An hypoechoic pattern of the thyroid at ultrasound does not indicate autoimmune thyroid diseases in patients with morbid obesity

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An hypoechoic pattern of the thyroid at ultrasound does not indicate autoimmune thyroid diseases in patients with morbid obesity.

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ABSTRACT

OBJECTIVE: Thyroid ultrasound (US) scan is a valuable tool for diagnosing thyroid diseases. In autoimmune thyroid disease (AITD), an hypoechoic pattern of the thyroid at US is related to circulating thyroid antibodies. Aim of this study was to evaluate the diagnostic accuracy of thyroid US for the detection of AITD in patients with morbid obesity.

DESIGN: Thyroid US scans showing an hypoecoic pattern of the thyroid were collected from 105 patients with morbid obesity (BMI > 40 kg/m^2) and 105 non-obese (BMI ≤30 kg/m^2) patients.

RESULTS: A thyroid hypoechoic pattern at US was consistent with clinical/biochemical features of AITD in 90/105 (85.7%) non-obese and in 22/105 (20.9%) morbid-obese patients (p<0.0001). By performing a complete thyroid work-up, including clinical examination, thyroid morphology, serum hormones and auto-Ab measurements, the discrepancy between the US pattern and the results of the thyroid Ab tests was justified in 6/15 non obese patients, and only in 1/83 morbid obese patients. Thus, an unexplained hypoechoic pattern of the thyroid at US, defined as negative tests for thyroid Ab and absence of justifying thyroid disturbances, was found in 2/105 (1.9 %) non-obese and in 68/105 (64.8 %) patients with morbid obesity (p<0.0001).

CONCLUSIONS: Our results suggest that: 1) Morbid obesity may affect thyroid morphology 2) an hypoechoic pattern of the thyroid at US, a well established parameter for diagnosing AITD, has a poor diagnostic accuracy when patients with morbid obesity are taken into account.

INTRODUCTION

Over the last decade, ultrasound (US) scan proved to be a valuable tool for the diagnostic work-up of thyroid diseases (1-8). Besides estimation of thyroid volume and identification of non palpable thyroid nodules (9), US scan is able to characterize the echographic structure of thyroid tissue (10). The normal thyroid parenchyma has a peculiar high echo density due to the typical follicle structure (9). The interface between thyroid cells and the colloid exhibits an elevated acoustic impedance, causing high frequency acoustic waves to be reflected back to the probe. In autoimmune thyroid diseases (AITD), however, both lymphocytic infiltration and disruption of normal tissue architecture cause a reduction in thyroid echogenicity (1,4,6,10-11). Thyroid hypoechogenicity is currently viewed as an early sign of thyroid autoimmunity, which may be present even when the thyroid disorder is not suspected from a clinical point of view (4,6-7,12-13). Rapid improvement in US equipments and the use of standardized computerized algorithms have permitted an objective and quantitative measurement of tissue echogenicity in thyroid diseases (11-13), as well as in other pathological conditions (14-15). Using a subjective measure of thyroid echogenicity, previous studies demonstrated that in patients with thyroid autoimmune diseases the presence of circulating thyroid antibodies (Ab) as well as the development of hypothyroidism was closely correlated with the degree of thyroid hypoechogenicity (1, 5, 11, 12, 16).

It is a common observation that a significant proportion of patients with morbid obesity display slightly increased serum levels of TSH (17). The elevation of serum TSH, also within the normal range, is associated with an increase in the occurrence of obesity (18) However, there is still considerable disagreement as to the physiopathological mechanism responsible for this phenomenon and the clinical significance of this hyperthyrotropinemia (17). A recent study from our group questioned whether an elevated serum TSH alone provides sufficient evidence for a diagnosis of subclinical hypothyroidism in patients with morbid obesity (19). Little has been reported on the morphology of the thyroid gland in adults with morbid obesity (20, 21). A recent

study, performed in obese children, showed for the first time that obesity is associated with structural changes of thyroid morphology, as assessed by US, which are unrelated to thyroid autoimmunity (23). Aim of the current study was to evaluate the diagnostic accuracy of thyroid US for the detection of thyroid autoimmune diseases in adult patients with morbid obesity. To this purpose, patients with an hypoechoic pattern of the thyroid at US were enrolled and stratified according to their body weight status.

PATIENTS AND METHODS

Subjects

Obese patients and controls were recruited by searching the computerized database of thyroid US performed at the Unit of Internal Medicine and Endocrinology of the Fondazione Salvatore Maugeri from January 2007 to July 2009. Searching criteria were an hypoecoic pattern of the thyroid at US and the patient's BMI. A total of 105 consecutive patients with morbid obesity (BMI > 40) were collected.

The control group was constituted by normo-weight and/or slightly overweight (BMI ≤30 kg/m^2) patients who had performed a thyroid US scan, which revealed an hypoechoic pattern of the gland. Starting from January 2007, consecutive non obese patients were recruited until the same number of morbid obese patients was reached. In the control group, 76 (72.4%) patients were normo-weight (BMI ≤25 kg/m^2), and 29 (27.6%) were slightly overweight (BMI between 25 and 30 kg/m^2).

A two-steps searching procedure was used: 1) All the scans performed in patients with a BMI>40 kg/m^2 showing the presence of thyroid hypoechogenicity were collected. When more than one scan for a single patient was available, only the first one was considered. A total of 105 scans were collected; 2) Starting from the date when the first obese patient was enrolled, 105 consecutive US scans performed in patients with BMI ≤30 kg/m^2 and showing the presence of thyroid hypoechogenicity were collected. The last collected scan was performed 45 days later and no

patient had performed more than one scan. The procedure by no means could discriminate any clinical characteristics other than name, sex and BMI of the patient, together with the name of the US operator. A total of 210 scans showing an hypoechoic pattern of the thyroid at US were collected. The clinical data of the correspondent patients were obtained from computerized and written hospital notes. These included: age, FT4, FT3, TSH, thyroglobulin Ab (Tg Ab), thyroid peroxidase Ab (TPO Ab) TSH-receptor Ab (TR Ab) and a detailed drug history.

BMI was calculated as the weight (kg) measured to the nearest kg divided by the square of height determined to the nearest cm (m). Isolated hyperthyrotropinemia (a condition frequently encountered in patients with morbid obesity) (20) was defined as a raised serum level of TSH with normal FT4 and FT3 levels, in the absence of circulating thyroid Ab.

All subjects gave their informed consent to participate in the study, which was performed in accordance to the guidelines of the Declaration of Helsinki.

Thyroid ultrasound

Thyroid ultrasounds were performed using a real-time US device (Sonosite 180 plus) equipped with a linear transducer operating at 7.5 MHz for morphologic study (L38 linear probe). The volume of the thyroid, as assessed by measuring the three largest perpendicular diameters, and the US pattern of the thyroid parenchyma are recorded for each scan. In order to minimize the operator variability in assessing thyroid echogenicity, only those scans performed by the same operator (S.C.), who was well trained and had a 5 years experience in thyroid imaging, were selected. According to previous studies, echogenicity was evaluated in both thyroid lobes and in the surrounding neck muscles on the transverse section (12, 16). The isthmus was excluded to avoid the interference of reflecting echoes from the tracheal cartilage. Hypoechogenicity was ascertained by comparison of the echo distribution in the thyroid parenchyma with respect to the surrounding neck muscles and only those scans showing from mild to severe generalized hypoechogenicity were selected (12, 16).

Serum assays

Serum concentrations of FT4 (normal range: 8.0-19.0 pg/mL), FT3 (normal range: 1.8-4.2 pg/mL), and TSH (third generation TSH assay; normal range: 0.4-4.0 mIU/L) were measured using immunochemoluminiscent assays by an automated analyser (Immulite 2000, DPC Cirrus, Los Angeles, CA, USA) employing commercial kits (Diagnostic Products Corporation, Los Angeles, CA, USA). The serum concentrations of Tg-Ab (normal range: <60 U/ml), TPO-Ab (normal range: <60 U/ml), and TR-Ab (normal range: <1 U/ml) were measured using immunochemiluminiscent assays employing commercial kits (Brahms, Hennigsdorf, Germany).

Statistical analysis

Statistical analysis was performed using the SPSS software (SPSS, Inc., Evanston, IL). Between groups comparisons were performed by Student-t test for unpaired data and by Mann–Whitney *U*-test according to a normal or a nonparametric distribution of the variable tested. Frequencies among groups were compared by χ^2 test with Fisher's correction, when appropriate. A *p*-value <0.05 was considered statistically significant.

RESULTS

The clinical and biochemical data of the patients with an hypoechoic pattern of the thyroid at US, subdivided according to their body weight phenotype (non-obese *vs.* morbid obese), are reported in **Table 1.** The two groups of patients displayed significant differences for all parameters except for age and thyroid volume. The percentage of patients in whom thyroid US hypoechogenicity was consistent with the biochemical features of AITD (positive thyroid Ab tests) were significantly different ($p<0.0001$) between the two groups. By means of US, 90 out of 105 patients (85.7%) in the non-obese group were correctly identified as having AITD. In details, 77 out of 90 (85.5%) had a clinical diagnosis of chronic autoimmune thyroiditis and 13 out of 90 (14.5%) were affected by Graves'disease. In the obese group there were only 22 out of 105 (20.9%) patients showing a correspondence between an hypoechoic pattern of the thyroid at US and positive tests for thyroid Ab, being their clinical diagnosis chronic autoimmune thyroiditis in 21 out of 22 (95.5%) and Graves'disease in 1 out of 22 (4.5%). Overall, there were 15 out of 105 patients in the non obese

group and 83 out of 105 in the obese group who showed an hypoechoic pattern of the thyroid at US not accompanied by positivity for any humoral immune marker of AITD. Possible causes explaining the occurrence of an hypoechoic pattern of the thyroid at US in the absence of positive tests for thyroid Ab were searched. As shown in **Table 2**, in 6 out of 15 non obese patients, the discrepancy between the US pattern and the results of the thyroid Ab tests was justified by the following condition: amiodarone induced hypothyroidism in two cases; amiodarone induced type II thyrotoxicosis in one patient; atrophic thyroiditis in one patient; subacute thyroiditis in one patient; and Graves'disease in remission after medical treatment with disappearance of thyroid Ab in one patient. By contrast, in only 1 out of 83 morbid obese patients showing a discrepancy between the US pattern and the results for circulating thyroid Ab, the hypoechoic pattern could be explained by the presence of atrophic thyroiditis. Other clinical conditions not potentially related to the hypoechoic pattern of the thyroid at US were: non-toxic multinodular goiter in six patients and toxic multinodular goiter in one case among non-obese patients. In the group of patients with morbid obesity, three had non-toxic multinodular goiter and eleven an isolated hyperthyreotropinemia. Thus, in 2 out of 105 (1.9 %) non obese patients and in 68 out of 105 (64.8 %) patients with morbid obesity an hypoechoic pattern of the thyroid was found in the absence of any thyroid abnormality as assessed by a complete thyroid work-up, including clinical examination, thyroid morphology, hormones and auto-Ab measurements ($p<0.00001$).

DISCUSSION

This study shows that the finding of a thyroid hypoechoic pattern at US has a different clinical meaning when observed in non-obese patients as compared to those with morbid obesity. In line with previous evidences, we report that a thyroid hypoechoic pattern was strongly suggestive for the presence of AITD, as assessed by positive thyroid Ab tests and/or clinical data, but only in non-obese patients. A correspondence between the US hypoechoic pattern and the biochemical evidence of AITD was found in 85.7% of the non-obese patients. On the other hand, patients with morbid obesity displayed as little as a 20.9% concordance rate between thyroid morphology at US and

humoral or clinical evidence of thyroid autoimmunity. Thyroid volumes were similar between morbid obese patients and controls. Ayturk et al in a specifically designed study reported that euthyroid patients with metabolic syndrome have significantly higher mean thyroid volume and nodule prevalence as compared with euthyroid controls (22). This apparent discrepancy can be solved by considering that our patients had a wide spectrum of thyroid disease, thus preventing to draw conclusions on thyroid volume. Indeed, the current study was specifically designed to include only patients with an hypoechoic pattern, thus allowing to compare the underlying thyroid conditions in US-matched patients stratified according to a different body weight status. The results would support the concept that thyroid US, a well established tool for diagnosing AITD (1,4-6), may be less effective when patients with morbid obesity are taken into account. A considerable percentage (10.5%) of patients with morbid obesity had isolated hyperthyrotropinemia (a laboratory picture which was not observed in non-obese patients). Isolated hyperthyrotropinemia is often observed in patients with morbid obesity, but its pathogenesis remains poorly understood (17, 19). Recent evidences showing lack of female gender prevalence, normal FT3/FT4 ratios and normalization of serum TSH following weight loss, all support the concept that these patients should not be considered as having subclinical hypothyroidism (19, 24-26). In agreement with this concept, we recently demonstrated that morbid obese patients with a raised serum TSH have a significantly lower rate of thyroid antibody positivity when compared with TSH-matched normo-weight patients (19). These data suggest that autoimmunity is not a major cause of raised serum TSH in morbid obese patients.

An hypoechoic pattern of the thyroid at US in the absence of any thyroid abnormality, as assessed by a complete thyroid work-up, including clinical examination, thyroid morphology, hormones and auto-Ab measurements, is a relatively rare finding in non-obese patients (1.9%), while it is observed in the majority of patients with morbid obesity (64.8%). These data indicate profound differences as to the clinical meaning of an hypoechoic pattern of the thyroid at US in relation to adiposity. The question arises of which is the cause of thyroid ultrasound findings in the two groups of patients. It

seems clear from our and other results that thyroid hypoechogenicity is strongly related to AITD in non-obese patients. On the other hand, the cause of thyroid hypoechogenicity in patients with morbid obesity is difficult to be understood. The hypothesis that patients with an extreme weight excess may have a tendency to accumulate fat in the thyroid could be an attractive one. Radetti et al, recently reported that a thyroid hypoechoic pattern at US was found in a high proportion of obese children with no evidence of AITD (23). Thyroid cytology performed in some of these children turned out to be normal, showing only colloid drops and thyrocytes with no inflammatory cell suggesting AITD (23). The issue of thyroid repercussions of fat-excess remains open as cytology does not represent an appropriate technique for elucidating the histopathological basis of the imaging abnormalities. Histological examination, specifically focused at studying fat accumulation within the thyroid tissue, would be required to firmly demonstrate this hypothesis. Some clinically relevant considerations stem from this study. First, the complex and yet poorly understood repercussions of morbid obesity on the thyroid gland are not limited to thyroid function, but may also affect thyroid morphology as evaluated by US. Only a minority of morbid obese patients with an hypoechoic pattern of the thyroid at US display humoral signs of autoimmunity . Thus, a thyroid hypoechoic pattern at US has a poor diagnostic accuracy for AITD when patients with morbid obesity are taken into account.

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Table 1 Clinical and biochemical characteristics of patients with an hypoechoic pattern of the thyroid at US, subdivided according to their body weight status

	Thyroid Hypoechoic Pattern		
	Non-Obese Patients	**Morbid Obese Patients**	***p* value**
Number of cases	105	105	
Age (years)	48.4±14.1	46.2±12.4	0.391
Sex (M/F)	7/98	34/71	**<0.0001**
BMI (kg/m^2)	**23.9 ± 3.1**	**44.2 ± 6.2**	**<0.0001**
Thyroid Volume (ml)	15.9 ± 11.1	16.2 ± 14.6	0.903
Thyroid Ab* (%)	**90/105 (85.7%)**	**22/105 (20.9%)**	**<0.0001**

***positive test for at least one among Tg Ab, TPO Ab or TR Ab**

Table 2 Thyroid condition found in non-obese and obese patients showing a thyroid hypoechoic pattern at US and negative tests for thyroid Ab

	Non-Obese Patients	**Morbid Obese Patients**
Number of cases	15/105	83/105
Atrophic Thyroiditis	1	1
Subacute Thyroiditis	1	-
Graves' disease in remission after thionamides	1	-
Amiodarone-Induced-Hypothyroidism	2	-
Amiodarone-Induced- Type II thyrotoxicosis	1	-
Non-Toxic Multinodular goiter	6	3
Toxic Multinodular goiter	1	-
Isolated Hyperthyrotropinemia*	-	11
Lack of detectable thyroid abnormality**	2	68

*defined as a raised serum TSH with normal FT4 and FT3 levels in the absence of circulating thyroid Ab

** patients in whom a complete thyroid work-up including clinical examination, circulating hormones and auto Ab measurements did not provide evidence for thyroid disease