Endocrinología, Diabetes y Nutrición 69 (2022) 686–693

Endocrinología, Diabetes y Nutrición

www.elsevier.es/endo

ORIGINAL ARTICLE

Clinical usefulness of thyroid ultrasonography in patients with primary hypothyroidism

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Received 8 July 2021; accepted 4 November 2021
Available online 22 November 2022

KEYWORDS
Hypothyroidism;
Chronic autoimmune thyroiditis;
Thyroid ultrasonography

Abstract
Background and objective: Despite the value of ultrasonography in the detection of chronic thyroiditis (CT) as well as in nodular goitre, it is often only indicated in patients with hypothyroidism if a palpable goitre or a thyroid mass is identified. The objective of the study is to evaluate the clinical usefulness of thyroid ultrasonography in patients with primary hypothyroidism without clinical suspicion of nodular goitre. And more specifically, to analyse its value in the aetiological diagnosis of hypothyroidism, and to evaluate its contribution in the detection and characterisation of coexisting subclinical thyroid nodular disease.
Patients and method: Prospective cross-sectional observational study of 114 patients with primary hypothyroidism of CT or idiopathic aetiology, without symptoms or cervical palpation suspected of nodular goitre, who underwent a thyroid function test, a serological study of antithyroid antibodies, a thyroid ultrasonound and, when appropriate, a cytological study of the nodules found.
Results: Ultrasonound allowed CT to be recognised as the cause of hypothyroidism in 19% of patients who had a negative serological study, and detected nodules larger than 9 mm in 22 patients (16 with antithyroid antibodies). A cytological study was performed in 18 of the cases. Five patients underwent surgery, with carcinoma found in two of them.
Conclusions: Thyroid ultrasound is useful in the aetiological diagnosis of primary hypothyroidism as well as in the detection of a coexisting, unsuspected, but clinically relevant nodular goitre, so this examination should be indicated in the initial study of patients with primary hypothyroidism.
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PALABRAS CLAVE
Hipotiroidismo;
Tiroiditis crónica autoinmune;
Ecografía tiroidea

Utilidad clínica de la ecografía tiroidea en los pacientes con hipotiroidismo primario

Resumen
Antecedentes y objetivo: A pesar del valor de la ecografía en la observación de la tiroiditis crónica (TC) así como del bocio nodular, con frecuencia esta exploración solo se indica a los pacientes con hipotiroidismo si clínicamente se les aprecia bocio o una masa tiroidea palpable. El objetivo del estudio es evaluar la utilidad clínica de la ecografía en los pacientes con hipotiroidismo primario sin sospecha clínica de bocio nodular. En concreto, analizar su rendimiento en el diagnóstico etiológico del hipotiroidismo y evaluar su aportación en la detección y caracterización de patología nodular tiroidea subclínica coexistente.
Pacientes y método: Estudio prospectivo observacional transversal sobre 114 pacientes con hipotiroidismo primario de etiología TC o idiopática, sin síntomas ni palpación cervical sospechosos de bocio nodular, a quienes se les realizó un estudio hormonal tiroideo, serológico de anticuerpos antitiroideos, una ecografía tiroidea y cuando procedió, un estudio citológico de los nódulos encontrados.
Resultados: La ecografía permitió reconocer la TC como causa del hipotiroidismo en el 19% de los pacientes que tuvieron el estudio serológico negativo, detectó nódulos mayores de 9 mm en 22 pacientes (16 con anticuerpos antitiroideos) sobre los cuales se realizó estudio citológico en 18 casos y fueron intervenidos quirúrgicamente 5 con resultado de carcinoma en 2.
Conclusiones: La ecografía tiroidea resulta útil en el diagnóstico etiológico del hipotiroidismo primario así como en la detección de bocio nodular coexistente no sospechado pero clínicamente relevante, por lo que debería indicarse en el estudio inicial los pacientes con hipotiroidismo primario.
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Introduction

Chronic thyroiditis (CT) is the main cause of primary hypothyroidism.[1–3] It is usually diagnosed with clinical and hormonal data and mainly based on detecting antithyroid antibodies in the serum. Since the serological study can be falsely negative in at least a quarter of cases,[4,5] the aetiological diagnosis of hypothyroidism is not correctly made in this group of patients. On the other hand, studies show that thyroid ultrasound can reveal CT in up to 34% of patients with a negative serological study with histologically proven CT.[3–6] Therefore, in patients with primary hypothyroidism, the rate of correct aetiological diagnoses may increase when thyroid ultrasound assessment is added to the clinical and serological study.

Establishing the aetiological diagnosis of hypothyroidism is of interest since it allows other causes to be excluded, its natural progression to be foreseen, and the associated comorbidity to be known. It is well known that the progression of hypothyroidism is faster in patients with CT,[3,7] and especially in pregnant women with CT, who, regardless of hypothyroidism, have a higher risk of miscarriage and premature birth,[8,9] and therefore are patients who need closer monitoring and earlier hormone replacement therapy.[8] On the other hand, some studies have shown a higher incidence of cancer associated with CT, lymphoma and papillary carcinoma, which appear as thyroid nodules with the typical ultrasound characteristics of malignant thyroid nodules.[1,10]

Although in most patients with hypothyroidism, it is not recommended to start hormone replacement therapy until thyrotropin does not exceed 10 mIU/L,[7] some conditions can modify this procedure. Among them, nodular goitre may make it advisable to start treatment earlier.[3] Some studies have shown a reduction in post-surgical recurrences of nodular goitre in patients receiving hormone replacement therapy,[11,12] others have confirmed a reduction in the volume of the nodules and a lower rate of appearance of new thyroid nodules when managing to maintain normal or subnormal thyrotropin values with levothyroxine-based treatment,[13–17] and other studies have reported a reduction in the incidence of papillary thyroid carcinoma in CT patients treated with levothyroxine,[18] all of which demonstrates the influence of thyrotropin levels on the development and growth of thyroid nodules. Thyroid ultrasound in patients with hypothyroidism could be useful to detect coexisting nodular goitre, which, although clinically silent, could motivate the indication to start hormone replacement therapy even if the thyrotropin level is not higher than 10 mU/L.

Despite the performance of ultrasound in the diagnosis of CT and in the diagnosis and characterisation of nodular goitre, this examination is not usually indicated in patients with primary hypothyroidism unless a glandular abnormality or a palpable thyroid mass is clinically observed.[5,19] This is probably due to the underlying idea that hypothyroidism is a functional disorder and that ultrasound is useful for evaluating structural alterations. Therefore, the indication of thyroid ultrasound in patients presenting with primary hypothyroidism may be a topic of interest.

The objective of the study is to evaluate the clinical utility of thyroid ultrasound in patients with primary

hypothyroidism without clinical suspicion of nodular goitre. Specifically, to analyse its performance in the aetiological diagnosis of hypothyroidism while evaluating its contribution to the detection and characterisation of coexisting subclinical thyroid nodular pathology.

Material and methods

This study is a prospective, cross-sectional, observational study based on routine clinical practice in an outpatient clinic. Between July 2020 and March 2021, 114 patients over 18 years of age referred for primary hypothyroidism (increased serum thyrotropin and normal or decreased serum free thyroxine) that had not been previously studied or treated were consecutively included, in whom other idiopathic causes other than CT were ruled out. A cervical ultrasound was performed on all of them at the first visit, and a new hormonal determination of thyrotropin, free thyroxine, antithyroperoxidase and antithyroglobulin antibodies was scheduled after 6–8 weeks. Based on the ultrasound findings, when indicated,[20] a cytological study of the patient's thyroid nodular pathology was performed, and according to the results obtained, surgical treatment was indicated.[21] Patients with clinical suspicion of nodular goitre (symptoms of cervical tumour or palpation of an irregular goitre) were excluded because it made no sense to investigate the usefulness of thyroid ultrasound examination in them as it is widely recommended, as well as pregnant women. After all, their reference hormonal values are different as well as the criterion of substitutive treatment,[7] and those in whom the values of thyrotropin and free thyroxine spontaneously normalised in the analytical tests at 6–8 weeks, to avoid the inclusion of patients with transient hypothyroidism. The Clinical Research Ethics Committee has approved the study of the Fundació Asistencial Mútua de Terrassa [Terrassa Health Insurance Foundation]. Informed consent was obtained from all the participants.

The variables collected from each patient were: personal data: age, sex, weight, height; laboratory tests: initial serum thyrotropin and free thyroxine values (without receiving treatment with levothyroxine), antithyroperoxidase and antithyroglobulin antibodies (if one or both were positive, antithyroid antibodies were considered positive); ultrasound pattern (a: normal; b: typical CT pattern; c: typical CT pattern with nodules; d: nodular pattern without typical CT findings); larger diameter of nodules when present; the result of cytology according to the Bethesda classification,[21] and type of pathological lesion found in the resected nodule of patients who underwent surgery.

Thyroid ultrasound and ultrasound-guided puncture for the cytological study of thyroid nodules were performed by the same operator (LGP) with extensive experience, using a Toshiba Aplio 300 model ultrasound machine with a 10-MHz linear probe, following the ultrasound classification of risk of malignancy of the nodules and the indications for cytological study in the American Thyroid Association guidelines.[20] The echogenicity of the thyroid was evaluated by comparison with the adjacent muscles (sternohyoid, sternothyroid and sternocleidomastoid). A typical CT pattern was considered to be one defined by homogeneous glandular hypoechogenicity or diffuse heterogeneity, with or without hyperechoic septa or multiple small areas of altered echogenicity with ill-defined borders (pseudonodules).[10] Thyrotropin and free thyroxine were determined by electrochemiluminescent immunoassay (normal values 0.30–4.20 mIU/L and 0.61–1.12 ng/dL, respectively), and antithyroperoxidase and antithyroglobulin antibodies were determined by electrochemiluminescence (negative <9 IU/mL and <60 IU/mL, respectively).

The sample size was calculated based on the estimation of the percentage of patients who can be diagnosed with CT by ultrasound within the set of subjects who have a negative serological study but confirmed histological CT. According to the study by Guan et al.,[5] this figure is 34%. In our case, being patients with hypothyroidism without proven CT histology, it can be assumed that this percentage will be somewhat lower since in some cases the aetiology of hypothyroidism will be idiopathic. In a sample of 55 patients, it has been verified that this figure is 19%. The formula used was N = (Z⟨2P(1-P))/i2 where N is the number of subjects needed, Z⟨2 is the value of the standardised normal distribution corresponding to the fixed ⟨ risk (5%) in the two-sided statistical tests, P is the value of the proportion assumed to exist in the population (19%), and i is the precision with which the parameter is estimated (7.5 %).[22] The estimated sample size was 105 subjects.

A descriptive analysis of the collected variables was performed. Univariate analysis of differences between continuous and categorical variables for pooled data was performed using Student's t-test or analysis of variance. In contrast, the relationship between categorical variables was investigated using the Chi-square test. Diagnostic concordance between thyroid ultrasound findings and antithyroid antibody results was measured using the Kappa index (0 to 0.20 = poor concordance; 0.21 to 0.40 = weak concordance; 0.41 to 0.60 = moderate concordance; 0.61 to 0.80 = good concordance; 0.81–1 = very good concordance). Statistical significance was set at $p < 0.05$ (two-tailed). Statistical analysis was performed with the software Epidat version 3.1 (Servizo Galego de Saúde [Galician Health Service], Galicia, Spain).

Results

A total of 114 patients with primary hypothyroidism were included, 104 women and 10 men, with a mean age of 43.4 ± 14 years, TSH 16.2 ± 37.7 mIU/L, free thyroxine 0.89 ± 0.23 ng/dl, and one or both antithyroid antibodies positive in 63.2% of cases (Table 1).

Thyroid ultrasound was used to diagnose CT in 19% of patients with primary hypothyroidism and negative antithyroid antibodies. The diagnostic concordance for CT between the ultrasound pattern and the result of antithyroid antibodies was moderate (kappa index 0.58–95% confidence interval: 0.43—0.73)

In addition, ultrasound revealed the presence of clinically unsuspected nodular goitre in 42.1% of these patients. In all, 45.8% of the nodules detected were larger than 9 mm. Of the 48 patients with nodular goitre, 39 cases had thyrotropin values less than 10 mIU/L. Based on the ultrasound findings, a cytological study of the nodules was carried out in 18 patients. The results were indeterminate in four cases (three

Table 1 Characteristics of the patients included in the study.

	Total cases (n = 114)	Cases with negative AT-Ab (n = 42)	Cases with positive AT-Ab (n = 72)	p-value*
Age (mean ± SD, years)	43.4 ± 14	40.2 ± 14.1	45.3 ± 13.8	ns
Gender				ns
Female (n)	104	37	67	
Male (n)	10	5	5	
Weight (mean ± SD, kg)	70.1 ± 13.9	72.6 ± 15	68.7 ± 13	ns
Height (mean ± SD, cm)	162.5 ± 7.8	163.4 ± 7.9	161.9 ± 7.9	ns
BMI (mean ± SD, kg/m^2)	26.6 ± 5.2	27.2 ± 5.3	26.3 ± 5.1	ns
Thyrotropin (mean ± SD, mIU/L)	16.2 ± 37.7	6.7 ± 2.9	21.6 ± 46.7	<0.01
Free thyroxine (median ± SD, ng/dl)	0.89 ± 0.23	0.98 ± 0.19	0.85 ± 0.23	<0.01
Ultrasound pattern				<0.001
Normal (n)	27	20	7	
Thyroiditis (n)	39	4	35	
Thyroiditis with nodules (n)	26	4	22	
Nodules without thyroiditis (n)	22	14	8	
Nodule size (mean ± SD, mm)	11.2 ± 7.5	10.2 ± 6.3	12 ± 8.1	ns
Nodules <10 mm (n)	26	12	15	
Nodules ≥10 mm (n)	22	6	16	ns
Cytology of the nodule (n)	18	5	13	ns
Bethesda I	0	0	0	
Bethesda II	13	4	9	
Bethesda III	3	0	3	
Bethesda IV	1	0	1	
Bethesda V	0	0	0	
Bethesda VI	1	1	0	
Surgical intervention (n)	5	1	4	ns
Carcinoma (n)	2	1	1	ns
Lymphoma (n)	0	0	0	ns

AT-Ab: antithyroid antibodies; SD: standard deviation; BMI: body mass index; ns: not significant.
* p-value when comparing the cases with negative AT-Ab versus those with positive AT-Ab.

Bethesda III and one Bethesda IV) and malignant in one case. A thyroidectomy surgical intervention was performed in five patients whose definitive pathological study was benign in three cases and malignant in two (Table 1). One of them, a 52-year-old woman, had a pT1a(m)N0bM0 multiple papillary microcarcinoma of up to 9 mm in size. The other patient, a 26-year-old woman, had a minimally angioinvasive pT2N0bM0 follicular carcinoma of 36 mm with a pT1aN0bM0 synchronous papillary microcarcinoma of 8 mm.

The relationship between the size of the thyroid nodules and the body mass index (BMI) and the number of cases with a thyrotropin value equal to or less than 10 mU/L or greater than 10 mU/L, is shown in Table 2.

Discussion

Thyroid ultrasound in patients with primary hypothyroidism has allowed us to diagnose CT in 19% of those with negative antithyroid antibodies. It has also detected subclinical nodular pathology in 42.1% of patients with hypothyroidism, whose nodules have turned out to be larger than 9 mm in 45.8% of cases. A total of 81.2% of the patients with nodules had thyrotropin values below 10 mIU/L. The information from the ultrasound has led to the performance of an ultrasound-guided biopsy for cytological analysis in 15.7% of patients with primary hypothyroidism, and its result has indicated surgical intervention in 4.4% of the cases with a positive result of carcinoma in 1.7%.

Many studies have positively assessed the role of thyroid ultrasound in the diagnosis of CT, even in the early stages of the process when there is still no hypothyroidism. One of the first was that of Gutekunst et al.[23] in patients with cytologically proven CT, where ultrasound had a diagnostic sensitivity of 94.6% and a specificity of over 95%. Antithyroid antibodies were absent in 13% and present in low titre in 17% of these patients. In the study by Nordmeyer et al.[6] all patients with antithyroid antibodies in a functional situation of euthyroidism or hypothyroidism had ultrasound findings of chronic thyroiditis. Ultrasound also established the absence of chronic thyroiditis in another large group of patients. In the study by Pedersen et al.[4] of 452 patients with routine CT ultrasound, it was confirmed by cytological study and by antithyroperoxidase antibody study that 78% had CT compared to 7% of patients diagnosed with CT in a group of 100 controls with normal ultrasound. Those testing positive for antithyroperoxidase antibodies and TSH eleva-

Table 2 Relationship between the size of the thyroid nodules, the BMI (kg/m^2) and the number of patients with a thyrotropin value less than or equal to 10 mU/L or greater than 10 mU/L.

Size of thyroid nodule	Total cases	BMI (mean ± SD)* (kg/m^2)	TSH ≤10 mU/L (n)	TSH >10 mU/L (n)
Without nodule	66	25.7 ± 4.4	52	14
Less than 10 mm	26	27.9 ± 5.1	21	5
10–19 mm	16	26.7 ± 4.8	13	3
20–29 mm	4	29.8 ± 8.5	3	1
30–39 mm	2	32.9 ± 17	2	0

SD: standard deviation; BMI: body mass index.
* p: ns.

tion were 66.8% and 64.4%, respectively, in the group with altered echogenicity and 10% and 2% in the group with normal echogenicity. In a recent study[5] of 277 patients with proven CT histology, the diagnostic performance of serological tests and thyroid ultrasound was evaluated. The results showed a diagnostic sensitivity and specificity of 63.9% and 89.4% for the serological test and 49.1% and 88.9% for the ultrasound. The positive and negative predictive values were 75.3% and 83.1% for the serological test and 69% and 77.6% for the ultrasound. Of the 100 subjects with histological CT and a negative serological test, the ultrasound showed signs of CT in 34. In conclusion, thyroid ultrasound has shown its value. It is complementary to serological tests for the diagnosis of CT, and therefore it can help to make the correct aetiological diagnosis of primary hypothyroidism. In our study, 79% of the patients with a positive serological test had ultrasound findings of CT, which reaffirms the diagnostic value of ultrasound in determining CT. In turn, of the patients with a negative serological test, 81% did not have ultrasound findings of CT either, which indicates the usefulness of ultrasound in ruling out CT as an aetiology of hypothyroidism. However, diagnostic concordance for CT between serological testing and ultrasound was only moderate. These figures could be higher if we were able to know in which subjects there are false serological results, as often occurs in patients with low titres of antithyroid antibodies in whom there is no true CT, or also, in those with CT who do not yet show positivity of said antibodies.[3,5,7,23] Bearing in mind that today thyroid ultrasound has become an examination that can increasingly be performed easily during the patient's first consultation, its speed of execution and the results it provides give it additional interest concerning the serological analysis of antithyroid antibodies that require a new blood draw and a delay of days or weeks until the result is known.

The aetiological diagnosis of hypothyroidism is clinically useful in predicting its progression. The specific CT marker consists of antithyroid antibodies in the patient's serum, which reflects the progressive lymphocytic infiltration that will end up causing glandular failure.[1] Due to this pathogenesis, the progression of hypothyroidism is more common and faster than in patients with idiopathic hypothyroidism,[3] which was also reflected in our series of patients where those with positive antibodies had a significantly higher thyrotropin value. This increased risk of hypothyroidism and its faster progression has also been seen in pregnant women with antithyroid antibodies, in whom the most common cause of thyroid deficiency is undertreatment.[3] Regardless of the adverse effects of maternal hypothyroidism in pregnant women, pregnant women with CT have a higher risk of miscarriage and premature delivery.[8,9] In addition, CT reduces the functional capacity of the gland, increasing the risk of developing subclinical hypothyroidism during pregnancy by eight times due to the deterioration in the stimulatory physiological response of pregnancy mediated by the beta-chorionic gonadotrophin hormone on the thyroid.[8,9] For this reason, in patients with hypothyroidism due to CT, the progression of hypothyroidism is more intense in the first trimester of pregnancy, which requires closer monitoring and earlier hormone replacement therapy.[3,8] Unfortunately, for the clinical diagnosis of CT, detecting antithyroid antibodies in serum can give false negative results between 26% and 36% of the time.[4,5] In this sense, our study demonstrates the usefulness of thyroid ultrasound in establishing the aetiological diagnosis of CT in 19% of patients with primary hypothyroidism of idiopathic aetiology or whose serological test was negative, which allowed us to obtain a higher proportion of correct aetiological diagnoses, with the clinical consequences derived from it.

Another interesting aspect of the aetiological diagnosis of hypothyroidism results from the knowledge of its comorbidities. Although the incidence of thyroid lymphoma is very low, the risk of this neoplasm is much higher in patients with CT, in whom it is up to 67 times more common.[1,10] Likewise, the incidence of papillary thyroid carcinoma is higher in patients with CT, both in the first observation and during follow-up of its progression, and it appears with signs of greater aggressiveness such as the greater frequency of aggressive histological variants, multicentricity, extrathyroidal extension, vascular invasion and lymph node metastases.[10,18,24,25] In the study by Fiore et al.[18] on 13,738 patients referred for cytological study of nodular goitre, a higher incidence of papillary carcinoma was documented in cases with nodular CT compared to those with nodular goitre without CT (9.4% vs 6.4%; $p = 0.008$), which also occurred at a younger age (39.6 ± 13.1 years vs 44.2 ± 15.1 years; $p < 0.003$) and with a higher frequency of lymph node metastases (35.5% vs 25.3%, $p = 0.03$). On the other hand, the incidence of CT is 2.77 times higher in patients with papillary thyroid cancer compared to a control population, and in the group of patients with thyroid cancer, CT is 1.99 times more common when the variety of cancer is papillary.[26] These relationships suggest that CT patients are more predisposed to develop papillary thyroid carcinoma. The ultrasound findings of malignant

nodules in CT patients are similar to those for the general population[10] so the indication for a cytology study based on ultrasound findings does not change for these patients. Our study was not specifically designed to assess the incidence of thyroid cancer in patients with hypothyroidism or CT. This aspect was considered a secondary objective to assess the clinical relevance of the coexisting nodular pathology revealed in the thyroid ultrasound performed in patients who consulted for primary hypothyroidism without clinical suspicion of nodular goitre. In these circumstances, having diagnosed carcinoma in 1.7% of the total number of patients with hypothyroidism, or put another way, in 11.1% of the cases biopsied or in 40% of those operated on, seems to us to be clinically relevant given that these figures are higher than those reported in the series of patients studied for nodular goitre in our setting.[27] Likewise, the diagnosed carcinoma cases did not have extraglandular extension, probably thanks to the early diagnosis based on the ultrasound examination.

Except in pregnant patients, it is generally recommended to treat hypothyroidism when the thyrotropin level is greater than 10 mU/L and, in some cases, when it is less than 10 mU/L. Clinical guidelines allow replacement therapy to be considered if the patient has symptoms of hypothyroidism, antithyroid antibodies, atherosclerotic cardiovascular disease or heart failure, or risk factors for both conditions.[7] However, other particular situations could influence the decision to start hormone replacement therapy in patients with hypothyroidism and thyrotropin values below 10 mU/L. The coexistence of nodular goitre may be a reason to start treatment earlier.[3] Thyrotropin acts as a growth factor on thyroid follicular cells and thyroid nodules.[25,28] Hormone therapy with levothyroxine (at suppressive and non-suppressive doses of thyrotropin) can reduce the postoperative recurrence of nodular goitre, especially in patients exposed to radiation or residents in areas with iodine deficiency.[11,12] It can also reduce the size of benign thyroid nodules[14,16,17] and prevent the appearance of new nodules.[13,15] In the study by Fiore et al.[18] on 848 patients with nodules with cytology suggestive or indicative of papillary carcinoma and 12,890 patients with nodules with benign cytology, they found that the serum level of thyrotropin was the main factor associated with the presence of papillary carcinoma. Likewise, in the group of patients with nodular CT treated with levothyroxine, the level of thyrotropin and the incidence of papillary carcinoma were reduced. Consequently, an ultrasound scan in patients with hypothyroidism can reveal the possible coexistence of nodular goitre, which, although clinically silent, could constitute an indication to start hormone treatment with levothyroxine, even though the thyrotropin level is not higher than 10 mU/L. This series is the first to document that 42% of patients who consulted for primary hypothyroidism without clinical suspicion of nodular goitre were asymptomatic carriers of nodules. Of these, 81% had thyrotropin values below 10 mU/L, which could benefit from replacement therapy with levothyroxine.

Given the performance of thyroid ultrasound in the diagnosis of CT, as well as in the detection and characterisation of nodular goitre, this examination is currently not usually indicated in patients with primary hypothyroidism, except if a glandular abnormality (unspecified whether diffuse or nodular) or a palpable thyroid mass are clinically observed.[5,19] However, ultrasound detects nodules in up to 50% of patients with a normal cervical clinical examination, a third of which are larger than 20 mm, and nodule size equal to or greater than 10 mm is considered relevant.[29] In our series, the patients did not have a clinical suspicion of nodular goitre, but 42% had nodules on ultrasound, and almost 46% had nodules 10 mm or larger. Although we did not find a statistically significant relationship between the body mass index of the patients and the size of the thyroid nodules, those with nodules had a body mass index in the range of overweight or obesity that was higher in those with larger nodules, which, aside from a possible aetiopathogenic relationship, could explain why the relatively large nodules had not been clinically perceived. Some guidelines on hypothyroidism, such as those of the American Association of Clinical Endocrinologists and the American Thyroid Association,[7] do not even address the issue of when to perform thyroid ultrasound examinations in patients with hypothyroidism. In the Consensus statement on the use and technical requirements of thyroid ultrasound in endocrinology and nutrition services published by the Sociedad Española de Endocrinología y Nutrición (SEEN) [Spanish Society of Endocrinology and Nutrition],[30] thyroid functional abnormalities (hypo- and hyperthyroidism) and thyroiditis are considered to be indications for a thyroid ultrasound. However, in the Manual of Endocrinology and Nutrition published by the SEEN, in chapter 28, ''Hypothyroidism'',[31] an ultrasound study is not considered in patients with hypothyroidism. Chapter 33 of this same manual en, titled Imaging diagnosis in thyroid pathology, says that ultrasound is not indicated in evaluating suspected thyroid dysfunction or Hashimoto's thyroiditis.[32] In the same manual, in chapter 56, Cervical ultrasound in thyroid and parathyroid pathology, it is argued that ultrasound can be useful in diffuse thyroid disease and, specifically, in chronic autoimmune thyroiditis, to establish the diagnosis of CT when the serological test is negative, and to rule out the presence of focal lesions, both independent of possible thyroiditis and linked to it.[33] This lack of agreement is probably determined, in addition to economic criteria where they exist, because ultrasound is usually used to evaluate structural alterations of the gland. At the same time, hypothyroidism is a functional disorder, and the intersection between both pathologies is not considered, even though it is often recognised.

The study has some limitations. As all the ultrasound scans were interpreted by a single operator, there may be a bias in this regard. Higher magnification of the selected ultrasound image in some patients may have masked the heterogeneous hypoechoic CT pattern, while lower magnification may have led to a false diagnosis of CT.[4]

In conclusion, thyroid ultrasound in patients with primary hypothyroidism is useful for making the aetiological diagnosis, especially when the serological test is negative. It can reveal the presence of unrecognised nodular goitre indicating early replacement therapy for hypothyroidism and detecting associated malignancy. For all these reasons, thyroid ultrasound should be indicated in the initial study of patients with primary hypothyroidism. These findings should be confirmed in future studies, and if so, it would also be useful to define the periodicity of ultrasound follow-up of

patients with CT with and without nodular goitre, as well as to evaluate the cost-benefit ratio of these procedures.

Authorship/collaborators

Each author has contributed materially to the research and preparation of the article. Lluís García González: conception and design of the study, interpretation of results, writing of the draft and approval of the final version.

Luis García Pascual: conception and design of the study, acquisition and analysis of data, interpretation of results, critical review of the draft and approval of the final version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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