Prevalence of Thyroid Autoimmunity in Patients with Spondyloarthropathies

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ABSTRACT. ***Objective.*** To evaluate the prevalence of chronic autoimmune thyroiditis or Hashimoto's thyroiditis (HT) in a group of patients with spondyloarthritis (SpA).

Methods. We evaluated serum levels of thyroid-stimulating hormone, free triiodothyronine, and free thyroxine, and titers of antithyroglobulin and antithyroid peroxidase (anti-TPO) antibodies in 357 consecutive patients with SpA. We also recruited 318 healthy age-matched controls. Ultrasonography of the thyroid gland was performed in all subjects and rheumatic activity was evaluated.

Results. Indices of thyroid autoimmunity were significantly more frequent in patients with SpA than in controls (24.09% vs 10.69%, respectively; $p < 0.05$). In the SpA group, a higher prevalence of HT was found in patients with an active disease than in those with low-moderate disease levels. Also in the SpA group, patients with a disease duration > 2 years had a higher prevalence of HT and anti-TPO antibodies positivity than patients with a disease duration ≤ 2 years. Ultrasonography detected a significantly higher frequency of thyroid nodules and hypoechoic pattern in patients with SpA than in controls. Among patients with SpA, HT and anti-TPO antibodies positivity were significantly more frequent in patients with peripheral involvement (68.6%) than in patients with axial involvement (31.4%; $p < 0.05$).

Conclusion. Our study shows a significantly higher prevalence of thyroid autoimmunity in patients with SpA as compared to controls. Thyroiditis occurs more frequently in patients with longer disease duration and active rheumatic disease. We suggest that thyroid function tests be part of the clinical evaluation in patients with SpA. (First Release April 15 2011; J Rheumatol 2011;38:1371–7; doi:10.3899/jrheum.101012)

Key Indexing Terms:
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Chronic autoimmune thyroiditis, or Hashimoto's thyroiditis (HT), is an organ-specific autoimmune disease characterized by the presence in serum of autoantibodies against thyroglobulin (TG) and thyroid peroxidase (TPO) and clinical evidence of goiter or atrophic gland[1,2]. Its relationship with rheumatic diseases such as systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), systemic sclerosis, or rheumatoid arthritis (RA) is well recognized[3,4,5,6,7,8,9]. Moreover, RA was the most prevalent coexisting autoimmune disease in subjects with HT and their parents, suggesting a strong disease association[10]. Hemminki, *et al* recently compared the familial risk of RA in relation to a large number of autoimmune diseases and showed an increased risk of RA when patients were hospitalized for other autoimmune diseases such as HT (standardized ratio 1.54)[11]. This result suggests extensive genetic sharing among these autoimmune diseases. Many rheumatic manifestations, such as fibrositis, myositis, myalgias, carpal tunnel syndrome, joint stiffness, and joint effusion have been described in association with HT. These symptoms seem to be due to hypothyroidism[12,13], which is frequently caused by HT[14]. Nevertheless, it has recently been reported that rheumatic features may occur in HT even in the absence of thyroid dysfunction. In addition to arthritis, conditions such as bilateral capsulitis[15], chest-wall pain[16], polyarthralgia[17,18], and erosive osteoarthritis[19] have been observed in euthyroid patients with HT. In particular, in 1984 LeRiche and Bell proposed that a benign form of seronegative polyarthritis resembling mild RA could be associated with HT, in

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the absence of hypothyroidism[20]. Punzi, *et al* have demonstrated that in HT a variety of inflammatory arthritides exists; they are characterized by a mild nonerosive progression, similar in many aspects to the arthritis found in connective tissue diseases[21].

Data regarding the association of HT with seronegative spondyloarthritis (SpA) are lacking[22]. Our aim was to evaluate the prevalence of thyroid disorders in a group of patients with SpA.

MATERIALS AND METHODS

Our study included 357 patients with SpA (172 women and 185 men; mean age 37.86 ± 11.03 yrs; range 17–70 yrs), consecutively admitted to the Rheumatology Unit of the University of Naples "Federico II" between January and December 2009. One hundred eight patients had psoriatic arthritis (PsA; 57 women, 51 men; mean age 39.86 ± 10.89 yrs), 24 had ankylosing spondylitis (AS; 3 women, 21 men; mean age 36.23 ± 10.42 yrs), 85 had undifferentiated spondyloarthritides (USpA; 41 women, 44 men; mean age 35.56 ± 10.79 yrs), 68 had reactive arthritis (ReA; 33 women, 35 men; mean age 31.85 ± 11.69 yrs), and 72 had enteropathic spondyloarthritides (EA; 38 women, 34 men; mean age 34.65 ± 9.37 yrs).

The diagnosis of SpA was made according to the European Spondylarthropathy Study Group (ESSG) criteria[23]. In particular, the diagnosis of PsA was based on the Classification of Psoriatic Arthritis study group criteria[24] and the diagnosis of AS on the criteria of the American College of Rheumatology[25]. No "gold standard" for the diagnosis of ReA or EA was available, and the ESSG criteria were applied. USpA was diagnosed if the ESSG criteria were fulfilled but no diagnosis of AS, PsA, ReA, or EA could be made.

Patients with SpA were classified on the basis of the articular involvement into peripheral (phSpA) and axial (axSpA) subsets. Patients with phSpA were also classified into oligoarticular and polyarticular subsets.

Disease duration of SpA was categorized as "early" if the time since the first symptom was < 2 years and "late" if it was ≥ 2 years. Disease activity of phSpA was classified according to the 28-joint count Disease Activity Score (DAS28) as remission (< 2.6), low (2.6 to 3.2), moderate (3.2 to 5.1), and high (> 5.1), and further categorized as low-moderate (DAS28 < 3.2) and active (DAS > 3.2). Disease activity of axSpA was classified according to Bath Ankylosing Spondylitis Disease Activity Index score as low (< 4.0) and active (> 4.0), as suggested by Kavanaugh and Cassell[26].

We recruited 318 subjects from the hospital staff as controls (149 women and 169 men; mean age 39.54 ± 10.51 yrs; range 26–67 yrs). All patients and controls underwent both a rheumatological and an endocrinological clinical examination.

A physician blinded to laboratory findings performed thyroid sonography in all subjects in order to define thyroid volume, thyroid tissue abnormalities, and possible presence of nodules. Thyroid blood flow was studied by color-flow Doppler defined according to Vitti, *et al*[27] as suggested by Antonelli, *et al*[28].

Laboratory tests included serum levels of free triiodothyronine, free thyroxine, thyroid-stimulating hormone (TSH), TG antibodies, and TPO antibodies titers, determined by immunochemiluminescence (Cobas, Roche Diagnostics, Indianapolis, IN, USA). Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) were evaluated by ELISA. The normal ranges were free thyroxine 0.9–1.7 ng/dl; free triiodothyronine 2.0–4.4 pg/ml; TSH 0.3–4.2 μU/ml; TG antibodies < 115 IU/ml; TPO antibodies < 34 IU/ml; RF ≤ 20 IU/ml; and anti-CCP ≤ 5 IU/ml. Diagnosis of autoimmune thyroiditis was made in the presence of elevated TPO antibodies and/or TG antibodies values and of a typical pattern of the thyroid ultrasound[29].

Informed consent was obtained from all subjects and the study protocol was approved by the Ethics Committee.

Statistical analysis was performed with SPSS for Windows. The chi-squared test and Fisher's exact test, when appropriate, were used to compare cases and controls. P values < 0.05 were considered statistically significant.

RESULTS

The demographic characteristics of the patients with SpA are summarized in Table 1. Among patients with PsA, 35 had spondylitis, 38 symmetric polyarthritis, 18 asymmetric oligoarthritis, 13 arthritis with predominant interphalangeal joint involvement, and 4 arthritis mutilans, according to the Moll and Wright classification[30]. Moreover, 6 had PsA "sine psoriasis" (4 of these among patients with arthritis with predominant interphalangeal joint involvement and 3 with spondylitis), according to Scarpa, *et al*[31]. In addition, among patients with EA, 44 had Crohn's disease and 28 had ulcerative colitis.

One hundred forty-five out of 357 patients with SpA had axial and 212 peripheral involvement. Ninety-nine of these were classified in the oligoarticular and 113 in the polyarticular subset (Table 1).

Disease duration and disease activity are summarized in Table 1 for all patients and for each group of SpA.

SpA group. HT (TG antibodies and/or TPO antibodies positivity and ultrasonographic diagnosis of thyroiditis) was significantly more frequent in patients with SpA than in controls (24.09% vs 10.69%, respectively; p < 0.05; Table 2). The OR for patients with SpA compared to controls was 2.65 (95% CI 1.72–4.08) for HT, 2.77 (95% CI 1.77–4.35) for TPO antibody positivity, and 2.47 (95% CI 1.75–3.50) for hypoechoic pattern. Among these patients, HT was more frequent in women (68.60%) than men (31.40%; p < 0.05).

Patients with a disease duration > 2 years had a higher prevalence of HT and TPO antibodies positivity than patients with a disease duration ≤ 2 years (79.07% vs 20.93%, respectively; p < 0.05; Table 3). Compared to patients with SpA with duration ≤ 2 years, the OR for patients with disease duration > 2 years of having HT was 3.38 (95% CI 1.91–5.99) and for TPO antibodies positivity was 3.89 (95% CI 2.11–7.15).

Moreover, in patients with phSpA, a higher prevalence of HT was found in patients with an active disease (DAS28 > 3.2) than in those with low-moderate disease (DAS28 < 3.2; 69.49% vs 30.51%, respectively; p < 0.05). In particular, DAS < 2.6 was found in 5 patients with phSpA with HT (8.47%), DAS 2.6–3.2 in 13 patients (22.04%), DAS 3.2–5.1 in 32 (54.24%), and DAS > 5.1 in 9 patients (15.25%; Table 4). Compared to patients with phSpA with low-moderate disease, the OR for patients with active disease having HT was 2.69 (95% CI 1.62–4.46) and it was 3.01 for TPO antibodies (95% CI 1.78–5.10). In contrast, in patients with axSpA, no significant difference in prevalence of HT and TPO antibodies

Table 1. Characteristics of the study population.

Characteristics	SpA	PsA	USpA	ReA	EA	AS
Patients, n	357	108	85	68	72	24
Age, yrs, mean ± SD	37.86 ± 11.03	39.86 ± 10.89	35.56 ± 10.79	31.85 ± 11.69	34.65 ± 9.37	36.23 ± 10.42
Women/men	172/185	57/51	41/44	33/35	38/34	3/21
Rheumatoid factor, n (%)	41 (11.48)	14 (12.96)	11 (12.94)	12 (17.65)	3 (4.17)	1 (4.17)
Anti-CCP, no. patients (%)	12/127 (9.45)	4/37 (10.81)	3/29 (10.34)	3/28 (10.71)	1/25 (4.00)	1/8 (12.50)
Articular involvement, n (%)						
Axial	145 (40.62)	35 (32.41)	41 (48.23)	24 (35.29)	25 (34.72)	20 (83.33)
Peripheral	212 (59.38)	73 (67.59)	44 (51.77)	44 (64.71)	47 (65.28)	4 (16.67)
Oligoarticular	99 (27.73)	31 (28.70)	15 (17.65)	25 (36.76)	25 (34.72)	3 (12.50)
Polyarticular	113 (31.65)	42 (38.89)	29 (34.12)	19 (27.94)	22 (30.56)	1 (4.17)
Disease duration, yrs (%)						
Early, ≤ 2	146 (40.90)	42 (38.89)	37 (43.53)	29 (42.65)	33 (45.83)	5 (20.83)
Late, > 2	211 (59.10)	66 (61.11)	48 (56.47)	39 (57.35)	39 (54.17)	19 (79.17)
Disease activity (DAS28), n (%)						
< 2.6	21 (9.91)	7 (9.59)	5 (11.36)	4 (9.09)	5 (10.64)	0 (0.00)
2.6–3.2	89 (41.98)	27 (36.99)	17 (38.64)	22 (50.00)	21 (44.68)	2 (50.00)
3.2–5.1	77 (36.32)	30 (41.09)	17 (38.64)	14 (31.82)	15 (31.91)	1 (25.00)
> 5.1	25 (11.79)	9 (12.33)	5 (11.36)	4 (9.09)	6 (12.77)	1 (25.00)
BASDAI, n (%)						
< 4.0	79 (54.48)	21 (60.00)	20 (48.78)	15 (62.50)	16 (64.00)	7 (35.00)
> 4.0	66 (45.52)	14 (40.00)	21 (51.22)	9 (37.50)	9 (36.00)	13 (65.00)

DAS28: 28-joint count Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; anti-CCP: anticyclic citrullinated peptide antibodies. SpA: spondyloarthropathy; PsA: psoriatic arthritis; USpA: undifferentiated SpA; ReA: reactive arthritis; EA: enteropathic spondyloarthritides; AS: ankylosing spondylitis.

Table 2. Comparison of thyroid status between patients with SpA and controls. Values are number of patients (%).

Characteristics	SpA	PsA	USpA	ReA	EA	AS	Control	p*
Patients, n	357	108	85	68	72	24	318	
Thyroiditis, n (%)	86 (24.09)	28 (25.93)	21 (24.71)	16 (23.53)	17 (23.61)	4 (16.67)	34 (10.69)	0.0005[a,b,c,d,e]
TPO antibodies > 34 IU/ml and TG antibodies > 115 IU/ml	46 (13.17)	12 (11.11)	11 (12.94)	10 (14.70)	11 (15.28)	2 (8.33)	23 (7.23)	0.0155[a]
TPO antibodies > 34 IU ml	80 (22.41)	25 (23.15)	20 (23.53)	15 (22.06)	17 (23.61)	3 (12.50)	30 (9.43)	0.0005[a,b,c,d,e]
TG antibodies > 115 IU ml	51 (14.29)	15 (13.89)	12 (14.12)	11 (16.18)	11 (15.28)	3 (12.50)	27 (8.49)	0.0187[a]
Ultrasound pattern								
Thyroid nodules	163 (45.66)	52 (48.15)	39 (48.88)	29 (42.65)	32 (44.44)	11 (45.83)	177 (55.67)	NS
Hypoechoic	137 (38.37)	42 (38.89)	33 (38.82)	26 (38.24)	28 (38.89)	8 (33.33)	64 (20.13)	0.00005[a,b,c,d,e]
Thyroid volume > 20 ml	43 (12.04)	11 (10.19)	9 (10.59)	9 (13.24)	10 (13.89)	4 (16.67)	52 (16.35)	NS
TSH > 4.2 μU/ml	47 (13.16)	15 (13.89)	9 (10.59)	10 (14.71)	9 (12.50)	4 (16.67)	42 (13.21)	NS
TSH < 0.3 μU/ml	15 (4.20)	4 (3.70)	3 (3.53)	3 (4.41)	3 (4.17)	2 (8.33)	13 (4.09)	NS

* $p < 0.05$ by chi-squared test ([a] SPA vs control; [b] PsA vs control; [c] USpA vs control; [d] ReA vs control; [e] EA vs control); NS: not significant; SpA: spondyloarthropathy; TPO antibodies: antithyroid peroxidase antibody; TG antibodies: antithyroglobulin antibody; TSH: thyroid-stimulating hormone; PsA: psoriatic arthritis; USpA: undifferentiated SpA; ReA: reactive arthritis; EA: enteropathic spondyloarthritides; AS: ankylosing spondylitis.

positivity was observed between patients with active and those with low disease levels ($p = 0.245$).

Ultrasonography detected a significantly higher frequency of hypoechoic pattern in patients with SpA than in controls ($p < 0.0005$). No significant difference in thyroid blood flow was observed between patients with SpA and controls with HT.

Among patients with SpA, HT and TPO antibodies positivity were significantly more frequent in patients with peripheral involvement (68.60%) than in patients with axial involvement (31.40%; $p < 0.05$); moreover, among patients with SpA who had peripheral involvement, HT and TPO antibodies positivity were significantly more frequent in patients with polyarticular involvement than in patients with oligoarticular involvement (51.16% vs 17.44%; $p < 0.05$; Table 5).

PsA group. HT, TPO antibodies positivity, and the hypoechoic pattern were significantly more frequent in patients

Table 3. Disease duration of SpA in patients with Hashimoto's thyroiditis. Values are number of patients [no. patients with TPO antibodies positivity] (%).

Disease	Disease Duration ≤ 2 Yrs	> 2 Yrs	p*
SpA	18 [15] (20.93)	68 [65] (79.07)	< 0.0005
PsA	6 [4] (21.43)	22 [21] (78.57)	0.027
USpA	5 [4] (23.81)	16 [16] (76.19)	0.023
ReA	3 [3] (18.75)	13 [12] (81.25)	0.020
EA	3 [3] (17.65)	14 [14] (82.35)	0.006
AS	1 [1] (25.00)	3 [2] (75.00)	NS

* $p < 0.05$ by chi-squared test (disease duration > 2 yrs vs disease duration < 2 yrs). SpA: spondyloarthropathy; TPO antibodies: antithyroid peroxidase antibody; PsA: psoriatic arthritis; USpA: undifferentiated SpA; ReA: reactive arthritis; EA: enteropathic spondyloarthritides; AS: ankylosing spondylitis.

with PsA than in controls (25.93 vs 10.69%, 23.15 vs 9.43%, and 38.89 vs 20.13%, respectively; $p < 0.05$; Table 2). Compared to controls, the OR for patients with PsA having HT was 2.92 (95% CI 1.67–5.11), for TPO antibodies positivity 2.89 (95% CI 1.61–5.19), and for hypoechoic pattern 2.53 (95% CI 1.57–4.06).

Patients with PsA with a disease duration > 2 years had a higher prevalence of HT and TPO antibodies positivity than patients with a disease duration ≤ 2 years ($p < 0.05$; Table 3). Compared to patients with PsA with disease duration ≤ 2 years, the OR for patients with disease duration > 2 years having HT was 3.00 (95% CI 1.10–7.19) and for TPO antibodies positivity was 3.06 (95% CI 1.19–6.90).

Moreover, in the peripheral subset of the PsA group, a higher frequency of HT (28.87%) and TPO antibodies positivity (28.07%) was found in patients with active disease than in patients with a low-moderate disease activity level (11.86% and 10.53%, respectively; $p < 0.05$). No significant difference in prevalence of HT and TPO antibodies positivity was observed in the axial subset of the PsA group between patients with active and those with low disease levels ($p = 0.664$; Table 4).

Among patients with PsA, HT and TPO antibodies positivity were significantly more frequent in patients with peripheral involvement (85.72%) than in patients with axial involvement (14.28%; $p < 0.05$); moreover, among patients with PsA who had peripheral involvement, HT and TPO antibodies positivity were significantly more frequent in patients with polyarticular involvement than in patients with oligoarticular involvement (67.86% vs 17.86%; $p < 0.05$; Table 5).

USpA group. HT, TPO antibodies positivity, and the hypoechoic pattern were significantly more frequent in patients with USpA than in controls (24.71% vs 10.69%, 23.53% vs 9.43%, and 38.82% vs 20.13%, respectively; $p < 0.05$; Table 2). Compared to controls, the OR for patients with USpA having HT was 2.74 (95% CI 1.49–5.03), for TPO antibodies positivity 2.95 (95% CI 1.58–5.53), and for hypoechoic pattern 2.52 (95% CI 1.50–4.22).

Patients with USpA with a disease duration > 2 years had a higher prevalence of HT and TPO antibodies positivity than patients with a disease duration ≤ 2 years ($p < 0.05$; Table 3). Compared to patients with USpA with disease duration ≤ 2 years, the OR for patients with disease duration > 2 years having HT was 3.20 (95% CI 1.05–7.78) and for TPO antibodies positivity it was 4.13 (95% CI 1.24–8.68).

No statistically significant difference were observed in the prevalence of thyroiditis between peripheral (52.38%) and axial involvement (47.61%; Table 5).

ReA group. HT, TPO antibodies positivity, and the hypoechoic pattern were significantly more frequent in patients with ReA than in controls (23.53% vs 10.69%, 22.06 vs 9.43%, and 38.24 vs 20.13%, respectively; $p < 0.05$; Table 2). Compared to controls, the OR for patients with ReA having HT was 2.57 (95% CI 1.32–4.99), for TPO antibodies positivity 2.72 (95% CI 1.37–5.39), and for the hypoechoic pattern 2.46 (95% CI 1.40–4.30).

Patients with ReA with a disease duration > 2 years had a higher prevalence of HT and TPO antibodies positivity than patients with a disease duration ≤ 2 years ($p < 0.05$; Table 3). Compared to patients with ReA with disease dura-

Table 4. Disease activity of SpA (DAS28 for peripheral subset and BASDAI for axial subset) in patients with Hashimoto's thyroiditis. Values are number of patients [no. patients with TPO antibodies positivity] (%).

Disease	Disease Activity (DAS28) Low-Moderate < 2.6	2.6–3.2	Active 3.2–5.1	> 5.1	p*	Disease Activity (BASDAI) Low < 4.0	Active > 4.0	p
SpA	5 [4] (8.47)	13 [13] (22.04)	32 [31] (54.24)	9 [9] (15.22)	0.0005	12 [11] (44.44)	15 [12] (55.56)	0.245 (NS)
PsA	2 [1] (3.40)	5 [5] (8.47)	14 [13] (23.75)	3 [3] (5.06)	0.0369	2 [2] (7.41)	2 [1] (7.41)	0.664 (NS)
USpA	1 [1] (1.69)	4 [4] (6.78)	5 [5] (8.47)	1 [1] (1.69)	NS	4 [4] (14.81)	6 [5] (22.22)	0.408 (NS)
ReA	1 [1] (1.69)	1 [1] (1.69)	5 [5] (8.47)	1 [1] (1.69)	0.0301	3 [3] (11.11)	5 [4] (18.52)	0.073 (NS)
EA	1 [1] (1.69)	3 [3] (5.06)	7 [7] (11.86)	4 [4] (6.78)	0.0068	1 [1] (3.70)	1 [1] (3.70)	0.667 (NS)
AS	0 [0] (0.00)	0 [0] (0.00)	1 [1] (1.69)	0 [0] (0.00)	NS	2 [1] (7.41)	1 [1] (3.70)	0.212 (NS)

* $p < 0.05$ by chi-squared test (low-moderate disease vs active disease). SpA: spondyloarthropathy; DAS28: 28-joint count Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; TPO antibodies: antithyroid peroxidase antibody; PsA: psoriatic arthritis; USpA: undifferentiated SpA; ReA: reactive arthritis; EA: enteropathic spondyloarthritides; AS: ankylosing spondylitis; NS: not significant.

Table 5. Articular involvement of SpA in patients with Hashimoto's thyroiditis. Values are number of patients [no. patients with TPO antibodies positivity] (%).

Disease	Articular Involvement					
	Axial	Total	p†	Peripheral Poly	Oligo	p*
SpA	27 [23] (31.40)	59 [57] (68.60)	0.0457	44 [42] (51.16)	15 [13] (17.44)	< 0.0005
PsA	4 [3] (14.28)	24 [22] (85.72)	0.0173	19 [19] (67.86)	5 [3] (17.86)	0.0089
USpA	10 [9] (47.61)	11 [11] (52.38)	NS	8 [8] (38.10)	3 [3] (14.28)	NS
ReA	8 [7] (50.00)	8 [8] (50.00)	NS	5 [5] (31.25)	3 [3] (18.75)	NS
EA	2 [2] (11.76)	15 [15] (88.24)	0.0122	11 [11] (64.71)	4 [4] (23.53)	0.0126
AS	3 [2] (75.00)	1 [1] (25.00)	NS	1 [1] (25.00)	0 [0] (0.00)	NS

$p < 0.05$ by chi-squared test (†axial involvement vs peripheral involvement; * polyarticulr involvement vs oligoarticular involvement). SpA: spondyloarthropathy; TPO antibodies: antithyroid peroxidase antibody; PsA: psoriatic arthritis; USpA: undifferentiated SpA; ReA: reactive arthritis; EA: enteropathic spondyloarthritides; AS: ankylosing spondylitis; NS: not significant.

tion ≤ 2 years, the OR for patients with disease duration > 2 years having HT was 4.33 (95% CI 1.10–9.02) and for TPO antibodies positivity it was 4.44 (95% CI 1.13–9.45). Moreover, in the peripheral subset of the ReA group, a higher frequency of HT (10.16%) and TPO antibodies positivity (10.16%) was found in patients with active disease than in patients with low-moderate disease activity (3.38% and 3.38%, respectively; $p < 0.05$). No significant difference in the prevalence of HT and TPO antibodies positivity was observed in the axial subset of the ReA group between patients with active and those with low disease levels ($p = 0.073$; Table 4).

No statistically significant differences were observed in the prevalence of thyroiditis between peripheral (50%) and axial involvement (50%; Table 5).

EA group. HT, TPO antibodies positivity, and the hypoechoic pattern were significantly more frequent in patients with EA than in controls (23.61 vs 10.69%, 23.61 vs 9.43%, and 38.89 vs 20.13%, respectively; $p < 0.05$; Table 2). Compared to controls, the OR for patients with EA having HT was 2.58 (95% CI 1.35–4.94), for TPO antibodies positivity 2.97 (95% CI 1.53–5.75), and for the hypoechoic pattern 2.53 (95% CI 1.46–4.37).

Patients with EA with a disease duration > 2 years had a higher prevalence of HT and TPO antibodies positivity than patients with a disease duration ≤ 2 years ($p < 0.05$; Table 3). Compared to patients who had EA ≤ 2 years, the OR for patients with disease duration > 2 years having HT was 5.60 (95% CI 1.10–9.02) and for TPO antibodies positivity it was 5.60 (95% CI 1.44–9.71).

Moreover, in the peripheral subset of the EA group, a higher frequency of thyroid autoimmunity (18.64%) and TPO positivity (19.29%) was found in patients with active disease than in patients with low-moderate disease activity (6.77% and 5.26%, respectively; $p < 0.05$). No significant difference in prevalence of HT and TPO antibodies positivity was observed in the axial subset of the EA group between patients with active and low disease levels ($p = 0.667$; Table 4).

Among patients with EA, HT and TPO antibodies positivity were significantly more frequent in patients with peripheral involvement (88.24%) than in patients with axial involvement (11.76%; $p < 0.05$); among patients with EA with peripheral involvement, HT and TPO antibodies positivity were significantly more frequent in patients with polyarticular involvement than in patients with oligoarticular involvement (64.71% vs 23.53%; $p < 0.05$; Table 5).

AS group. Compared to controls, no statistically significant differences in the prevalence of thyroid autoimmunity, TPO antibodies positivity, and ultrasound pattern were observed in this group.

DISCUSSION

The association of HT with rheumatic diseases is well known and the most commonly described association is with RA, SLE, and Sjögren's syndrome (SS)[3,4,5,6,7,8,9,32,33]. Bianchi, *et al* showed a 2 to 4-fold increase in the prevalence of thyroid antibodies in rheumatologic disorders as compared to the general population[22]. In patients with SLE and RA, many authors recognized a prevalence of thyroid antibodies ranging from 9% to 37%[34,35,36,37]; specifically, Chan, *et al* reported positive TPO antibodies in 23% of patients with SLE and 11% of patients with RA, in a study population of 133 women (69 with SLE, 64 with RA)[5]. Recently, Lazurova, *et al* reported in patients with SLE and RA a prevalence of HT of 24%, that is, higher than reported in previous studies[38]. Concerning RA, Silman, *et al* also reported a high frequency of HT not only in patients with RA but also in their families[39].

In a population of subjects with SS, Perez, *et al* found autoimmune thyroiditis in 24% of patients, TPO antibodies positivity in 45%, and TG antibodies positivity in 18%[3]; Punzi, *et al* described in patients with SS a higher frequency of thyroid antibodies than in patients with RA[40]. Jara, *et al*, in a review analyzing the association between HT and SS, reported that HT occurs in more than one-third of patients with SS, and that SS is present with similar frequency in those with HT[8].

In patients with SpA, data regarding the frequency of HT

are lacking. Antonelli, *et al* recognized a significantly higher prevalence of HT in men and women with PsA and of clinical hypothyroidism in women with PsA as compared to the general population[28]. In contrast, Gul, *et al*, reported no difference in the prevalence of thyroid autoimmunity in a cohort of patients with psoriasis[41].

HT is known to be an extraintestinal complication of inflammatory bowel disease, and the increased prevalence of thyroid antibodies in patients with ulcerative colitis has been reported to range from 0.82%[42] to 3.7%[43]. Morphological and immunological abnormalities of the thyroid have been observed with high frequency in Crohn's disease[44]; thyroid enlargement has been reported in 62%–70% of patients with Crohn's disease, with thyroid antibody positivity in 12.5%–14.8%[44,45]. Nevertheless, there are no data about the frequency of HT in patients with EA.

Lange, *et al*, in a study performed on a cohort of women, reported a high prevalence of thyroid antibodies in patients with AS[46].

To our knowledge, ours is the first study evaluating the prevalence of HT in a cohort of patients with SpA. We found a significantly high prevalence of thyroid autoimmunity as compared to controls, not only in patients with PsA[28] but also globally among the patients with SpA.

Our results show that autoimmune thyroiditis occurs more frequently in all subsets of SpA, with the exception of AS. In the AS group the number of patients was very small and all patients with HT were men; there is a single study reporting a high prevalence of HT in patients with AS, but it was performed in a cohort of women[46].

In our experience, TPO antibodies positivity occurs more frequently in patients with a long disease duration and active rheumatic disease than in the other patients; this suggests a possible relationship between the maintenance of the inflammatory process in patients with SpA and the positivity of TPO antibodies.

Further, in our study, patients with SpA, and in particular patients with PsA and EA who had thyroiditis, show a peripheral involvement, with a significantly high prevalence of polyarticular joint involvement. The last point suggests that in this subset of SpA the autoimmune thyroid pattern may contribute to the development of a polyarticular joint involvement as it occurs in rheumatic manifestations related to thyroid autoimmunity[7,18].

SpA and HT are complex diseases believed to result from the combined effects of genetic and nongenetic factors. Among genetic factors, HLA class II genes are relevant, considering that the corresponding gene products are aberrantly expressed in tissue samples from both diseases; moreover, only some HLA class II genes (and therefore, HLA class II proteins) predispose to these diseases. Indeed, HLA-DR is associated with both HT[47] and SpA, and specifically with peripheral arthritis in patients with PsA[48] and patients with EA[49]. Another genetic factor that may also play a role is the *CTLA4* gene, a non-HLA gene, which is reported to be associated with HT[50] and recently also with SpA[51]. Among nongenetic factors, environmental influences such as negative life events causing stress, chemical pollutants, and exposure to a number of microorganisms seem to be relevant.

Among microorganisms, *Yersinia enterocolitica* provides a good model of interaction between genetic and nongenetic factors in both HT[52,53] and SpA[54]. The mechanism for this interaction is molecular mimicry.

Nevertheless, at present there is no clear explanation for the coexistence of HT and SpA; therefore, new studies or longer followup might be useful to clarify the etiology of this association. Our study demonstrates that autoimmune thyroiditis occurs in patients with SpA, with a prevalence higher than expected. Thus our results indicate that thyroid function tests could be part of the clinical and laboratory evaluation in patients with SpA.

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