of normal thyroid volume would be larger.

The data of Delange *et al.* (11) have now been recommended by the WHO/ICCIDD (12) as an international reference for general use. Based on the age/sex-specific cut-off points of this reference, Baling, with a median urinary iodine concentration of 53.5 µg/l, would be classified as having no IDD while Ranau, with a median urinary iodine concentration of 10.8 µg/l, would be classified as having very mild IDD. The recommended BSA/sex-specific reference could not be applied to the Baling and Ranau data because of the lack of reference values for children with small BSAs. The inapplicability of the WHO/ICCIDD reference to the Malaysian population is apparent, and suggests the need for population-specific references, even for BSA-adjusted thyroid volumes. This is because BSA reflects different aetiologies in different populations (16). For example, in populations with marginal or poor protein-energy nutritional status, such as those found in the developing countries, variations in BSA usually reflect variations in lean body mass, besides height. In contrast, BSA variation in populations with adequate or high protein and energy intakes, such as those found in the developed economies, generally reflects, besides height, degrees of adiposity and obesity at one end of the distribution, and levels of lean body mass that are often related to greater physical fitness (less fatness) at the lower end of the distribution. How these affect thyroid volume is unclear, but thyroid volume for BSA can be expected to differ between populations. A recent report has suggested that, in adults, thyroid size is determined largely by lean body mass (22). Whether this is also true in growing children remains to be established.

It is worthy of note that our age-specific 97th percentile thyroid volumes for boys correspond almost exactly with the previous WHO/UNICEF/ICCIDD-recommended age-specific (sexes combined) upper limits of normal (23, 24). This earlier WHO/UNICEF/ICCIDD reference was formulated from data of children living in different continents including Asia and Africa. Application of this reference to the data of the children from Baling and Ranau yielded results (goitre prevalences: 14.6 and 54.8% respectively) that were comparable with those obtained using the local reference. This suggests that the reference can be used in Malaysian children. It also suggests that, for population-based screening of children aged 7–10 years, a unisex age-specific reference may suffice. Based on the results of

the present study, there was no significant difference in thyroid volume between boys and girls at age 7–8 years. The volume was only larger in girls from the age of 9 years onwards (similar observations were made by Chanoine *et al.* (25) and Delange *et al.* (11)). However, sex differences in thyroid volume at age 9–10 years, although statistically significant, were not great. Thus, a unisex reference for children of this age range is not untenable.

The results of the present study confirmed previous observations (4, 9) of the inadequacy of palpation for the assessment of thyroid enlargement in children.

In conclusion, the updated WHO/ICCIDD thyroid volume reference is inapplicable to Malaysian children. The previous WHO/UNICEF/ICCIDD reference, on the other hand, appears acceptable for local use. A review of the process of adopting data as an international reference for general use is necessary. For the proper assessment and interpretation of thyroid volume measurements, the local reference, where available, is favoured.

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