Abstract

Objective: The determination of goiter prevalence in children by thyroid ultrasound is an important tool for assessing iodine deficiency disorders. The current World Health Organization/International Council for the Control of Iodine Deficiency Disorders (WHO/ICCIDD) normative values, based on thyroid volume in iodine-sufficient European children, have recently been questioned, as thyroid volumes in iodine-sufficient children from the USA and Malaysia are smaller than the WHO/ICCIDD reference data. Our objective was to describe ultrasonographic thyroid volumes in a representative national sample of iodine-sufficient Swiss school children, and to compare these with the current reference data for thyroid volume.

Design and Methods: A 3-stage, probability proportionate-to-size cluster sampling method was used to obtain a representative national sample of 600 Swiss children aged 6–12 years. The following data were collected: thyroid size by ultrasound, urinary iodine concentration, weight, height, sex and age.

Results: The median urinary iodine concentration (range) of the children was 115 μg/l (5–413). Application of the WHO/ICCIDD thyroid volume references to the Swiss children resulted in a prevalence of 0%, using either age/sex-specific or body surface area (BSA)/sex-specific cut-off values. Upper limits of normal (97th percentile) of thyroid volume from Swiss children calculated 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.

Conclusions: Swiss children had smaller thyroids than the European children on which the WHO/ICCIDD references are based, perhaps due to a residual effect of a recent past history of iodine deficiency in many European regions. However, there were sharp differences between our data and a recent set of thyroid volume data in Swiss children produced by the operator and equipment that generated the WHO/ICCIDD reference data. This suggests that interobserver and/or interequipment variability may contribute to the current disagreement on normative values for thyroid size by ultrasound in iodine-sufficient children.

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Introduction

The median urinary iodine concentration (UI) and goiter prevalence are the most widely used indicators for assessing iodine deficiency disorders (IDD) in a population (1). In areas of mild endemicity, ultrasonographic measurement of thyroid volume is preferable to inspection and palpation for determination of goiter prevalence (2). However, interpretation of thyroid ultrasonography requires valid reference criteria from iodine-sufficient populations. Although school-age children are a useful target group for IDD surveillance (1), defining normal values for thyroid size in children has proven difficult. The original normative criteria for thyroid volume proposed by Gutekunst and Martin-Teichert (3) were criticized as too low because the 97th percentiles classified a high percentage of children as goitrous in areas where iodine supply was sufficient (4).

The World Health Organization/International Council for the Control of Iodine Deficiency Disorders (WHO/ICCIDD) adopted a new thyroid volume reference in 1997 (2). However, recent reports have suggested that...
the WHO/ICCIDD reference criteria may be too high (5, 6). Thyroid volumes in iodine-sufficient children from the USA (5) and iodine-sufficient Malaysian children (6) are distinctly smaller than those of the European children from whom the WHO reference data are derived (4). The reason for this discrepancy is unclear: it may be due to interobserver/equipment variability in ultrasonography and/or may be a residual effect of iodine deficiency that existed in many European countries up to the early 1990s (5, 7, 8).

In contrast to much of Europe, iodized table salt has been available nationwide in Switzerland for 50 years and has been iodized at 15 mg iodine/kg since 1980 (9). Swiss children who are 6 to 12 years old today very likely have had a steady and sufficient iodine intake since birth (10–12). It would, therefore, be valuable to evaluate the current WHO/ICCIDD reference data in Swiss children. Bürgi et al. reported that age-adjusted median thyroid volumes and 97th percentiles measured in early 1997 in children from two cities in Switzerland closely agreed with WHO/ICCIDD reference data (12). The study by Bürgi et al. (12) employed identical equipment and the same operator whose ultrasound measurements had been used to generate the WHO/ICCIDD reference data (4).

We recently completed a national survey of iodine nutrition in Switzerland, to assess iodine status 1 year after the iodine content in salt was increased from 15 to 20 mg/kg. One objective was to describe thyroid volumes by ultrasonography in a representative national sample of 6- to 12-year-old Swiss school children with an assumed lifetime of iodine sufficiency, and to compare these with the WHO reference data. In addition, by comparing our data with those of Bürgi et al. (12), we wished to examine if interobserver/equipment variability in thyroid ultrasound may contribute to the current disagreement on normative values for thyroid size in iodine-sufficient children.

**Subjects and methods**

**Subjects**

A 3-stage probability proportionate-to-size (PPS) cluster sampling method (1) was used to obtain a representative national sample of 600 Swiss children aged 6–12 years. The design used current census data to provide a systematic sampling of communities based on the cumulative population. Stage 1 of the sampling involved a stratified random selection and recruitment of 30 schools for participation in the study. Written consent was then obtained from the community school boards. If a school declined participation another randomly selected school from the same stratum replaced it. In the second stage, 2 classrooms at the appropriate grade level were randomly selected from each school. Finally, the teachers of the classrooms randomly selected students to participate. An average of 20 students was sampled at each school, the number varying depending on the size of the classrooms. Data were collected from April until October 1999. Ethical approval for the study was obtained from the Human Subjects Committee of the Swiss Federal Institute of Technology in Zürich. Written consent was obtained from the community school boards, as well as the teachers and parents of the children involved.

**Methods**

Height and weight were measured using standard anthropometric techniques (13). For the measurements, subjects removed their shoes, emptied their pockets and wore light indoor summer clothing. Height was recorded to the nearest cm and weight to the nearest 100 g. Body surface area (BSA) was calculated from weight and height measurements using the formula: BSA = weight (kg)⁰.⁴₂⁵ × height (cm)⁰.⁷₂⁵ × 71.84 × 10⁻⁴ (2). Spot urine samples were collected from all children and stored at −20°C until analysis. The iodine concentration in the urine was measured using a modification of the Sandell-Kolthoff reaction as described by Pino et al. (14) with ammonium persulfate as the oxidizing reagent. Thyroid gland volume was measured using an Aloka SSD-500 Echocamera (Aloka, Mure, Japan) with a 7.5 MHz linear transducer. Measurements were performed on subjects sitting upright with the neck slightly extended. Volume of each lobe was calculated according to the formula: width × length × thickness × 0.479 and the lobe volumes were summed (2). The volume of the isthmus was not included. SH or MZ performed the ultrasound measurements. To estimate intra- and interobserver variability, SH measured 20 school children twice and MZ measured the same children once. The mean (SD) intra- and interobserver errors were 4.9 (4.0)% and 3.7 (3.5)% respectively.

**Statistical analysis**

Data processing and statistics were carried out using SPLUS 4.5 (Mathsoft, Seattle, WA, USA) and Excel (Microsoft, Seattle, WA, USA). The thyroid volume distributions for each age and BSA group for both sexes were skewed to the right. The distributions were logarithmically transformed and the Kolmogorov-Smirnov test was used to verify normality of the transformed data. Means and standard deviations of the logarithm of the thyroid volume were then used as parameters to fit a normal distribution, and 97th percentiles (P97) were calculated from the P97 of the standard normal distribution. Differences in thyroid volume between groups were tested using the Mann–Whitney test. Curves of the P97 thyroid volumes against age and BSA were constructed and smoothed using regression.
Results

A total of 612 students from 30 schools throughout Switzerland were studied. This represents approximately 1 in 1000 children in this age group in Switzerland (15). The sample included 302 females and 310 males aged 6–12 years. Mean age (s.d.) was 9.3 (1.9). The median UI (range) of the children was 115 μg/l (5–413). The goiter prevalences in our sample using the P97 of the original normative data of Gutekunst and Martin-Teichert and the current WHO/ICCIDD recommended cut-off values were 3.9% (n = 23) and 0% respectively. There were significant gender differences in median thyroid volume (P < 0.01) only at age 12 years, when females had a median thyroid volume 17% greater than males. By BSA, significant differences (P < 0.05) between females and males were found only when BSA was >1.4 m². At a BSA of 1.5 and 1.6, females had a median thyroid volume 9% and 10% greater than males respectively.

Figure 1 compares our age/sex-specific P97 curve of thyroid volume with the WHO/ICCIDD recommended reference curves (2), as well as the original normative data proposed by Gutekunst and Martin-Teichert (3). Our age/sex-specific P97 volumes are similar to the values of Gutekunst and Martin-Teichert (3) but are 20–42% smaller than the WHO/ICCIDD cut-off values (2). Figure 2 compares our BSA/sex-specific P97 curve of thyroid volume with the WHO/ICCIDD recommended reference curves (2) and recent data from Xu et al. on iodine-sufficient children in the USA (5). Our BSA/sex-specific P97 volumes are similar to the values of Xu et al. (5), but are 30–56% smaller than the WHO/ICCIDD cut-off values (2).

Discussion

Using age/sex-specific or BSA/sex-specific criteria, the Swiss children in this study had distinctly smaller thyroid volumes than the iodine-sufficient European children from which the WHO/ICCIDD reference data are derived (4). Because the WHO/ICCIDD reference cut-off points are the 97th percentiles of thyroid volume in iodine-sufficient European children, applying the WHO/ICCIDD references to this population of iodine-sufficient Swiss children should yield a goiter prevalence of approximately 3%. However, using either the age/sex-specific or the BSA/sex-specific WHO/ICCIDD cut-offs, there were no goitrous children in our sample.

The difference in thyroid size between the Swiss children in this study and the iodine-sufficient European children studied by Delange et al. (4) may be explained by the residual, long-term effects of a recent past history of iodine deficiency in Europe (5, 7). Enlarged thyroids in children who are iodine deficient during the first
years of life may not regress completely after introduction of iodized salt (16). Iodine deficiency existed in many European countries up to the early 1990s (8). This may help explain why differences in thyroid volume increase sharply with age and/or BSA when the European children of Delange et al. (4) are compared with US children (5) and our Swiss children (with a lifetime of iodine sufficiency) (Figs 1 and 2).

Interobserver and/or interequipment variation in ultrasonographic thyroid measurement may also contribute to reported differences in thyroid volume from iodine-sufficient children (7). In 40 Malaysian children aged 7–10 years, Foo et al. found an interobserver error (s.d.) in ultrason sound measurement of thyroid volume of 3.4 (3.7)% (6). In 20 Italian children aged 6–14 years, Vitti et al. reported an interobserver error of 4.2–5.2% (17). These values are similar to the interobserver error (s.d.) of 3.7 (3.5)% reported in the present study. In contrast, Özgen et al. recently reported a mean interobserver error (s.d.) of 13.4 (8.3)% in the ultrason sound measurement of thyroid volume in 30 healthy 7- to 16-year-old Turkish children (18).

In attempting to distinguish between interobserver/equipment error and a past history of iodine deficiency to explain the current discrepancies in thyroid volume measurements from iodine-sufficient children, it is of particular interest to compare the results of our study with those of Bürgi et al. (12) and Truong et al. (11). These three studies report ultrasonographic thyroid volume measurements in iodine-sufficient Swiss school children between 1994 and 1999 (Table 1). Bürgi et al. (12) employed identical equipment and the same operator whose ultrason sound measurements had been used to generate the 1997 WHO/ICCIDD reference data. They found that age/sex-specific median thyroid volumes and 97th percentiles measured in 1997 in 6- to 16-year-old children from two cities in Switzerland closely agreed with the WHO/ICCIDD reference data (2, 12). In contrast, the age/sex-specific median thyroid volumes reported in this study – which used different investigators and equipment – are 10–56% smaller than the median volumes of Bürgi et al. (Table 1). Moreover, our age/sex-specific median thyroid volumes are similar to those of Truong et al. (11), who measured thyroid volumes in iodine-sufficient Swiss children in 1994. Although 5 years separate the three data collections and the iodine level in Swiss table salt was increased from 15 to 20 mg/kg in the intervening period, it is unlikely that this could account for the sharp differences in thyroid volumes obtained by the different investigators. These data strongly suggest that interobserver and/or interequipment variability may contribute to the current disagreement on normative values for thyroid size by ultrasound in iodine-sufficient children. It also argues for the intercalibration of the methods used for ultrasonography in the measurement of thyroid volume in children.

### References


Table 1 Age specific median thyroid volume (ml) by ultrasound in iodine-sufficient Swiss school children: 1994–1999.

<table>
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<tr>
<th>Age (years)</th>
<th>Truong et al. 1994 (11) (n=217)</th>
<th>Bürgi et al. 1997 (12) (n=280)</th>
<th>Present study (n=612)</th>
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