

## Thyroid Function and Structure are Affected In Childhood Obesity

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## Abstract

**Objective:** Alterations in thyroid function are reported in obesity although no relevant data exist, on the thyroid structure of these patients and the frequency of autoimmunity. The aim of our study was to evaluate the involvement of the thyroid gland in a large group of obese children.

**Design:** A cross-sectional study

**Methods:** The study was conducted between March 2004 and December 2007 in 186 overweight and obese children. In all subjects, serum fT3, fT4, TSH, anti-thyroid-antibodies and a thyroid ultrasound were assessed. Forty healthy children matched for age and of normal weight for height served as controls.

**Results:** Twenty-three children (12.4%) showed anti-thyroid antibodies and an ultrasound pattern suggestive of Hashimoto's thyroiditis (group A). Twenty of them (10.8%) showed anti-thyroid antibodies and normal ultrasound (group B). Seventy subjects (37.6%) showed absent anti-thyroid antibodies and an ultrasound pattern suggestive of Hashimoto thyroiditis (group C), and 73 children (39.2%) showed no thyroid-antibodies with normal ultrasound (group D). TSH was higher in groups A and C compared to group B, group C and controls ( $P<0.05$ ). Mean fT4 was lower in group B ( $P<0.05$ ) than in controls, while fT3 was higher in group C than in controls ( $P<0.05$ ). TSH and BMI SDS were significantly correlated in group C ( $P<0.001$ ) and TSH was also significantly associated with the degree of thyroid structure alterations ( $P_s<0.05$ ).

**Conclusions:** Obese children frequently show alterations of thyroid structure and function that are not completely explained by the presence of an autoimmune involvement.

## Introduction

Thyroid hormones and TSH concentration have been variously described as normal, elevated or even low in obese subjects as compared to normal weight controls (1-7). High serum TSH and thyroid hormone concentration have been reported in obese children as well (1,8-9). Several mechanisms leading to hyperthyrotropinemia have been hypothesized, including increased leptin-mediated production of pro-TRH (10-12), impaired feedback due to a lowered number of T3 receptors in the hypothalamus (13) and variations in peripheral deiodinase activity (12,13). Nevertheless, abnormalities in thyroid function and TSH mostly normalize after weight loss, independent of whether the loss is obtained with diet or bariatric surgery (1,8,14-17), suggesting that these biochemical alterations are reversible.

Despite the uncertainty regarding the underlying mechanism, it has been suggested that neither autoimmunity nor iodine deficiency seem to play a critical role (7-9, 14). On the other hand, little has been reported on the morphology of the thyroid gland in obesity and only a few papers report an increased thyroid volume in obese adults (14, 18). Hence, with the goal of better defining thyroid involvement in obese children, we evaluated thyroid morphology and function together with the presence of autoimmunity in a large cohort of overweight and obese children.

## Material and methods

### *Subjects*

Between March 2004 and December 2007 we evaluated 186 consecutive overweight and obese children (103 males, 83 females), aged  $10.7 \pm 2.8$  years with a height SDS of  $0.92 \pm 1.08$  and BMI SDS of  $5.22 \pm 2.38$  who were enrolled in the obesity outpatient clinic of three Pediatric Endocrinology Centres. All were born full-term. The appropriate review board approved the clinical protocol, and written informed consent for all procedures was obtained from all subjects or from their legal guardians before enrolment. The children were all diagnosed with simple obesity, other syndromic, organic and hormonal causes having been excluded. The clinical characteristics of the children are shown in Table 1.

### **Study protocol**

The children were admitted to the ward following overnight fasting. The auxological data were recorded and blood samples were obtained for assessment of fT4, fT3, TSH, thyroglobulin antibodies (TG-Ab) and thyroid peroxidase antibodies (TPO-Ab). At the same time a thyroid ultrasound was performed. All children met a trained dietician and were fully instructed on having regular physical activity.

## ***Methods***

For reasons of homogeneity, height and body mass index (BMI) were expressed as standard deviation scores (SDS), according to Italian normative data (19). Pubertal status was evaluated according to Tanner (20). The percentage of body fat mass (%F) was assessed by skinfold thickness using the equations of Slaughter (21). To facilitate reproducibility, measurements of sub scapular and triceps skinfolds were performed in triplicate to the nearest millimeter by the same observers in the three centres (W.K., N.D.I, F.B.). Waist circumference was measured midway between the lowest rib and the top of the iliac crest after gentle expiration. Thyroid function was also evaluated in forty healthy controls, with a mean age of  $10.4 \pm 2.1$  years, height SDS of  $-0.2 \pm 1.8$ , BMI SDS of  $-0.1 \pm 1.5$ , matched for gender.

### ***Thyroid ultrasound***

Ultrasound was performed in each centre, using a 7.5 MHz transducer, by the same observer, well trained in thyroid imaging. The ultrasound data were stored and then reviewed by a different, experienced radiologist who was unaware of the content of the study. In cases of disagreement, the opinion of the experienced radiologist was given priority. Typical ultrasound findings for a diagnosis of Hashimoto's thyroiditis were considered a hypoechogenic signal with a dyshomogeneous structure. The alterations of echogenicity and homogeneity of the

parenchyma were further quantified according to a pediatric scoring system (22): score 0: normal; score 1: mild parcelled hypoechogenicity; score 2: severe parcelled hypoechogenicity; score 3: mild generalized hypoechogenicity; score 4: severe generalized hypoechogenicity; score 5: near-anechogenicity. The patients were then categorized as follows: ninety-three patients showed score 0, sixty-six patients score 1; fourteen patients score 2; and thirteen patients score 3.

### ***Fine needle aspiration cytology***

Ultrasound-guided fine needle aspiration cytology (FNAC) of the thyroid was performed in the first 12 consecutive patients with ultrasound pattern suggestive of thyroiditis but absence of thyroid antibody. Based on the negative results, the study protocol was re-submitted to the Ethical Committee who agreed to modify the original study protocol and thereafter no additional FNAC were performed as they were judged to be inessential. Although we are aware that this could be a drawback of the study, we thought it unethical to proceed causing a useless discomfort to the children.

### ***Assays***

TSH was measured by a chemiluminescent immunometric assay (Roche Diagnostics GmbH, Mannheim, Germany); the intra- and inter-assay C.V. were 2.7% and 3.2%, and sensitivity limit was

0.005 mU/l. Measurement of fT3 was effected by chemiluminescent immunometric assay (Roche Diagnostics GmbH, Mannheim, Germany); the intra- and inter-assay C.V. were 2.0% and 2.5%, and sensitivity limit was 0.400 pmol/l. Measurement of fT4 was performed by chemiluminescent immunometric assay (Roche Diagnostics GmbH, Mannheim, Germany); the intra- and inter-assay C.V. were 1.8% and 2.6%, and sensitivity limit was 0.3 pmol/l. Thyroglobulin antibodies (TG-Ab) were measured by a chemiluminescent immunometric assay (Immulite 2000 Anti-TG Ab, DPC, LA, USA) with an intra- and inter-assay C.V. of 3.2% and 4.6%, and sensitivity limit of 2.2 U/ml; thyroid peroxidase antibodies (TPO-Ab) were measured by chemiluminescent immunometric assay (Immulite 2000 Anti-TG Ab, DPC, LA, USA) with an intra- and inter-assay C.V. of 5.2% and 3.2%, and sensitivity limit of 5 U/ml.

### **Statistical analysis**

Apart from TSH, data were normally distributed and are expressed as mean  $\pm$  SD. Differences between patients and controls were assessed by using the one-way analysis of variance with Bonferroni correction as post-hoc test for the normally distributed parameters. The Mann-Whitney and the Kruskal-Wallis test followed by the Dunn's Multiple comparison test were used to verify differences in TSH serum values between and among the identified groups. Correlations

between the parameters of thyroid function, TSH, thyroid score and anthropometric findings were calculated with the Pearson coefficient. A P value of less than 0.05 indicated statistical significance. All the analyses were performed with the SPSS program.

## **Results**

### ***Anti-thyroid antibody and thyroid structure***

Twenty-three children (12.4%) showed anti-thyroid antibodies and ultrasound pattern suggestive of Hashimoto thyroiditis (group A). Twenty (10.8%) showed normal ultrasound together with anti-thyroid antibodies (group B). Seventy (37.6%) also showed an ultrasound pattern suggestive of Hashimoto thyroiditis but with no anti-thyroid antibodies (group C) and 73 children (39.2%) showed a normal ultrasound and no anti-thyroid antibodies (group D) (Table 2). In figure 1, the ultrasound picture of a patient with well-established Hashimoto thyroiditis is shown together with that of an obese subject with a pattern suggestive of Hashimoto thyroiditis without serological markers of thyroid autoimmunity (Figure 1).

### ***TSH and thyroid function***

TSH was higher in group A and C than in groups B and D and controls ( $P < 0.05$ ) (Table 2). Specifically, serum TSH was above normal range in 11 patients (23.4%) from group A, 2 (4.3%) from group B, 27 (57.4%) from group C, and 7 (14.9%) from group D

(Figure 2). Mean fT4 level was lower ( $P<0.05$ ) in group B than in controls, while fT3 was higher in group C ( $P<0.05$ ) than in controls (Table 2).

### ***FNAC***

The cytological smears obtained in the 12 patients from group C were normal, showing only colloid drops and isolated thyrocytes, and therefore no signs of Hashimoto thyroiditis were visible.

### ***Correlations and comparisons***

We excluded patients from groups A and B from the correlation analysis since they had been diagnosed with Hashimoto's thyroiditis and therefore alterations in function and structure would be expected and explained by the autoimmune disease. The analysis therefore concerns data from the patients of groups C and D.

A significant correlation was found between TSH serum levels and BMI SDS in group C ( $r=0.37$ ;  $p=0.00012$ ), which persisted after the exclusion of the patient with the BMI SDS of 17.5 ( $r=0.265$ ;  $P=0.0275$ ); no correlation was found between TSH and BMI SDS in group D (Figure 3). TSH serum levels was significantly different in children with or without thyroid alterations at ultrasound (Figure 4a). Moreover TSH increased significantly and steadily across the thyroid score categories ( $P<0.05$ ) (Figure 4b). After Dunn's correction, TSH in group 0 was significantly lower than in groups 1 and 2. Similarly, BMI SDS was also significantly

different in children with or without alterations at ultrasound (Figure 5a); it increased significantly and steadily across the thyroid score categories ( $P<0.01$ ) (Figure 5b).

No correlations were found between TSH serum levels and thyroid scores with the other anthropometric and/or laboratory values.

### **Discussion**

The present study demonstrates that alterations in thyroid function and structure can frequently be observed in children being overweight or obese. Some of these findings could be explained by the presence of typical Hashimoto's thyroiditis (HT), as in group A or by initial/focal HT (23, 24) where the characteristic structural changes are presumably not yet detectable at ultrasound due to the poor sensitivity of the device (group B). The likelihood that group B also suffer from a mild form of thyroiditis is supported by the postmortem study of Yoshida, showing a strict positive correlation between the lymphocytic infiltration of the thyroid and the serum antithyroid antibody concentration (23). If this hypothesis is correct, then the antithyroid antibodies should be considered a sensitive marker of subclinical autoimmune thyroiditis. The difference in antithyroid antibodies between group A and B is also in favor for a different degree of thyroid inflammation in the two groups. Conversely, Demers and Spencer

reported that ultrasound alteration precede the generation of the antithyroid antibodies (25).

Nevertheless, among the patients in groups C and D, functional/structural changes do not seem to be sustained by autoimmunity. These patients, in particular those in group C, frequently showed TSH levels above the upper limit, in agreement with other studies in children (1, 8, 9) and adults (2-7). The most striking finding, however, and to our knowledge one not previously reported in the literature, was that thyroid ultrasound images in group C were super-imposable onto that commonly observed in patients with the classical form of autoimmune thyroiditis. Since a minority of patients with Hashimoto's thyroiditis do not show circulating anti-thyroid antibodies, a cytological sample was obtained from the first twelve of them, which was normal, and thus excluded an autoimmune disorder. Hence, the association between BMI SD and both thyroid score and TSH concentration suggest that adiposity may be involved in the mechanisms causing thyroid dysfunction and morphological thyroid changes. Since the frequency of Hashimoto's thyroiditis in the whole group of obese patients was much higher than the 1.2% previously reported in normal children by Rallison (26), one could speculate that fat excess may have a role in thyroid tissue modification .

Previous papers have advocated leptin as a possible link between obesity and raised TSH levels. Leptin, in addition to regulating body-

weight and satiation, has also been reported to mediate the production of pro-TRH in cultured fetal rat hypothalamic neurons (10-12, 27). Partial TSH regulation by leptin has been reported in humans as well (28), but this hypothesis does not seem to be supported by our data, since fT4 values were not raised in our patients.

What are the causes of the thyroid ultrasound findings in our cohort? Although fat accumulation or early signs of local inflammatory reaction may appear attractive hypotheses, we were not able to answer this question by analyzing the thyroid tissue of our 12 obese subjects because FNAC is not an appropriate technique for elucidating the histopathological basis of imaging abnormalities. Moreover, the histological examination was not specifically focused on the potential study of fat accumulation within the thyroid tissue, and standard histological criteria for the diagnosis of pediatric types of fatty thyroid are still undeveloped. Thus, a possible explanation for the thyroid ultrasound picture observed could be the existence of a low-grade inflammation state, which has been known to characterize obesity (29, 30). It is well recognized that in obesity the adipose tissue secretes a distinct quantity of inflammatory cytokines, and some of these, such as tumor necrosis factor- $\alpha$ , interleukin-1 and interleukin-6 escape into general circulation provoking systemic symptoms (31). Moreover, cytokines, which have been proven to inhibit sodium iodide symporter

mRNA expression and iodide uptake activity in FRTL-5 and human thyroid cells (32-34) could play a role in compensatory raised TSH level. This would explain the tissue resistance to TSH and additionally its reversibility after weight loss. In fact, inflammatory cytokines may induce vasodilatation and increased permeability in the thyroid vessels with subsequent exudation of plasma (31). The subsequent parenchyma imbibition, which results might explain the ultrasound findings in our cohort. Another possible explanation could be that the changes we observed simply represent nodular degeneration, secondary to insufficient iodine supply. The geographical regions where the study was carried out, however, are all iodine sufficient, in particular the South Tirol, as shown by a 30-year survey of the school population (35).

Thyroid function has been reported to return to normal after weight loss (1, 8, 14-16), raising the question of the potential reversibility of thyroid abnormalities at ultrasound. On the other hand, we do not know whether the persistence of thyroid abnormalities in obese children may also progress into chronic thyroid disease in early adulthood. A careful follow-up protocol is therefore necessary to answer these questions.

In conclusion, obese children may show a different degree of thyroid impairment. To avoid unnecessary treatment, caution is recommended when diagnosing Hashimoto's thyroiditis in obese children based on a pathological ultrasound only and without anti-thyroid antibodies.



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Figure 1.

Ultrasound images of the thyroid of a subject with Hashimoto thyroiditis (A), of a obese child (B) and of a normal subject (C).

Figure 2.

TSH serum levels in the four groups of obese children subdivided based on the presence or absence of antithyroid-antibodies and of ultrasound picture. The dotted line represents the upper normal TSH level (n.v <3.6 mU/l). The Y axis is in logarithmic scale.

Group A: positive anti-thyroid-antibodies and ultrasound picture suggestive of Hashimoto's thyroiditis

Group B: positive anti-thyroid-antibodies and normal ultrasound picture

Group C: negative anti-thyroid-antibodies and ultrasound picture suggestive of Hashimoto's thyroiditis

Group D: negative anti-thyroid-antibodies and normal ultrasound picture

Figure 3. Correlation between serum TSH serum levels and BMI SDS in 70 overweight-obese children of group C (negative anti-thyroid-antibodies and ultrasound picture suggestive of Hashimoto' thyroiditis) and in 73 overweight-obese children of group D (negative antithyroid-antibodies and normal ultrasound picture).

Figure 4. (A) Mean serum TSH level according to the thyroid score in 74 subjects with score 0 and in 70 with score  $\geq 1$  (1-3) ( $P < 0.001$ ). (b). Mean serum TSH level according to the thyroid score in 74 subjects with score 0, 54 with score 1, 9 with score 2 and 7 with score 3 ( $P < 0.01$ ).

Figure 5 (a) BMI SDS according to the thyroid score in 74 subjects with score 0 and in 70 with score  $\geq 1$  (1-3) ( $P < 0.05$ ). (b) BMI SDS according to the thyroid score in 74 subjects with score 0, 54 with score 1, 9 with score 2 and 7 with score 3 ( $P < 0.05$ ).

Table 1. Clinical and anthropometric characteristics of the four groups of patients and controls

	Total	Group A	Group B	Group C	Group D	Controls
# of subjects	186	23 (15F/8M)	20 (9F/11M)	70 (25F/45M)	73 (34F/39M)	40 (17F/23M)
Age (years)	10.6 ± 2.8	11.5 ± 2.7	11.7 ± 2.1	10.4 ± 2.8	10.4 ± 2.9	10.4 ± 2.1
Height SDS	0.9 ± 1.1	0.9 ± 1.2	0.4 ± 0.9	1.2 ± 1.1	0.7 ± 1.0	-0.2 ± 1.8
BMI SDS	5.2 ± 2.4	4.6 ± 2.9	3.2 ± 1.6	6.0 ± 2.4	5.2 ± 2.0	-0.1 ± 1.5
% fat males	50.1 ± 10.2	48.9 ± 16.8	53.3 ± 2.1	49.6 ± 11.6	50.6 ± 7.5	-
% fat females	42.1 ± 7.4	46.2 ± 6.7	39.7 ± 5.4	41.5 ± 9.2	41.8 ± 5.4	-
waist males (cm)	89.7 ± 8.9	90.3 ± 9.2	84.0 ± 7.1	89.7 ± 10.6	90.3 ± 6.6	-
waist females (cm)	86.7 ± 11.2	95.0 ± 11.0	78.0 ± 5.6	87.7 ± 11.2	84.4 ± 10.9	-

Group A: positive anti-thyroid-antibodies and ultrasound picture suggestive of Hashimoto's thyroiditis

Group B: positive anti-thyroid-antibodies and normal ultrasound picture

Group C: negative anti-thyroid-antibodies and ultrasound picture suggestive of Hashimoto's thyroiditis

Group D: negative anti-thyroid-antibodies and normal ultrasound picture

Table 2. Thyroid function, thyroid antibodies and thyroid volume in patients and in controls

	# of subjects	TSH mU/l	fT4 pmol/l	fT3 pmol/l	TPO-Ab U/ml	TG-AbU/ml	Thyroid volume (ml)
Group A	23	7.3 ± 10.6*	14.1 ± 2.9	6.2 ± 1.3	273 ± 437	228 ± 274	3.5 ± 1.2
Group B	20	2.2 ± 1.4	13.1 ± 4.5#	6.6 ± 0.9	28 ± 14	35 ± 20	3.8 ± 1.4
Group C	70	3.9 ± 2.0*	14.3 ± 2.2	6.7 ± 0.8#	–	–	3.6 ± 1.5
Group D	73	2.7 ± 1.7	14.3 ± 2.7	6.5 ± 0.9	–	–	3.3 ± 1.4
All	186	3.6 ± 4.3	14.1 ± 5.5	6.5 ± 0.2	179 ± 361	142 ± 222	3.5 ± 1.4
Controls	40	2.1 ± 0.7	15.48 ± 2.1	5.9 ± 0.9	–	–	3.7 ± 1.2

Normal range: TSH 0.53-3.6 mU/l, fT4 11.96-21.8 pmol/l, fT3 3.94-6.80 pmol/l, TPO-Ab <10 U/ml, TG-Ab <20 U/ml

\*=P<0.05 vs groups B, D and controls

#=P<0.05 only vs controls

Group A: positive anti-thyroid-antibodies and ultrasound picture suggestive of Hashimoto's thyroiditis

Group B: positive anti-thyroid-antibodies and normal ultrasound picture

Group C: negative anti-thyroid-antibodies and ultrasound picture suggestive of Hashimoto's thyroiditis

Group D: negative anti-thyroid-antibodies and normal ultrasound picture

Figure 1

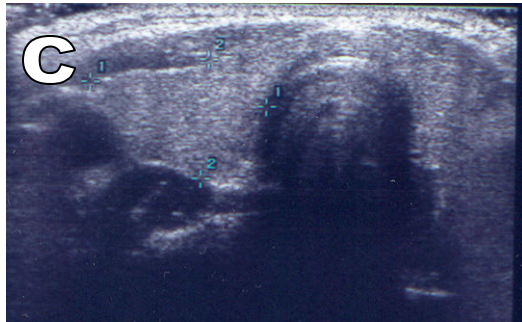
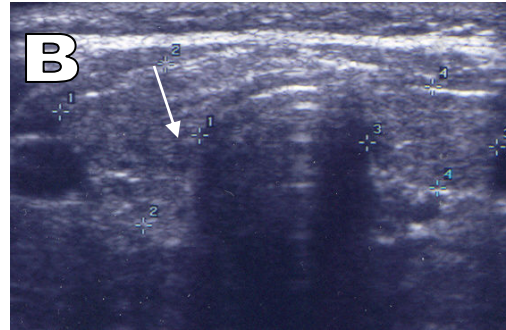
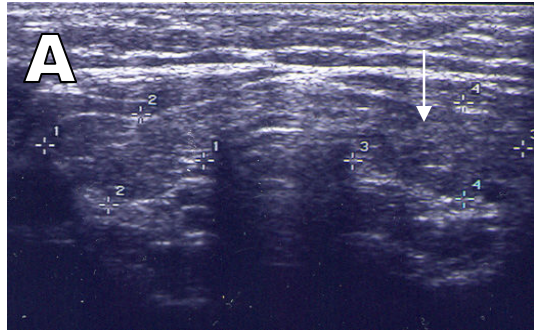




Figure 2

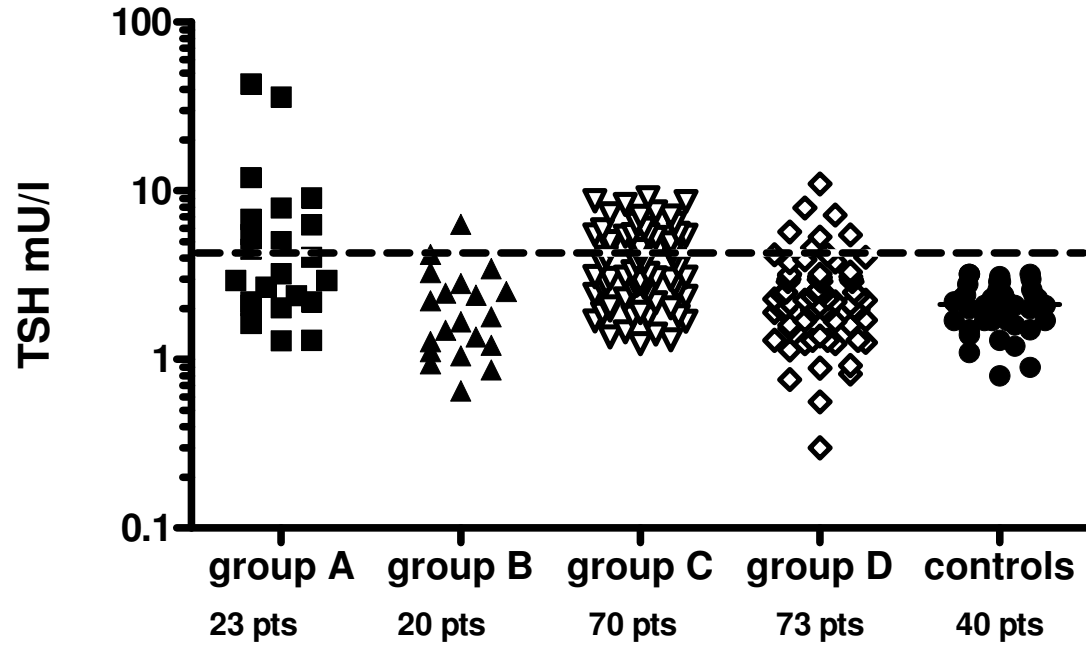


Figure 3

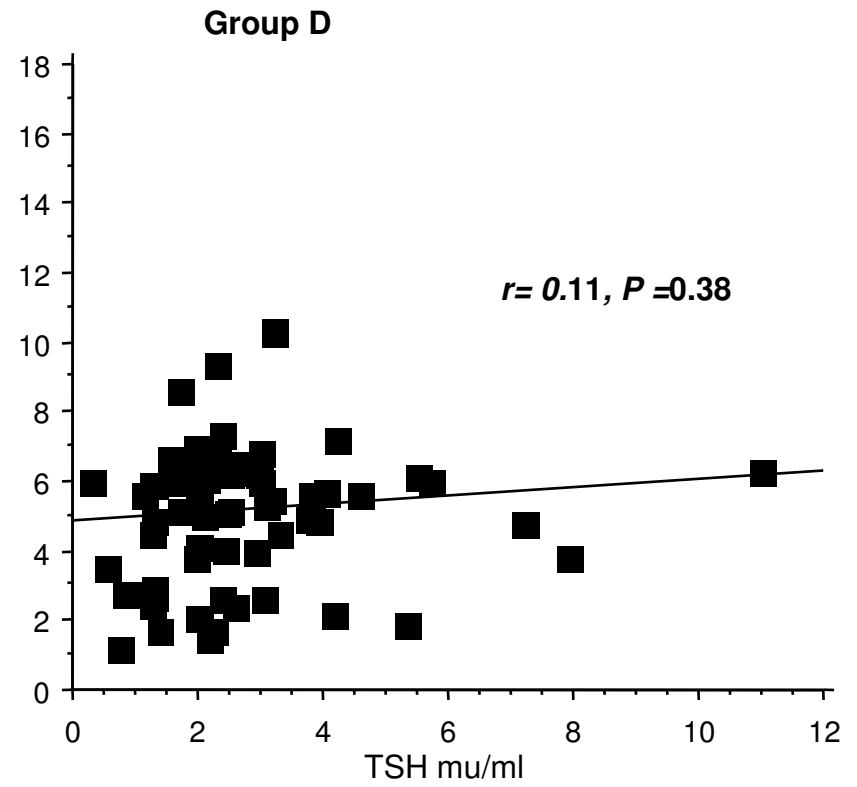
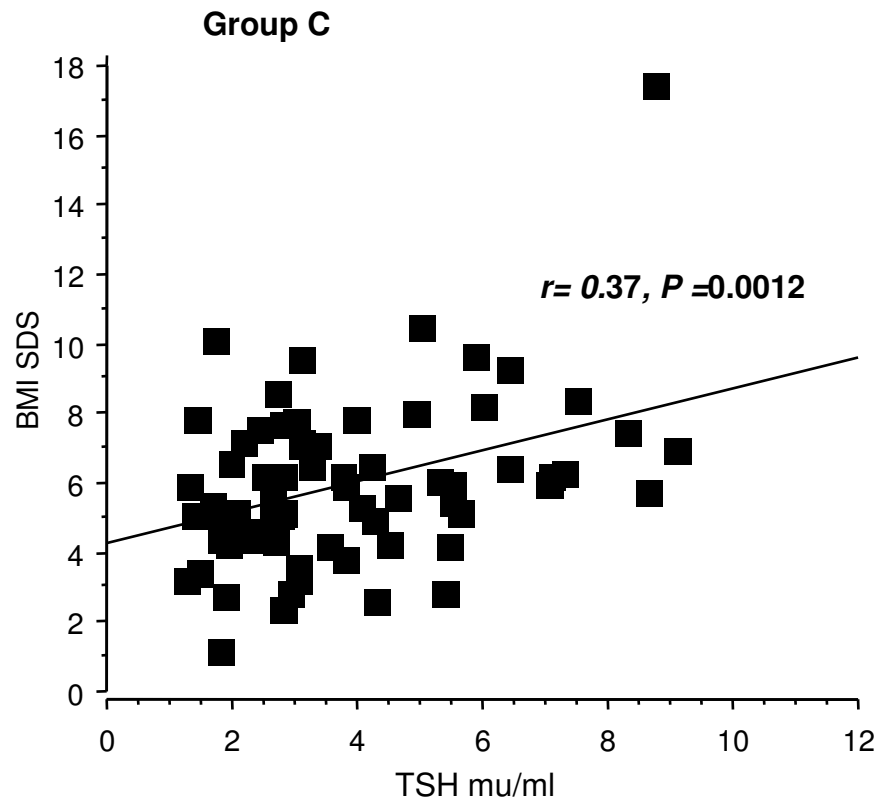


Figure 4A

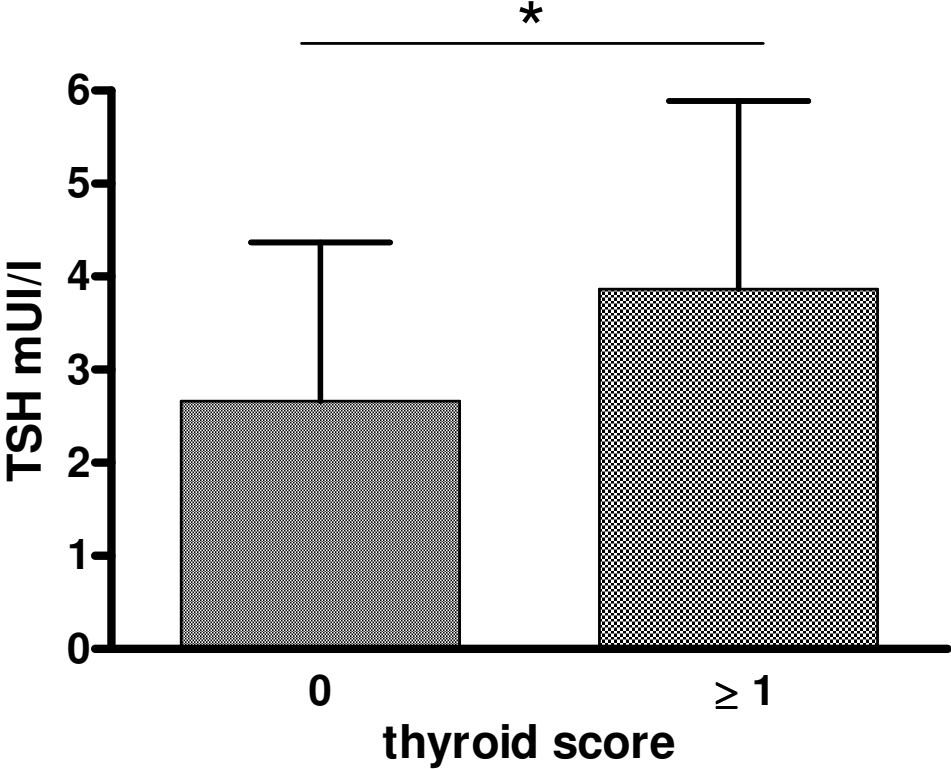


Figure 4B

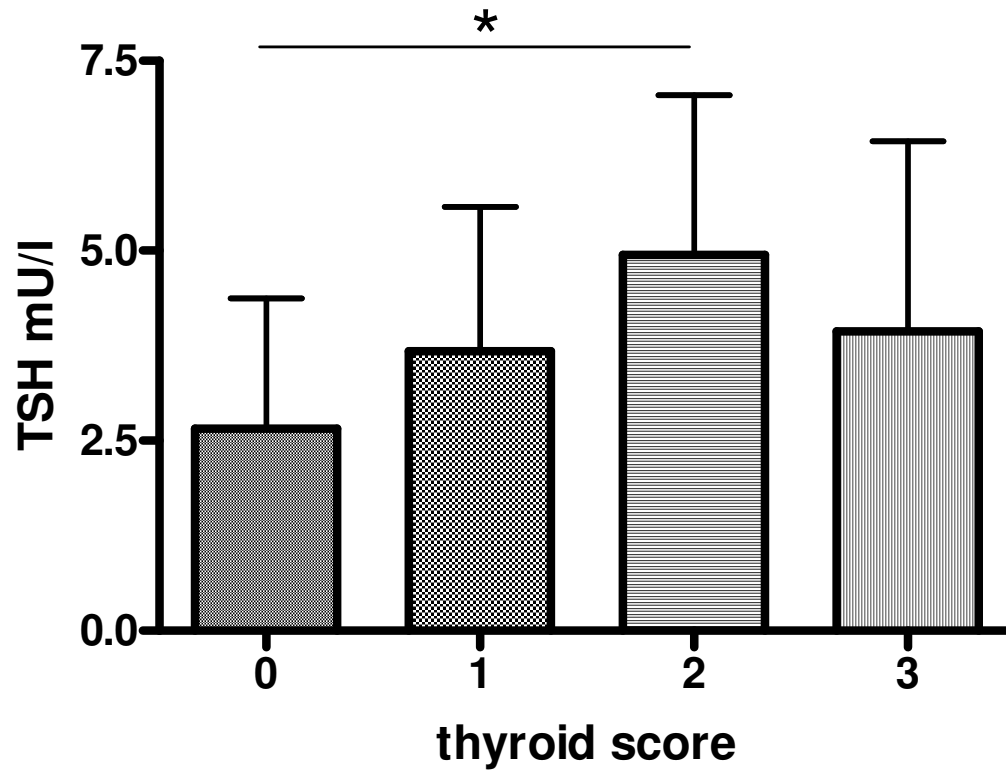


Figure 5A

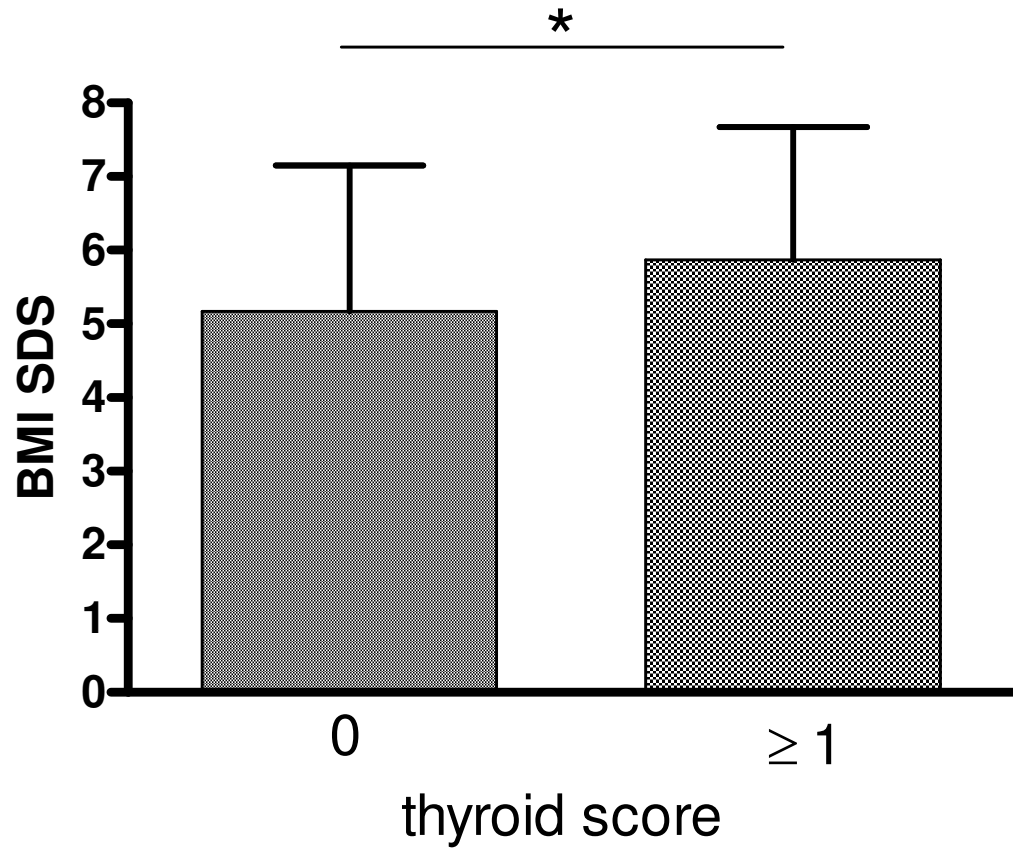


Figure 5B

