Clinical and ultrasound assessment of the thyroid gland in patients with rheumatoid arthritis

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Abstract

Introduction: *Patients with rheumatoid arthritis can develop autoimmune thyroid disease (ATD), the clinical diagnosis of which can be difficult because both entities share symptoms such as arthralgia, myalgia, morning stiffness or fatigue.* **Objective:** *To determine the prevalence of ATD in patients with rheumatoid arthritis.* **Method:** *Cross-sectional study that included 78 patients with rheumatoid arthritis and 81 clinically healthy controls matched by age and gender. Both groups underwent anti-thyroid antibodies quantification, thyroid function tests, thyroid ultrasound and thyroid gland biopsy when the Thyroid Imaging Reporting and Data System (TIRADS) score was ≥ 4.* **Results:** *Hypothyroidism was found in 24.4% of patients with rheumatoid arthritis (p = 0.003), as well as high titers of anti-thyroid antibodies versus clinically healthy controls; 53% of thyroid ultrasounds were normal in hypothyroid patients, and increased perfusion was found in 40% of rheumatoid arthritis patients who tested positive for anti-thyroid antibodies. Cases classified as TIRADS 4 underwent aspiration with benign histopathological results.* **Conclusions:** *Thyroid assessment added clinical value was demonstrated in patients with rheumatoid arthritis, according to the prevalence of subclinical hypothyroidism, anti-thyroid antibodies positivity and ultrasound abnormalities, regardless of normal or altered thyroid function.*

KEY WORDS: *Rheumatoid arthritis. TIRADS. Hypothyroidism.*

Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by damage to the joint synovium mediated by the expression of multiple cytokines, such as interleukins (IL) 1 and 6, tumor necrosis factor (TNF)-, metalloproteases and other molecules.[1,2]

Patients with RA can develop autoimmune thyroid disease (ATD),[3,4] which encompasses Graves' disease (GD), chronic autoimmune thyroiditis, subclinical hypothyroidism and Hashimoto's thyroiditis (HT).[5] In patients with RA, it can be difficult for clinical suspicion of ATD to be established because they share symptoms such as arthralgia, myalgia, morning stiffness or fatigue.[6]

ATD can develop autoantibodies against thyroid peroxidase (anti-TPO) (13 to 40 %) and thyroglobulin (anti-Tg) (23 %).[4,7-11] From 4 to 37 % of patients with ATD show anti-TPO and 6 to 30 % anti-Tg.[4,12] The prevalence of ATD and thyroid dysfunction in patients with RA has been recorded to range from 6 to 37 %.[5,6,8]

Little is reported about the usefulness of thyroid gland ultrasound (US) as a diagnostic tool in the clinical evaluation of patients with RA, with or without known thyroid dysfunction. In addition to the above, the practice of thyroid aspiration biopsies is unusual.

The purpose of the present study was to determine the prevalence of ATD by means of anti-thyroid antibodies detection, functional tests, thyroid gland US and aspiration biopsy according to the Thyroid

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Imaging Reporting and Data System (TIRADS) in patients with RA and in clinically healthy controls (CHC) matched by age and gender (controls).

Method

The protocol was approved by the ethics committee of Hospital Civil "Dr. Juan I. Menchaca", Universidad de Guadalajara, Jalisco, Mexico, with registration number 1068/10. Written informed consent was obtained from all patients.

A total of 78 patients RA who attended the hospital rheumatology department between 2010 and 2013 were recruited. They had to be older than 18 years and meet the American College of Rheumatology (ACR, 1987) or ACR/European League Against Rheumatism (ACR/EULAR, 2010) criteria.[13,14] Patients who were on treatment with high-dose steroids (> 15 mg/day of prednisone or its equivalent) were excluded. As CHCs, 81 blood donors, matched by age and gender, were taken into account. History of cardiovascular disease, hypertension, diabetes mellitus, kidney or liver failure, cancer, known dyslipidemia and premature menopause were considered to be exclusion criteria in both groups.

A questionnaire was applied to each individual in order to obtain clinical and demographic information. Disease activity was determined by C-reactive protein levels, according to the Disease Activity Score 28 (DAS28).[15]

Serum free triiodothyronine (T3L) and free thyroxine (T4L) were measured by chemiluminescence immunoassay. According to thyroid-stimulating hormone (TSH) serum levels, thyroid dysfunction was classified as follows:[16]

- Euthyroidism, TSH from 0.4 to 4.0 mU/L.
- Overt hypothyroidism, TSH > 4.0 mU/L and low T4L.
- Subclinical hypothyroidism, TSH > 4.0 mU/L and normal T4L.
- Hyperthyroidism, TSH < 0.4 mU/L.

Erythrocyte sedimentation rate (mm/h) was measured by the Wintrobe method. C-reactive protein levels were quantified by nephelometry. Rheumatoid factor (RF) was determined by turbidimetry. Anti-cyclic citrullinated peptide antibodies (anti-CCP, Axis-Shield Diagnostic, Dundee, Scotland), anti-TPO antibodies and anti-Tg antibodies (Orgentec Diagnostika, Mainz, Germany) were measured by enzyme-linked immunosorbent assay (ELISA).

The ultrasound evaluation was carried out using a high resolution B-mode US with a 9-MHz transducer. Three radiologists performed the evaluation and classification of images according to TIRADS:[17,18]

- TIRADS 1, normal thyroid gland.
- TIRADS 2, benign lesions.
- TIRADS 3, probability of benign lesions, usually in HT.
- TIRADS 4-6, lesions with increased cancer risk.

Patients classified as TIRADS ≥ 4 underwent a US-guided fine needle aspiration biopsy with a 22-G needle and a 10 mL syringe. The aspirate was fixed with 96 % alcohol and stained with hematoxylin-eosin. Cytological analyses were carried out by an expert pathologist according to the Bethesda system.[19,20]

Statistical analysis

Data were analyzed with the statistical program SPSS, version 24.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism, version 6.00 (GraphPad Software, La Jolla California, USA). Normal distribution variables were analyzed with the Skewness and Kurtosis tests. Continuous variables with normal distribution were calculated with Student's t-test for non-paired samples; in non-normal distribution, variables were compared with Mann-Whitney's U-test. The association between categorical variables was analyzed by means of the chi-square test or Fisher's exact test. A p-value ≤ 0.05 was considered to be significant.

Results

Clinical and demographic characteristics of the included cases are shown in table 1. Seventy-eight patients with RA were included, out of which 83.3 % were females. Average age and disease duration were 42.75 ± 12.15 years and 4.74 ± 6.04 years, respectively.

Subclinical hypothyroidism was the most common thyroid dysfunction in patients with RA. Hypothyroidism was found in 24.4 % of patients with RA versus 1.2 % of CHCs (p = 0.003). In the RA group with thyroid dysfunction, according to TSH and T4L levels, 89.5 % (n = 17/19) had subclinical hypothyroidism and 10.5 % (n = 2/19) overt hypothyroidism (data not shown).

Patients had high levels of anti-TPO (118.26 ± 538.60 versus 19.18 ± 55.28, p = 0.02) and anti-Tg antibodies (96.94 ± 321.27 versus 54.99 ± 46.43, p = 0.04) in comparison with CHCs. Thyroid nodules were observed in 23 % of patients versus 28.4 % (p = 0.13) in CHCs. The TIRADS 1 category was more common, followed by TIRADS 2, 4a, 3 and 4b.

Table 1. Demographic characteristics and thyroid function and anti-thyroid antibodies tests in patients with rheumatoid arthritis and clinically healthy controls

Characteristic	Mean ± SD		p
	RA (n = 78)	CHC (n = 81)	
Age	(n = 78)	41.80 ± 11.61	0.75
Disease duration (years)	4.74 ± 6.04	—	—
Anti-TPO (IU/mL)	118.26 ± 538.60	19.18 ± 55.28	0.02
Anti-Tg (IU/mL)	96.94 ± 321.27	54.99 ± 46.43	0.04
	n %	n %	
Female gender	65 83.3	75 92.6	0.77
Anti-TPO-positive	12 15.4	4 10.5	0.09
Anti-Tg-positive	10 19.6	5 13.2	0.57
Thyroid function			
Euthyroidism	59 75.6	80 98.7	—
Hypothyroidism	19 24.4	1 1.2	0.003
Hyperthyroidism	0	0	—
Thyroid ultrasound			
Normal echogenicity	52 66.6	47 71.2	—
Nodules	18 23.0	19 28.4	0.13
Hypoplasia	2 2.8	0	—
Increased perfusion	6 7.6	1 1.5	—
TIRADS			
1	54 69.2	75 92.6	—
2	12 15.4	3 3.7	—
3	5 6.4	2 2.5	0.01
4a	6 7.7	1 1.2	—
4b	1 1.3	0	—

Anti-TPO = anti-thyroid peroxidase, Anti-Tg = anti-thyroglobulin, US = ultrasound, TIRADS = Thyroid Imaging Reporting and Data System. The comparisons between proportions were performed with the chi-square test or Fisher's exact test. The comparisons between averages were carried out with Student's t-test for non-paired samples.

Patients with anti-TPO antibodies who were positive for anti-CCP in 83.3 %, p = 0.04, and RF in 75 %, p = 0.03 are described in table 2. Increased perfusion was observed in 40 % of patients who were positive for anti-TPO and anti-Tg antibodies. Approximately 30% of TIRADS 3-classified patients showed anti-TPO and anti-Tg antibodies (p < 0.001).

Noteworthy, approximately 40 % of patients with hypothyroidism were positive for anti-TPO and anti-Tg antibodies. In the US results according to thyroid function: 70 % were found with normal echogenicity, while 53 % showed hypothyroidism (p < 0.001) (Table 3).

Thyroid gland biopsy was practiced in 7 patients who were classified in TIRADS 4 (4a-4b): the lesions were benign (data not shown). Disease duration was 7.14 years (ranging from 1 to 22).

Discussion

Although a high prevalence of hypothyroidism was found in patients with RA in comparison with CHCs (24.4 % versus 1.2 %, p = 0.003), in 89.5 % of these patients it was subclinical, and overt in 10.5 %. According to other reports, worldwide prevalence of subclinical hypothyroidism is 3 to 15 %, and in RA, 2.5 to 10.7 %.[11,21,22]

Anti-thyroid antibody levels were higher in patients versus CHCs (anti-TPO, p = 0.02 and anti-Tg, p = 0.04).

In patients with hypothyroidism, the frequency of anti-TPO (36.8 % versus 8.5 %, p = 0.05) and anti-Tg (42.1 % versus 3.4 %, p = 0.01) was higher in comparison with euthyroid subjects.

One of the ATDs with the highest prevalence is HT, characterized by thyroid dysfunction, thyroid gland increased diffuse echogenicity, lymphocytic infiltrate in biopsy and ant-thyroid antibodies, especially anti-TPO in 90 %.[23-25] Buchanan et al. showed an association between HT and RA;[26] however, in our investigation it was not present.

Seven women with RA and one CHC were classified as TIRADS 4. All underwent aspiration biopsy; the result was mild acute thyroiditis, a benign condition related to ATD. It is important highlighting the possible contribution of female hormones in the development of thyroid gland goiter, nodules and cancer in women.[27]

As regards TIRADS 4 findings, it is important to remember the limitations of the TIRADS 4 classification system, since the risk of malignancy in this specific category is rather high.[17,18] One limitation of our study was its cross-sectional nature. Prospective studies with a large number of patients will be required in order to determine if all cases of mild acute thyroiditis in RA remain benign or progress to thyroid cancer.[28]

The TIRADS system was developed to establish the main characteristics that predict malignancy in thyroid nodular disease.[17] In the present work, thyroid nodules were identified in 23 % of the RA group versus 28. 4 % (p = 0.13) in the CHC group; this prevalence is consistent with previous reports.[11,29] Thyroid nodule biopsy indicated a 4a-4b TIRADS classification, which translates into risk for malignancy of 5 to 10 % and 10 to 80 %, respectively.[19]

Thyroid US is an affordable and sensitive method that can be used during outpatient consultation; in addition, it is able to identify small 1 to 2 mm parenchymal lesions, as well as changes related to thyroid

Table 2. Comparison of characteristics of patients with rheumatoid arthritis with regard to the presence or absence of anti-thyroid antibodies

Characteristic	Anti-TPO (+) (n = 12)		Anti-TPO (-) (n = 66)		p	Anti-Tg (+) (n = 10)		Anti-Tg (-) (n = 68)		p
	Mean ± SD		Mean ± SD			Mean ± SD		Mean ± SD		
Disease duration (years)	4.94 ± 6.64		3.38 ± 2.66		0.32	5.37 ± 7.17		2.97 ± 2.73		0.31
DAS 28 (units)	3.12 ± 1.23		3.14 ± 1.03		0.97	3.02 ± 1.06		3.51 ± 1.48		0.36
	n	%	n	%		n	%	n	%	
Rheumatoid factor-positive	9	75.0	24	36.4	0.03	6	60.0	24	35.3	0.25
Anti-CCP-positive	10	83.3	31	47.0	0.04	8	80.0	29	42.6	0.06
Thyroid ultrasound										
Normal echogenicity	3	25.0	49	74.2	< 0.001	4	40.0	51	75.0	0.07
Nodules	2	16.7	16	24.3	0.60	0		16	23.5	0.01
Hypoplasia	2	16.7	0		0.01	2	20.0	0		0.01
Increased perfusion	5	41.6	1	1.5	< 0.001	4	40.0	1	1.5	< 0.001
TIRADS										
1	4	33.3	50	75.8	< 0.001	3	10.0	51	77.9	0.07
2	4	33.3	8	12.1	0.78	3	10.0	9	16.2	0.67
3	4	33.3	1	1.5	0.001	4	30.0	1	2.9	< 0.001
4a	0		6	9.1	0.28	0		6	8.8	0.33
4b	0		1	1.5	0.67	0		1	1.5	0.70

DAS 28 = disease activity score 28, anti-CCP = anti-cyclic citrullinated peptide, Anti-TPO = anti-thyroid peroxidase, anti-Tg = anti-thyroglobulin, TIRADS = Thyroid Imaging Reporting and Data System. The comparisons between proportions were performed with the chi-square test or Fisher's exact test. The comparisons between averages were carried out with Student's t-test for non-paired samples.

Table 3. Comparison of characteristics between patients with rheumatoid arthritis with and without thyroid dysfunction

Characteristic	Mean ± SD				p
	Euthyroidism (n = 59)		Hypothyroidism (n = 19)		
Age (years)	41.79 ± 12.54		43.75 ± 7.10		0.75
Disease duration (years)	4.41 ± 6.45		5.30 ± 6.39		0.69
DAS 28 (units)	3.11 ± 1.26		3.39 ± 1.04		0.47
Anti-CCP (IU/mL)	114.76 ± 224.93		111.14 ± 72.06		0.93
Anti-TPO (IU/mL)	31.26 ± 27.13		310.38 ± 633.73		0.01
Anti-Tg (IU/mL)	18.40 ± 19.17		417.85 ± 1052.51		0.02
Rheumatoid factor (IU/mL)	143.83 ± 313.25		55.62 ± 67.12		0.12
	n	%	n	%	
Anti-CCP-positive	27	45.8	6	31.6	0.21
Rheumatoid factor-positive	19	32.2	9	47.4	0.10
Anti-TPO-positive	5	8.5	7	36.8	0.05
Anti-Tg-positive	2	3.4	8	42.1	0.01
Thyroid ultrasound					
Normal echogenicity	42	71.2	10	52.6	< 0.001
Nodules	10	17.0	8	42.1	0.12
Hypoplasia	1	1.7	1	5.3	0.72
Increased perfusion	6	10.1	0		0.08
TIRADS					
1	41	69.5	13	68.3	1.00
2	8	13.6	4	21.1	0.43
3	4	6.8	1	5.3	0.60
4a	5	8.5	1	5.3	0.64
4b	1	1.6	0		0.59

DAS 28 = disease activity score 28, anti-CCP = anti-cyclic citrullinated peptide, RF = rheumatoid factor, Anti-TPO = anti-thyroid peroxidase, anti-Tg = anti-thyroglobulin, TIRADS = Thyroid Imaging Reporting and Data System. The comparisons between proportions were carried out with the chi-square test or Fisher's exact test. The comparisons between averages were analyzed with Student's t-test for non-paired samples.

autoimmunity, not necessarily associated with anti-thyroid antibodies or thyroid hormone dysfunction; it might detect thyroid dysfunction preclinical stages in RA.

Based on our findings, patients with RA can benefit from US thyroid evaluation, since 10 % of patients were classified as TIRADS 4 despite being negative for anti-thyroid antibodies and having normal thyroid function.

Given the high number of patients with subclinical hypothyroidism, we suggest annual review of thyroid function tests, which are accurate and economically accessible examinations.

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