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Determinants of thyroid volume in healthy young adults of Dalmatia

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Abbreviations:

BMI, body mass index
BSA, body surface area
fT4, free thyroxine
Tg, thyroglobulin
TgAb, thyroglobulin antibodies
TSH, thyroid-stimulating hormone
TPOAb, thyroid peroxidase antibodies
TV, Thyroid volume

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Abstract

Background and purpose: The aim of this study was to investigate thyroid volume (TV) and its determinants in healthy young adults without present or previous thyroid disease.

Materials and methods: The study was performed in a sample of 145 healthy young participants aged 19–29 years, living in an iodine-sufficient area of Dalmatia. Dimensions of the thyroid gland were obtained by ultrasound and used to determine TV. Anthropometric data was collected, and measurements of serum TSH, fT4, Tg, TgAb, and TPOAb levels were determined. Correlations between TV and other continuous variables were determined using the Pearson correlation test, while multivariate linear regression analysis was used to determine the associations of the potential predictors for the TV.

Results: TV in men was larger than in women ($p = 3.53 \times 10^{-8}$) and was positively correlated with anthropometric measurements, with the highest correlation coefficient for height ($r = 0.53$, $p = 6.36 \times 10^{-12}$), then body surface area, BSA ($r = 0.48$, $p = 1.68 \times 10^{-9}$), weight ($r = 0.43$, $p = 8.28 \times 10^{-8}$) and body mass index, BMI ($r = 0.17$, $p = 0.04$). Age and cigarette smoking did not appear to be significantly associated with TV ($p = 0.13$ and $p = 0.95$, respectively). Univariate analysis showed TV correlated with fT4 plasma levels ($\beta = 0.79$, $p = 1.73 \times 10^{-5}$), while multivariate analysis showed height and fT4 levels to be important parameters with a significant role in TV.

Conclusions: We confirmed previously observed association of TV with sex and anthropometric parameters and reported a significant correlation between TV and fT4 levels. Furthermore, fT4 levels and height were found to be the important parameters for predicting TV.

INTRODUCTION

The thyroid gland is one of the largest endocrine glands, located in the anterior neck consisting of two lobes connected by the isthmus. Size, shape, and volume of thyroid gland vary widely between individuals without thyroid dysfunction (1, 2). Evaluation of thyroid volume (TV) is significant for accurate diagnosis of goiter and for monitoring thyroid disorders. One of the reliable methods used for the estimation of TV is ultrasonography, a noninvasive technique that provides a three-dimensional measurement of the thyroid gland, where volume of each lobe can then be calculated using the ellipsoid formula with a correction factor (3).

Besides genetic factors, TV is affected by age, gender, cigarette smoking, and dietary iodine intake (4, 5). Also, anthropometric measures like

weight, height, body mass index (BMI), body fat, waist-to-hip ratio, and body surface area (BSA) have been positively correlated with TV (1, 2, 6). Clinical and anthropometric determinants of TV have been investigated in different studies in adults and children, but the relationship between TV, age, gender, anthropometric characteristics, and thyroid hormones still remains controversial (6, 7).

The aim of this study was to investigate factors that influence TV and to determine their correlation and relative importance in a sample of 145 healthy young subjects without present or previous thyroid disease.

SUBJECTS AND METHODS

This study was performed on a sample of 145 healthy participants, including 26 men and 119 women aged 19–29 years, living in an iodine-sufficient area of Dalmatia, from the city of Split. Prior to inclusion in the study, written informed consent was obtained from all study participants. Data regarding age, sex, weight, height, TV, and smoking were collected.

Thyroid ultrasonography was performed using Medison Accuvix V10 (Samsung Medison Co., Ltd, Seoul, Korea) high-frequency linear probe (8–12 MHz). Dimensions of the thyroid gland were obtained by ultrasound and used to determine TV, which was calculated as a sum of volumes of both lobes of the thyroid gland. The volume of each lobe was calculated as length \times width \times depth \times 0.479. BMI was calculated as body weight (kg) divided by height squared (m^2), while the BSA was calculated according to the following formula: $BSA (m^2) = W^{0.425} \times H^{0.725} \times 71.8 \times 10^{-4}$, where W is the weight in kg and H the height in cm.

Plasma thyroid-stimulating hormone (TSH), free thyroxine (fT4), and thyroglobulin (Tg) together with thyroid antibodies (thyroglobulin antibodies, TgAb and thyroid peroxidase antibodies, TPOAb) were determined by an immunoassay method performed in a fully automated instrument “Liaison” Biomedica Chemiluminescence Analyzer. The reference values used for our population were: TSH 0.3–3.6 mIU/L, fT4 10.1–22.3 pmol/L, Tg 0.2–50 ng/mL, TgAb 5–100 IU/mL, TPOAb 1–16 IU/mL.

The data are presented as the mean \pm standard deviation (SD) for continuous variables and as frequencies (percentages) for categorical variables in Table 1. The comparisons of TV in the two groups were performed using Student's *t*-test. We used the Pearson correlation test to check the correlations between TV and other continuous variables. A multivariate linear regression analysis was used to determine the associations of the potential predictors with the TV. To avoid multicollinearity, only one variable was retained in a set of anthropometric parameters. *P*-values of less than 0.05 were considered as statistically significant. The statistical analysis was carried out using R software.

RESULTS

A total of 145 healthy subjects (119 women and 26 men) aged 19–29 years were enrolled in this study. Descriptive information on study participants is presented in Table 1, along with TSH, fT4, TgAb, TPOAb, and Tg concentrations, as well as TV.

Results showed that TV in men (mean \pm SD: 14.20 \pm 3.11 ml) was larger than in women (mean \pm SD: 9.81 \pm 2.99 ml) ($p = 3.53 \times 10^{-8}$), while no statistically significant association was observed between TV and age ($p = 0.13$). Cigarette smoking did not appear to be significantly associated with TV ($p = 0.95$).

TV was positively correlated with anthropometric measurements, the highest correlation coefficient was observed for height ($r = 0.53$, $p = 6.36 \times 10^{-12}$), followed by BSA ($r = 0.48$, $p = 1.68 \times 10^{-9}$), weight ($r = 0.43$, $p = 8.28 \times 10^{-8}$) and BMI ($r = 0.17$, $p = 0.04$).

All correlations between thyroid hormones (TSH, fT4, Tg), antibodies (TgAb, TPOAb), and TV are shown in Table 2. We have detected a significant positive correlation between TV and fT4 concentrations ($r = 0.35$), while other thyroid hormones and antibodies were not significantly correlated with TV. Univariate linear regression with fT4 levels as an independent variable ($\beta = 0.79$, $p = 1.73 \times 10^{-5}$) explained 11.5% of the variance in TV. The regression line of the relationship between fT4 levels and TV is presented in Figure 1.

To analyse possible predictors of the TV, we performed a multivariate linear regression analysis using only variables that were significant in the univariate model. After

Table 1. Characteristics of the included participants.

Variable	Mean (SD) or N(%)
Sex	Men 26 (18%)
	Women 119 (82%)
Age (years)	23.03 (1.83)
Height (cm)	172.9 (8.40)
Weight (kg)	66.07 (11.67)
BMI (kg/m ²)	22.03 (2.96)
BSA (m ²)	1.78 (0.18)
Smoking	Yes 26 (18%)
	No 119 (82%)
TSH (mIU/L)	1.55 (0.68)
fT4 (pmol/L)	13.18 (1.52)
TgAb (IU/mL)	33.56 (21.98)
TPOAb (IU/mL)	13.4 (7.21)
Tg (ng/mL)	10.01 (8.18)
Thyroid volume (cm ³)	10.59 (3.44)

Table 2. Correlation between thyroid hormones, antibodies, and TV.

Variable	Correlation coefficient	P value
TSH	-0.07	0.42
fT4	0.35	1.73×10^{-5}
TgAb	0.05	0.58
TPOAb	0.03	0.69
Tg	-0.06	0.45

taking into account multicollinearity between anthropometric parameters, we included sex, weight, and fT4 levels in the linear regression model and tested their association with the TV. Regression analysis suggested that height and fT4 levels were associated with TV ($\beta = 0.14$, $p = 5.37 \times 10^{-4}$ and $\beta = 0.44$, $p = 7.9 \times 10^{-3}$, respectively). This model explained 32.6% of the variance in the TV.

DISCUSSION

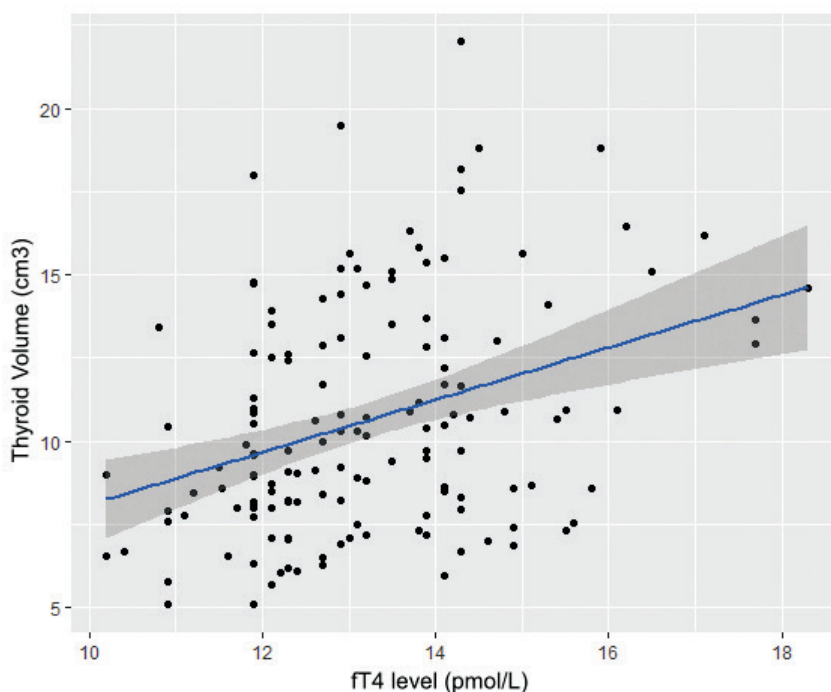
In this study, we found a significant association of TV with sex, weight, height, BSA, BMI, as well as fT4 levels in healthy young adults of Dalmatia, from the city of Split.

It has been estimated that genetic factors account for 71% of the individual variations in TV in euthyroid subjects with a clinically normal thyroid gland (8). Till now four independent genetic loci associated with TV were determined on a genome-wide level of significance. They

are located within or near *CAPZB*, *FGF7* and *LOC440389* (9). Besides genetic factors, TV is strongly affected by iodine intake and geographic region (10). Croatian population is a population with sufficient iodine intake since the regulation on obligatory salt iodination with 25 mg of potassium iodide per kg of salt was implemented in Croatia in 1996 (11). The study performed in 2009 showed that an overall median of urinary iodine concentration for schoolchildren from all four major geographic regions of Croatia was in the normal range in this population (11).

Till now, physiological factors known to affect TV are age, height, weight, BSA, season, smoking, alcohol, and menstrual cycle (12–14).

Although some studies observed sex differences in TV, it has been generally accepted that this difference is a result of higher body weight in males (12). However, the results of the Korean study were not in accordance with this point of view. They found a significant sex difference in body weight but did not show any difference in TV between males and females (15). In this study, the mean value of TV in 145 participants was higher in males than in females. Most studies have shown that TV increases with increasing age (15, 16). A possible reason for this observation could be increasing TSH levels in older age groups or, as some earlier studies suggested, because of increasing size and amount of follicles (12, 17). However, we did not observe any association between these two parameters since our study was performed in young adults of similar age (mean 23.03 ± 1.83 , range 19–29 years).

**Figure 1.** A scatter plot and the corresponding regression line for the relationship between thyroid volume and fT4 levels.

The present study showed a strong correlation of TV with height, body weight, and BSA, with the most significant correlation for height, while with BMI showed moderate correlation. Semiz *et al.* also showed a positive correlation between TV and height of the individuals (18). It seems that more appropriate parameters in the evaluation of TV correlation are BSA and BMI, indicators of person's body size and degree of overweight, rather than just body weight or height (1). The results of the study performed by Azizi *et al.* indicated that in the Tehranian children, the best predictors of TV were height, weight, and BSA (19). The same group of authors found identical results between schoolchildren of the Emirates (16). The TV of the children in these two studies was in accordance with those reported in a European survey (20). Lean body mass as a determinant of thyroid size was examined by Wesche *et al.* comparing results of non-obese healthy adults and adults with marked obesity. They concluded that in healthy adults, lean body mass rather than body weight explained the differences in TV between obese and non-obese subjects. Lean body mass seems to be a major determinant of TV (21).

Several studies observed positive association of smoking and TV in a negative interaction with iodine intake. In iodine-deficient populations, smoking was positively related to TV, while in populations where iodine intake was sufficient, cigarette smoking was not related to TV (6, 22–24). Even more, the influence on TV in Denmark was reduced by 12% after mandatory salt iodization in 2000 (25). In this study, we did not find any association between TV and smoking, probably because our participants belong to the population with sufficient iodine intake as well as most of our participants were non-smokers.

In the present study, there was a significant positive relationship between TV and fT4 levels. Study published by Barrere *et al.* observed a similar result in healthy French adults (22). Furthermore, Hansen *et al.* showed that serum TSH and fT4 played a small, but significant, role in the differences in TV (8). Besides fT4, other thyroid hormones and antibodies were not significantly correlated with TV in the present study. Several studies reported no significant correlation between TV and any of the thyroid hormone variables (26–28). On the other side, a study performed in 2987 healthy French adults reported an inverse, significant relationship between TV and TSH (22).

Finally, in the present study, we performed a multivariate linear regression analysis using only variables that were significant in the univariate model and showed that height and fT4 levels were associated with TV. In that way, 32.6% of the variance in the TV was explained.

A major strength of this study is the careful selection of healthy individuals based on detailed thyroid function assessment (including measurements of Tg, TSH, fT4, TgAb, and TPOAb) and inclusion of the ethnically homogeneous participants of Dalmatia of the similar age.

The main limitation of the study is the modest sample size.

In conclusion, this study was performed in young adults of the Dalmatian population considered as being exposed to iodine sufficient intake. As was expected, we showed a significant association of TV with sex, weight, height, BMI, and BSA. Additionally, we observed a very strong association between fT4 levels and TV and confirmed finding dated from 2000, performed on the large sample set of the French population. Our results also emphasise that smoking cannot affect TV in iodine sufficient populations. Finally, height and fT4 levels were shown to be the most important parameters that explained 32.6% of the variance in the TV.

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