

Can thyroid size still be considered as a useful tool for assessing iodine intake?

Arkadiusz Zygmunt^{1,2}, Agnieszka Zygmunt³, Małgorzata Karbownik-Lewińska^{1,4}, Andrzej Lewiński¹

¹ Polish Mother's Memorial Hospital – Research Institute, Lodz, Poland

² Department of Endocrinology and Metabolic Diseases, Medical University of Lodz, Poland

³ Department of Pediatric Cardiology and Rheumatology, Medical University of Lodz, Poland

⁴ Department of Oncological Endocrinology, Chair of Oncological Endocrinology, Medical University of Lodz, Poland

Zygmunt A, Zygmunt A, Karbownik-Lewińska M, Lewiński A. Can thyroid size still be considered as a useful tool for assessing iodine intake? *Ann Agric Environ Med.* 2015; 22(2): 301–306. doi: 10.5604/12321966.1152084

Abstract

Introduction. It has always been very difficult to precisely define a goitre. For years, the borderline values have been sought which could be universally used in such evaluations. However, presented reference values were very often disappointing as they proved to be either too restrictive or too liberal.

Objective. The aim of the study was to assess the two methods of goitre evaluation: 1) traditional, based on ultrasound reference ranges for the thyroid size, 2) based on the analysis of thyroid volume (V) referred to the body surface area (BSA).

Materials and Method. For this purpose, the study was conducted to evaluate the incidence of goitre and ioduria among 102 school-aged children in Opoczno, Poland. The study group comprised 59 girls and 43 boys; age range: 8–12 years.

Results. The incidence of goitre among the examined children varied from 1.0–11.8% in relation to the age, and from 0–14.5% in relation to the BSA, depending on the references ranges used.

Conclusion. Analysis of V/BSA ratio is a better estimation of the size of the thyroid gland than the evaluation of thyroid size based on traditional ultrasound reference values. Summing up, relating the size of the thyroid gland to BSA is a good, sensitive tool for such analysis, and can be used for comparisons of different populations, as well as surveys conducted at different time points.

Key words

iodine prophylaxis, goitre, schoolchildren, urine iodine concentration

INTRODUCTION

It has always been very difficult to precisely define a goitre. The borderline cases, when a distinction between healthy and abnormal thyroid has to be made, are especially problematic. Historically, large lima beans seeds, nail or distal phalanx of the thumb were often used as the reference point for such comparison [1].

In previous years, the WHO has changed the goitre classification based upon the palpation of thyroid gland several times; besides which other societies (e.g. PAHO) have proposed their own classification [2, 3, 4]. Imperfection of goitre classifications is connected with the high variability of thyroid palpation, both intra- and inter-observer – this variability increases with decreasing thyroid volume and decreasing goitre incidence [5].

Application of ultrasound examination of the thyroid has significantly decreased the variability of the data obtained; however, repeatability of this examination also depends on many factors, including the thyroid volume, position in which the assessment is being performed, width of the probe, as well as the experience and number of the researchers [6].

Before final analysis, results obtained in this way are interpreted by comparison of the measured thyroid volume

to the value considered as borderline. In such a way, the frequency of goitre can be evaluated.

When assessing the iodine intake, it is especially valuable to determine the goitre incidence among the school-aged children [7].

For years, the borderline values, which could be universally used in such evaluations have been searched for. However, the presented reference values were very often disappointing as they proved to be either too restrictive or too liberal [8]. This is one of the reasons why assessment of goitre incidence based even upon ultrasound examination has been losing its significance, giving way to assessment of ioduria which seems to be a more objective evaluation of iodine intake in the examined population. Although analysis of ioduria distribution is a very reliable test, it reflects only the current situation of iodine intake. Analysis of thyroid volume indirectly assesses the influence of iodine intake over the course of several years.

Therefore, in no way can these two examinations be treated interchangeably; on the other hand, they logically complement each other.

OBJECTIVE

The aim of the study was to assess the two methods of goitre evaluation: 1) traditional, based on ultrasound reference ranges for the thyroid size, 2) based on the analysis of thyroid volume (V) referred to the body surface area (BSA).

Address for correspondence: Andrzej Lewiński, Department of Endocrinology and Metabolic Diseases, Polish Mother's Memorial Hospital – Research Institute, Rzgowska 281/289, 93-338 Lodz, Poland
E-mail: alewin@csk.umed.lodz.pl

Received: 23 July 2013; accepted: 17 September 2013

For this purpose, the presented study evaluated the incidence of goitre and ioduria among school-aged children in Opoczno, Poland.

MATERIALS AND METHOD

Healthy children living in Opoczno, a town in the centre of Poland (Lodz Province) were included in the study. The children were recruited from Primary School No 1. One hundred and two children, 59 girls and 43 boys, age range 8–12 years, were examined in 2010.

Parents of all the children qualified for the study gave written consent for the participation of their children. The Ethical Committee approved the protocol ('ThyroMobil Project').

The height and the body mass of children were measured by using standard anthropometric techniques [9]. For the measurements, children took off their shoes and wore light indoor clothing. The heights were recorded to the nearest millimeter, and the weights of children were recorded to the nearest 100 g. Body surface area (BSA) was calculated from the following formula:

$$W^{0.425} \times H^{0.725} \times 71.84 \times 10^{-4},$$

where: W – weight (kg); H – height (cm).

Thyroid palpation was performed, followed by ultrasound examination of the thyroid gland with a Siemens Sonoline Prima with a 7.5 MHz linear array transducer. Measurements were performed while the subjects were lying on a medical couch. The sum of lateral thyroid lobes volumes, determined sonographically, constituted the actual volume of the thyroid gland: the volume of the isthmus was skipped. The volume of thyroid lobe was calculated according to the following formula, proposed by Brunn et al. [10]:

$$V \text{ (ml)} = 0.479 \times W \times D \times L,$$

where: W – width (cm); D – depth (cm); L – length (cm).

The obtained data were compared to reference values for thyroid volume proposed by Zimmermann et al. [11], adjusted for age and body surface area (BSA), Szybinski et al. [12], adjusted for age, and Delange et al. [13], adjusted for age and BSA.

Volume of the thyroid gland (V) to body surface area was also compared, calculating V/BSA ratio [m^3/m^2] [14]. In the opinion of the authors, this ratio (V/BSA) better reflects changes in thyroid volume at particular time points.

Urine samples were collected from each child, prior to the physical examination. In order to determine iodide concentration the modified catalytic method by Sandell and Kolthoff was used [15].

Data and statistical analyses. The data were statistically analyzed, using the following methods: non-parametric test for independent groups (Mann-Whitney rank sum test), Kruskal-Wallis one way analysis of variance on ranks, followed by Dunn's test, chi-square analysis and calculation of the Pearson correlation coefficient. In all analyses, statistical significance has been considered as achieved at a value of $p < 0.05$. Data processing, statistical analyses and figures were performed by using SigmaPlot 12.3 (Systat Software, Inc, San Jose, CA, USA) and Excel (Microsoft Corp., Redmond, WA, USA).

The mean values of age, BSA and UICs in the examined schoolchildren were presented in Table 1.

RESULTS

Goitre. The incidence of goitre in relation to the age among the examined children was 11.8%, according to Zimmermann et al. [11] reference values, 2.9% according to Szybinski et al. [12] reference values, and 1.0%, according to Delange et al. [13] reference values. The prevalence of goitre among boys was 7.0%, 2.3% and 2.3%, respectively, among girls – 18.6%, 4.7% and 0%.

Figure 1 shows the incidence of goitre in relation to age.

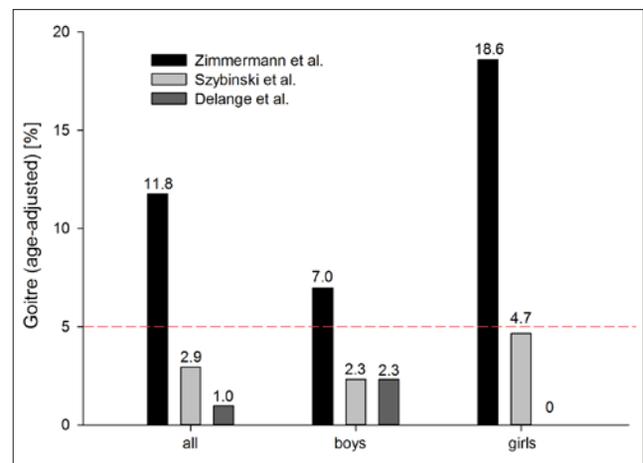


Figure 1. Incidence of goitre in relation to age (according to Zimmermann et al. [11], Szybinski et al. [12], Delange et al. [13] reference values). The dashed line indicates value (5%), above which there is endemic goitre

The incidence of goitre in relation to the BSA was 14.5%, according to Zimmermann et al. [11] reference values, and 0%, according to Delange et al. [13] reference values. Szybinski et al. in their report did not present reference values in relation to the BSA [12]. The prevalence of goitre

Table 1. Mean \pm standard deviation (SD) values of age, body surface area (BSA) and urinary iodine concentration (UIC) in examined schoolchildren

Age	Number			Mean \pm SD of BSA [m^2/m^2]			UIC [$\mu\text{g}/\text{L}$]	
	Boys	Girls	All	Boys	Girls	All	Mean \pm SD	Median
8	1	3	4	0.994	0.921 \pm 0.109	0.939 \pm 0.096	142.1 \pm 78.4	143.2
9	4	12	16	1.031 \pm 0.156	1.054 \pm 0.113	1.048 \pm 0.120	116.2 \pm 40.9	116
10	13	12	25	1.213 \pm 0.085	1.139 \pm 0.161	1.174 \pm 0.133	121.7 \pm 56.8	109.6
11	13	16	29	1.263 \pm 0.091	1.260 \pm 0.146	1.261 \pm 0.122	115.7 \pm 57.2	103.1
12	12	16	28	1.262 \pm 0.129	1.308 \pm 0.129	1.288 \pm 0.129	111.6 \pm 49.0	105.9
All	43	59	102	1.221 \pm 0.127	1.186 \pm 0.176	1.201 \pm 0.157	118.6 \pm 53.3	109.1

among boys was 9.3% and 0%, respectively, among girls – 15.3% and 0%.

Figure 2 presents the incidence of goitre in relation to the BSA.

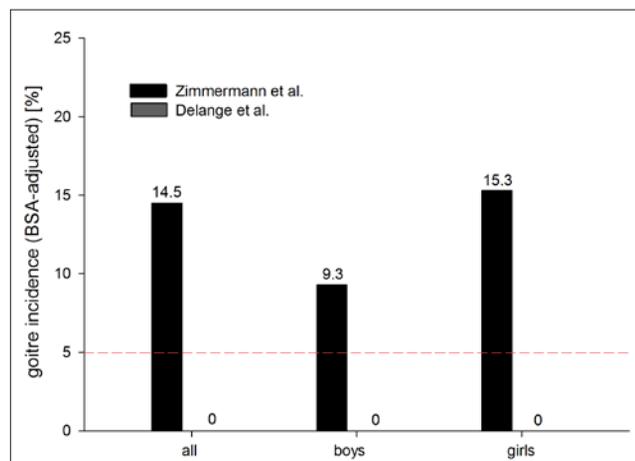


Figure 2. Incidence of goitre in relation to the BSA (according to Zimmermann et al. [11], Delange et al. [13] reference values)

A positive correlation between thyroid V and the BSA ($r=0.374$; $p<0.001$) was found; moreover, an even stronger, positive correlation was found between V/BSA and age ($r=0.665$; $p<0.001$).

Figure 3 shows the correlation V/BSA with respect to age. There was no correlation between thyroid V and age.

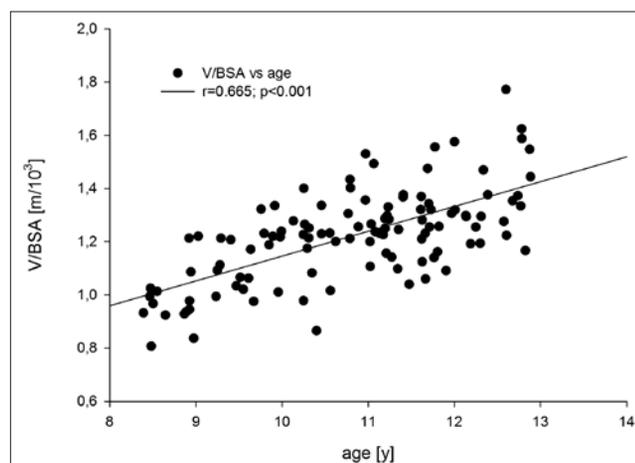


Figure 3. Correlation of V/BSA ratio (volume of thyroid gland to body surface area) with respect to age

V/BSA ratio. The values of V/BSA in particular groups are presented in Table 2 and Figure 4. The highest value of V/BSA was noted in a 10-year-old group. The girls from this group had a significantly higher value of V/BSA in comparison to 11- and 12-year-old girls ($p<0.05$). Children aged 12 years had a lower value of V/BSA compared to children aged 9 and 10 ($p<0.05$).

Urine iodine concentration. The values of UIC are presented in Table 1. The median values were within the range of normal values.

Table 2. Mean \pm standard deviation (SD) of V/BSA ratio (volume of thyroid gland to body surface area) [$m/10^3$]

Age	Mean \pm SD of V/BSA [$m/10^3$]		
	Boys	Girls	All
8	2.09	2.99 \pm 0.28	2.77 \pm 0.51
9	3.00 \pm 0.53	3.14 \pm 1.05	3.11 \pm 0.93
10	3.34 \pm 1.1	3.87 \pm 0.6	3.59 \pm 0.92
11	2.82 \pm 0.83	2.85 \pm 1.23	2.84 \pm 1.05
12	2.14 \pm 1.0	2.26 \pm 0.8	2.21 \pm 0.87

Table 3. Factors influencing thyroid size (of population significance)

Thyroid – size (factors of population significance)
– genetic (race)
– gender
– age
– goitrogenic agents: <ul style="list-style-type: none"> – naturally occurring – connected with pollution
– antibodies (autoimmune thyroid disorders)
– iodine supply (bioavailability): <ul style="list-style-type: none"> – diet: <ul style="list-style-type: none"> – cultural factors (diet rich in fish, algae, seaweed) – socio-economic factors (diet rich/low in fish) – iodine prophylaxis: <ul style="list-style-type: none"> – obligatory – optional

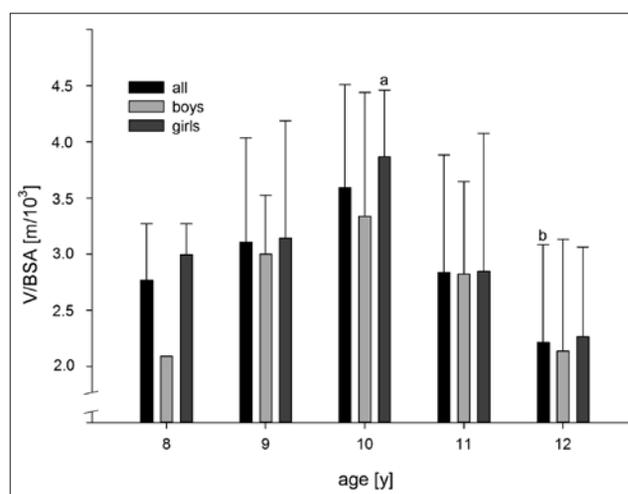


Figure 4. The mean value of V/BSA ratio (volume of thyroid gland to body surface area) in particular groups. Whiskers mean standard deviation (SD).

a – $p < 0.05$ vs 11- and 12-year-old girls; b – $p < 0.05$ vs children aged 9 and 10

DISCUSSION

Poland is a country with an adequate supply of iodine, which is also reflected in the value of UIC in the study population (median UIC above 100 $\mu\text{g/l}$). Expected values of the goitre frequency should also be below 5%, oscillating around this value.

Of the presented results, the standards reported by Szybinski et al. [12] seem to be the most representative and close to the expected values. On the other hand, the reference ranges proposed by Zimmermann et al. [11] appear to be

highly inadequate for our population (according to them, there is still an endemia of goitre in Poland).

Analysis of goitre incidence based on the BSA seems even less reliable. According to the standards by Zimmermann et al. [11], goitre endemia is still present on the territory of Poland, while according to the reference ranges by Delange et al. [13] there is no thyroid enlargement at all. Szybinski et al. [12] in their paper did not present any reference ranges based on the BSA.

Thus, analysis of the goitre incidence based on the BSA is impossible, even though it seems to be superior to the analysis of goitre incidence based on age (note the correlation between thyroid V and BSA and the lack of correlation between thyroid V and age).

The aforementioned data and their analysis speak in favour of limitations connected with setting standards based on studies of other populations.

Ultrasound reference ranges for children. Having analyzed the suggestions for ultrasound reference ranges in children, the conclusion was reached that their inadequacy resulted from an erroneous assumption which had been made during their development.

Examined population. The question arises whether reference ranges developed for children living in the region with adequate iodine intake, can be universally used for the classification of children residing in a different area? The answer is 'no' – this could only be possible if the thyroid size depended merely on the iodine intake. Although it is the iodine deficiency that is the most frequent cause of goitre, other factors can also influence the size of the thyroid, including goitrogenic agents naturally occurring in the environment (flavonoids and humus substances deriving from organic debris in the soil), as well as factors connected with pollution [16]. Many inorganic (like thiocyanates, chlorides, nitrates) and organic (like phenols, hydrocarbons, phthalic acid esters) compounds have goitrogenic activity.

The diet of the examined population is also important, as long-term consumption of vegetables from *Cruciferae sp.* or poorly cleaned *cassava*, which contains large quantities of glycosides releasing cyanides metabolized to thiocyanates, can result in a significant enlargement of the thyroid gland [17]. On the other hand, consumption of large amounts of saltwater fish or algae provides a large, often supra-physiological supply of iodine [18]. A large amount of iodine in ingested food does not always correlate with its high absorption by the organism. Although erythrosine, widely used in the food industry as a colouring agent (e.g. in cereals), contains large amounts of iodine, its bioavailability for the human body is low [19].

When analyzing the results, one should also consider genetic predisposition of the examined population (ethnic background), as well as incidence of autoimmune disorders, which might also influence the thyroid size. Factors affecting the thyroid size at the population level are presented in Table 3.

The assumption that the size of the thyroid depends only on iodine supply leads to errors, which must be realized when using reference ranges thus developed.

Cut-off point for abnormal values. Setting standards is based on analysis of the normally distributed values. Frequently, it is impossible to obtain normal distribution and – because

of this fact – the received data is converted logarithmically. The question arises: why does one so desperately seek normal distribution? This results from the fact that it has been arbitrarily acknowledged that the 97 percentile of such a distribution constitutes the cut-off value. The questions are:

- 1) Why it has been *a priori* assumed that as many as three out of 100 healthy children have an enlarged thyroid gland, without in-depth analysis whether this is true and what are the causes?
- 2) Why has the cut-off point not been attributed to a different percentile value? 3) Does the cut-off point set by double standard deviation always have to mean an abnormal value?

One should not forget that analysis of standard deviations in normal distribution has been primarily designed and is still used for testing statistical hypothesis, not for setting reference ranges; and, although this method of developing standards is especially close to pediatricians as anthropometric standards are determined on the basis of percentile grids, this does not mean that it must be appropriate. Many non-anthropometric standards are set absolutely irrespectively of normal distribution (e.g. the cut-off point for normal glucose level, 25(OH)D, normal blood pressure values).

Moreover, sometimes, when developing ultrasound reference ranges for thyroid based on the 97th percentile value, researchers exclude from the analysis children in whom – for instance – ioduria is less than 100 µg/l, which completely distorts the original assumptions of the analysis [12].

Metrical and anthropometric data. The reference ranges have the character of discrete/non-continuous (grouped) data. Depending on the age or BSA value, the thyroid size of the examined child is compared with a reference group. Groups ranges are quite wide and equal: for age – 8.3%-16.7% of the lower value of the range, for BSA – 6.25%-14.3%. Therefore, error resulting from rounding can be as high as 8.35% for children in the 6-year-old group, and 7.15% – in the group of children with BSA of 0.7 m² (these are the youngest and smallest children in whom the thyroid size is the smallest; thus they constitute the group with the highest intra- and inter-observer variability).

There is no doubt about how to compare the obtained results with the reference ranges based on BSA (given reference value constitutes the middle of the range); however, interpretation of the results obtained on the basis of the age may encounter difficulties. Age should be determined based on the date of the examination and the date of birth. However, frequently it is defined by the age declared by the parents in the questionnaire which leads to an error resulting from rounding the real data. Although in the presented analysis the difference between declared and calculated age was not statistically significant ($p=0.45$; mean declared age vs. calculated age was 9.653 vs. 9.715 respectively – Mann-Whitney Rank Sum Test – unpublished data based on surveys conducted in 1999 [20, 21]), in certain situations, such rounding might reach statistical significance.

Moreover, the age given in the reference values might be interpreted in two ways – as the middle of the range (like BSA) – in such a situation children aged 11.5–12.49 would fit in the 12-year-old group, or the inclusion in the 12-year-old group is possible only when the child turns 12 years of age (an 11.5-year-old child is still in the 11-year-old group).

One should also be aware of the phenomenon of acceleration, as this makes it difficult to compare data from different time points, as well as in the populations inhabiting different latitudes.

Regardless of the different interpretations of data, it should be remembered that the result obtained based on reference ranges set for the groups, contains an error resulting from rounding (conversion of continuous data into discrete data) (Fig. 5).

Variability in iodine intake. Iodine supply in the population is not a constant value and it may change over time [22]. The consumption of iodine in the population is influenced not only by the iodine prophylaxis, but also by education policy, aimed at presenting the consequences of iodine deficiency and the necessity for prevention of deficiency of this element in the surrounding environment. The integration processes between countries and more and more expanding free trade and movement of people also affect the iodine intake in the population. Foodstuffs (especially imported by private persons) do not necessarily have to meet the standards of the iodine content set by a given country. Models of iodine prophylaxis differ among particular countries – they do not need to be based on the obligatory use of iodized salt, as in Poland [23]. Moreover, in recent years a lot of effort has been made to decrease salt intake which is still the most common carrier of iodine [24]. These are all constant processes, changing the iodine supply in a population. There are examples of countries in which the iodine deficiency problem, once solved by introducing preventive measures, reappeared [25]. Once developed, standards may become outdated over time.

How to use obtained data? During analysis of the results, one should use as little rounding and generalizations as possible, because this is subject to error. The data should be processed as little as possible, they should be analyzed as continuous

data, and not discrete. Acquiring them should be burdened with the least intra- and inter-observer variability.

The analysis should be based on a comparison of the thyroid gland to the parts of the body (e.g. thumb phalanx or BSA) instead of age, due to high variability during the growth period.

In the opinion of the authors, analysis of V/BSA is the best estimation of the size of the thyroid gland (Fig. 5) in the study population. Potential error is only burdened with the error resulting from the measurements (intra- and inter-observer variability), such as ioduria level determination.

No need for relating the thyroid size to the reference values allows for comparison of the obtained results directly in different populations or at different time points. In this way, the effect of other factors on the size of the thyroid gland can be analyzed, after eliminating the iodine deficiency based on ioduria.

In the presented study, based on captured strong positive correlation of V/BSA index with age, it can be said that 10-year-old girls have a relatively bigger thyroid compared to 11- and 12-year-old girls. The same applies to 12-year-old children (both boys and girls). Such observation may lead to the considerations whether this age range (8–10 years) is not a period of increased iodine demand, which translates to 'transient' relative enlargement of the thyroid. However, such conclusions certainly require deeper analysis.

Analyzing the supply of iodine among children from Primary School No. 1 in Opoczno, the correct iodine intake was found. The previous method of analyzing goitre incidence, taking into account the reference values obtained from people living in other areas, is of little use. However, even the application of standards set on the basis of studies of children living in similar areas, may also lead to misleading conclusions because of the way in which the standards were created.

Analysis of the thyroid size, however, should not be neglected, as this information supplements ioduria data.

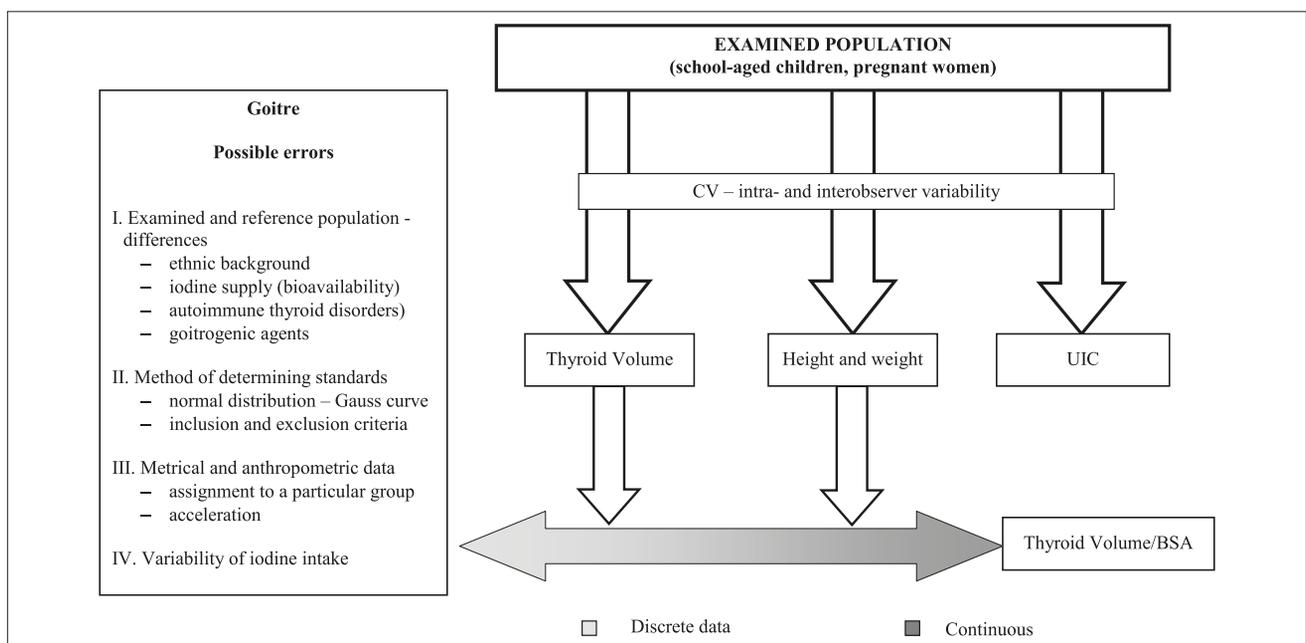


Figure 5. Algorithm of the evaluation of iodine intake in school-aged children. The obtained data (thyroid volume, height and weight) are compared to current standards (light grey arrow), which is associated with the error resulting from the various restrictions – see: the box on the left side of the figure and the text of the Discussion. Using continuous data (dark grey arrow) allows for the analysis of the obtained values without generalizations.

UIC – urinary iodine concentration, BSA – body surface area. CV – coefficient of variability

Relating the size of the thyroid gland to BSA is a good, sensitive tool for such analysis and can be used for comparisons of different populations, as well as surveys conducted at different time points.

Acknowledgement

The study was supported by the statutory funds (No. 2013/IV/40) from the Polish Mother's Memorial Hospital – Research Institute, Lodz, Poland.

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