Thyroid Volume and Its Relation to Anthropometric Measures in a Healthy Cuban Population

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Key Words

Thyroid volume · Ultrasound · Thyroid cancer risk factors · Case-control study

Abstract

Objectives: The aim of this study was to describe the thyroid volume in healthy adults by ultrasound and to correlate this volume with some anthropometric measures and other differentiated thyroid cancer risk factors. **Study Design:** Thyroid volume and anthropometric measures were recorded in a sample of 100 healthy adults, including 21 men and 79 women aged 18–50 years, living in a non-iodine-deficient area of Havana city. **Results:** The average thyroid volume was 6.6 ± 0.26 ml; it was higher in men (7.3 ml) than in women (6.4 ml; $p = 0.15$). In the univariate analysis, thyroid volume was correlated with all anthropometric measures, but in the multivariate analysis, body surface area was found to be the only significant anthropometric parameter. Thyroid volume was also higher in current or former smokers and in persons with blood group AB or B. **Conclusion:** Specific reference values of thyroid volume as a function of body surface

area could be used for evaluating thyroid volume in clinical practice. The relation between body surface area and thyroid volume is coherent with what is known about the relation of thyroid volume to thyroid cancer risk, but the same is not true about the relation between thyroid volume and smoking habit.

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Introduction

The thyroid is an important endocrine gland that plays a significant role in human development. Its size and shape vary widely in normal individuals. Several factors are involved in the growth of the thyroid gland, including dietary iodine intake, age, gender, smoking and some anthropometric measures such as weight, height, body mass index (BMI), waist-to-hip ratio (WHR), body fat (BF) and body surface area (BSA) [1, 2]. Additionally, the relation between a large body size and nonmedullary differentiated thyroid cancer (DTC) risk could be due to a com-

mon correlation with thyroid volume [3]. Anthropometric and clinical determinants of thyroid volume in adults [1, 4, 5] and children [6–8] have been investigated, particularly the potential interactions with other risk factors for DTC such as iodine intake, previous pregnancies in women, cigarette smoking and alcohol consumption [5].

Knowledge about thyroid volume is needed for the evaluation of a number of physiological and pathological factors such as iodine deficiency goiter, thyroiditis, multinodular goiter and thyroid cancer, as well as for evaluating the efficacy of levothyroxine therapy [9] and for identifying indications of minimally invasive surgery. Ultrasonography with a linear probe is a useful, practical, safe and comparatively cheap method for assessing thyroid volume [10].

Until recently, well-established risk factors for developing thyroid cancer were radiation exposure, a family history of thyroid cancer, residing in an iodine-deficient area, reproductive history and body size [11]. A recent case-control study on thyroid cancer risk factors, which has been performed in Cuba [12], has shown that thyroid cancer risk was lower in populations of African origin and increased with parity and BSA. Being rhesus factor positive, having a personal history of benign thyroid disorder, an agricultural occupation and an artesian well as the main source of drinking water were also factors associated with a significantly increased risk of developing DTC. In women, irregular cycles and menopause status were associated with a higher risk of DTC. On the other hand, thyroid cancer risk was lower in current or former smokers than in nonsmokers [12].

The aim of this study was to describe the volume of the thyroid gland in a control population and to determine its correlation with anthropometric measures and other selected parameters which have been found to be significantly associated with thyroid cancer risk in a case-control study [12].

Thyroid volume was measured by ultrasound in half of the controls of the case-control study in order to understand the relationship between the determinants of thyroid volume and those of the risk of DTC.

Subjects and Methods

Subjects

The case-control study included 203 patients with DTC aged between 17 and 60 years who were living in Havana and its surrounding municipality of Jaruco (30 km from Havana), and who were treated for DTC between 2000 and 2011 at the National Institute of Oncology and Radiobiology (INOR) and at the Institute

of Endocrinology, and 212 controls from the same area with matching age and gender. No biological thyroid parameter was used as an inclusion or exclusion criterion.

The thyroid measurements were conducted at the INOR in a sample of 100 controls. Several exclusion criteria were applied: subjects with a goiter (defined as a visible and/or palpable thyroid gland) and subjects with a personal or family history of thyroid disease or with signs of thyroid disease. Furthermore, we excluded women during menstruation, pregnant women and women who had delivered within the last 12 months because these conditions may affect thyroid size.

The study was approved by the Ethical Review Board of the INOR. All subjects agreed and signed an informed consent form for participating in the study.

Method

Subjects were interviewed face-to-face by trained professionals (nursing and medical staff) using a structured questionnaire between January 2009 and December 2011. A standardized questionnaire was used to collect data on demographic characteristics (age, gender, place of residence and occupation), blood group, rhesus factor, anthropometric parameters, reproductive and hormonal history, lifestyle (smoking habits, alcohol consumption), exposure to radiation or chemicals, personal medical history and family medical history in first-degree relatives. Size, blood group and rhesus factor obtained by interviewers were compared to the data on the national identity card and in the medical records of individual cases. Ethnicity of subjects was divided into three groups according to the ethnicity of their parents: European (both parents of European origin), African (both parents of African origin) and other (all other combinations of parental origin).

In this study, urinary iodine and thyroid-stimulating hormone (TSH) blood level were not measured; neither was autoimmune thyroiditis tested. Thyroid volume measurement was estimated by 3D ultrasonography using a linear 7.5-MHz probe. During the ultrasound examination, subjects lay in a supine position with the neck hyperextended and the shoulders were supported by a pillow. All the ultrasound examinations were conducted and interpreted by the same experienced radiologist.

The volume of one lobe of the thyroid was expressed in ml and estimated by the formula: volume of one lobe = length $\times$ depth $\times$ width $\times \pi/6$. The total thyroid volume was obtained by adding the volumes of both lobes, the isthmus not being taken into account in the volume calculation. In determining the volume, nodules smaller than 10 mm detected by ultrasound were included.

The measures were collected by physical examination according to standardized procedures [13] and were calculated as follows:

- BMI = weight (kg)/height (m)²
- BSA = $0.007184 \times [\text{height (m)}]^{0.725} \times [\text{weight (kg)}]^{0.425}$
- WHR = waist circumference/hip circumference (cm)
- BF % = $(1.2 \times \text{BMI}) + (0.23 \times \text{age}) - (10.8 \times 1) - 5.4$ for males and $(1.2 \times \text{BMI}) + (0.23 \times \text{age}) - (10.8 \times 0) - 5.4$ for females.

Statistical Methods

To describe the data, means $\pm$ standard deviations and percentages were used. The comparisons of thyroid volume in the two groups were performed using Student's *t* test. Multivariate analyses aimed at comparing the role of anthropometric parameters in thyroid volume were conducted using crude values and after tak-

Table 1. Anthropometric parameters by gender

	Whole population	Males	Females	p ^a
Age, years	38.2±0.9	39.6±2.0	37.9±1.0	0.4
Weight, kg	66.6±1.4	77±4	63.8±1.4	0.0001
Height, m	1.7±0.0	1.7±0.02	1.6±0	<0.0001
BSA, m ²	1.7±0.02	1.9±0.5	1.7±0.02	<0.0001
BMI, kg/m ²	24.4±0.4	26.0±1.0	24.0±0.5	<0.05
BF, %	30.4±0.6	24.2±1.3	32.1±0.6	<0.0001
WHR, cm	0.9±0.02	0.9±0.02	0.9±0.02	0.8
Thyroid volume, ml	6.6±0.3	7.3±0.3	6.4±0.3	0.2

Values are means ± SE. ^a p value for the difference between men and women; t test.

Table 2. Anthropometric parameters and thyroid volume

	Coefficient (95% CI) ^a	d.f. ^b	p value
Model 1			
BSA: increase per cm ²	3.22 (−1.10 to 7.54)	1	0.1
BMI: increase per unit	0.00 (−0.22 to 0.23)	1	0.9
Model 2			
BSA: increase per cm ²	3.06 (0.73–5.36)	1	0.01
WHR: increase per unit	1.80 (−1.22 to 4.82)	1	0.2
Model 3			
BSA: increase per cm ²	2.96 (0.48–5.44)	1	0.02
BF index: increase per unit	0.03 (−0.06 to 0.11)	1	0.5
Model 4			
BSA: increase per cm ²	3.26 (0.94–5.54)	1	0.006
Conicity index: increase per unit	0.00 (−0.03 to 0.03)	1	0.9

^a Multivariate linear regression. ^b Degree of freedom.

ing into account collinearity between these values by mean-centering the variables, the procedure being carried out separately for men and women. Because of the dependence between BMI and BSA, which are both calculated from height and weight, multivariate analysis was conducted by including anthropometric parameters only by pair (two by two). Data were analyzed using SPSS® and SAS® for Windows.

Results

The thyroid gland volume was estimated in 21 men and 79 women (age: 18–50 years). The characteristics of the study population are shown in table 1. The estimated average total thyroid volume was 6.6 ml; it was nonsignificantly higher in males (7.3 ml) than in females (6.4 ml).

In the univariate analysis, thyroid volume was positively linked to weight, height, BMI, BSA and BF (table 1).

In this young adult population, no significant correlation was observed between thyroid volume and age.

In the multivariate analysis, when analyzing the role of anthropometric parameters two by two, BSA was found to be the only anthropometric parameter with a significant role in thyroid volume. When taking into account BSA, no other anthropometric parameter remained significantly correlated to thyroid volume (table 2).

When analyzing the role of other parameters collected in the case-control study in a multivariate analysis including BSA, only BSA, blood group and smoking status remained independently, and positively, correlated with thyroid volume (table 3; fig. 1). Ethnicity, gender and age did not significantly interact with the relationships between these parameters and thyroid volume, but the population included too few men and was too homogenous concerning age for interaction tests to be powerful.

Table 3. Predictive model for thyroid volume

	Coefficient (95% CI) ^a	d.f.	p value
BSA: increase per cm ²	3.25 (0.95–5.54)	1	0.006
Blood group: B or AB/O or A	1.62 (0.25–2.98)	1	0.02
Smoking status: ever/never	0.73 (–0.29 to 1.75)	1	0.01

^a Multivariate linear regression.

Fig. 1. Thyroid volume as a function of BSA.

Discussion

Based on the measurements conducted in 100 controls from a case-control study carried out in a general population, we have shown that BSA, rather than other anthropometric parameters, was the key anthropometric parameter for predicting thyroid volume. Thyroid volume increased with increasing BSA and was higher in current or former smokers than in controls who had never smoked and higher in those with blood group AB or B than in others. No other parameter significantly interacted with these relationships.

Our study has some weaknesses, including the relatively small number ($n = 100$) of individuals and the homogeneity of the sample (mostly young adult women). On the other hand, the fact that anthropometric parameters have been measured in the control population of a case-control study is an advantage.

In this study, the mean total thyroid volume was 6.6 ml, a value similar to the one estimated in 485 Nepalese

individuals [1] and in 103 Sudanese healthy subjects [14] using ultrasound. In these two studies, the difference between genders was similar to the one we evidenced, but it was significant, due to a higher number of patients. On the other hand, thyroid volume in our study was lower than in some other studies (table 4) [15–23], in which thyroid volume, also measured using ultrasound, ranged mostly from 7 to 13 ml and was generally higher in men than in women.

Variations in thyroid volume could be related to dietary iodine intake, other dietary components such as goitrogenic vegetables (cruciferous), ethnic origin and, according to our results, anthropometric characteristics. In Cuba, a cross-sectional epidemiological study of iodine in urine estimated that, overall, 6.5% of children were iodine deficient, this proportion being higher in populations living in the mountains than in those from the cities [24], as in our study, where subjects lived in Havana city or in its surroundings. Dietary iodine intake may modulate TSH production, which could therefore lead to thyroid enlargement [25], but this relation is not always evidenced [26].

In line with our results, most of the studies showed a higher, significantly [4] or not [1, 27], thyroid volume in men than in women, this difference disappearing when adjusting for body weight [4].

Thyroid volume is well known to increase when increasing any anthropometric parameters, such as weight, height, BMI or BSA [4, 15, 21, 28, 29]. In our study, the best predictor of thyroid volume was BSA, in line with several other studies [1, 5, 15, 21]. In children, too, although less documented than in adults, thyroid volume has been found to increase with increasing anthropometric measures [6–8]. In line with our finding in adults, BSA was found to be the best predictor of thyroid volume, and it was recommended to use this criterion in order to evaluate the constitutional characteristics of child development [8]. In several studies, BSA is also the best anthropometric parameter for predicting thyroid cancer risk [27, 31, 32]. However, in most studies, obesity is used as a predicting parameter. Hence, the mechanisms whereby obesity increases the risk of thyroid cancer are not clear and may be very complex with a synergistic action of different factors. Thyroid cancer risk may be mediated by hormonal changes and inflammation that result from adiposity [35–37]. The hypothesis is that obesity leads to hypoadiponectinemia, a proinflammatory state, and insulin resistance, which, in turn, leads to high circulating insulin and insulin-like growth factor-1 levels, thereby possibly increasing the risk for thyroid cancer. Thus, in-

Table 4. Thyroid volume in healthy adults measured by ultrasonography reported in non-iodine-deficient populations

First author [Ref.], year	Sample size, n	Country	Men, ml	Women, ml
Gutekunst [18], 1986	1,397	Germany	26.9±17.0	16.5±12.2
	303	Sweden	11.1±4.7	7.7±4.3
Berghout [19], 1987	50	The Netherlands	13.2 [6.7–20.4]	8.2 [2.7–20.3]
Wesche [20], 1998	44	The Netherlands	10.3±3.3	6.9±2.9
Barrère [21], 2000	669	France (nonsmokers)	12.1 (11.6–12.6)	8.6 (8.3–8.9)
Maravall [22], 2004	268	Spain	9.9 (9.1–10.6)	6.6 (6.2–6.9)
Ivanac [15], 2004	51	Croatia	–	10.7±2.8
Adibi [23], 2008	200	Iran	10.7±3.4	7.7±2.6
Nafisi Moghadam [17], 2011	314	Iran	9.1±2.5	7.9±3.2

Values are means ± SD or [range] or (95% CI).

sulin resistance possibly plays a pivotal role in the observed association between obesity and thyroid cancer, potentially leading to the development and/or progression of thyroid cancer through its interconnections with other factors including insulin-like growth factor-1, adipocytokines/cytokines and thyroid-stimulating hormone [37].

Our finding of a higher thyroid volume in smokers than in nonsmokers is in line with what was observed in other studies [2, 38–40]. In the large French cohort SUIVIMAX [21], thyroid volume was significantly greater in current smokers and in former smokers than in nonsmokers, both in men and in women. In fact, this finding could appear to be surprising because smoking reduces the risk of goiter [2] and of thyroid cancer [40], this latter relationship having been confirmed in the Cuban case-control study [11]. This greater thyroid volume could be caused by competitive inhibition of thyroidal iodide uptake by thiocyanate [40]. Smoking is associated with a decrease in serum TSH and a rise in serum FT4 and FT3 induced by activation of the sympathetic nervous system. It has been hypothesized that this effect is larger in iodine deficiency areas [40–42], which has been confirmed in some studies, but not in all [21].

In addition to dietary iodine intake and the consumption of cruciferous vegetables which are known to influence the volume of the thyroid [43, 44], other environmental or dietary exposures may influence thyroid volume, especially exposure to pollutants. For example, long-term exposure to high nitrate intake by drinking water and home-made meals from local products has been shown to result in an increased thyroid volume and an increased frequency of signs of subclinical thyroid disorders (thyroid hypoechogenicity by ultrasound, increased TSH level and positive anti-thyroid peroxidase) [45], but

this relation was not found in another study where the level of alimentary nitrate intake was lower [46]. Interactions with dietary iodine intake may also exist [46]. A high exposure to polychlorinated biphenyls is also related to an increase in thyroid volume [47].

No other study has investigated the relation between blood group and thyroid volume. Therefore, our results need to be confirmed. However, in the case-control study, we evidenced a significant reduction in the risk of DTC associated with blood group B when compared to blood type O [12]. This association had not been reported before; nevertheless, several studies reveal that there is an inherited element in the susceptibility to or protection against different types of head and neck cancer linked to blood groups [48–50].

In our study, we did not test the association between thyroid volume and the risk of thyroid cancer because subjects belonged only to the control group. To our knowledge, the direct relation between thyroid volume and DTC risk has never been reported; however, it could even be a confounding factor, as a direct correlation of some anthropometric factors such as height, BMI and obesity with thyroid cancer and, in turn, with thyroid volume has previously been reported.

Conclusions

Specific reference values of thyroid volume as a function of BSA could be used for the evaluation of thyroid volume in clinical practice. The relation between BSA and thyroid volume is coherent with what is known about its relation with thyroid cancer risk, but the same is not true about the relation between thyroid volume and smoking habit.

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Disclosure Statement

The authors confirm that there are no commercial associations that might create a conflict of interest in connection with this article.

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