Frequency of rheumatoid arthritis in patients with autoimmune thyroid disease: a case–control study

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Introduction
Hashimoto's thyroiditis and Graves' disease both constitute autoimmune thyroid diseases (AITD) that frequently coexist with other autoimmune disorders (AID). This study was conducted to evaluate the frequency of rheumatoid arthritis (RA) in patients diagnosed with AITD in relation to the general population.
Patients and methods
This was a cross-sectional case–control study, conducted on 103 patients with AITD of either Hashimoto's thyroiditis or Graves' disease with positive antithyroid peroxidase (TPOAb). A group 100 volunteers, matched for age and sex, with normal thyroid function and negative history of AID, were investigated for the prevalence of RA in the general population (control group). Participants in the study were tested for thyroid profile, rheumatoid factor (RF), erythrocyte sedimentation rate, and C-reactive protein. When appropriate, anticitrullinated peptide antibody was checked.
Results
Patients with AITD had a higher frequency of RA than the control (P=0.031). Thyroid profile showed no significant difference between patients with and without RA within the group of AITD. In that group, a positive correlation between titers of both RF and TPOAb was observed (r=0.474, P<0.001). The coexistence of RA with AITD was noticed to be associated with higher RF, C-reactive protein, and TPOAb titers as well as. the presence of type 2 diabetes mellitus, other AID and family history of RA.
Conclusion
RA is more prevalent in patients with AITD than the general population, and the underlying autoimmunity is likely to be the link. Our data highlight the importance of screening thyroid patients for RA especially if present with type 2 diabetes mellitus, another AID, or having a family history of RA.

Keywords:
autoimmune, thyroid, rheumatoid arthritis

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Introduction

Patients with autoimmune thyroid diseases (AITD), namely Graves' disease and Hashimoto's thyroiditis, are at increased risk of developing other autoimmune diseases (AID) [1]. In particular, the association between thyroid disease and rheumatoid arthritis (RA) has been recognized [2]. Furthermore, the manifestations of both diseases occasionally overlap and mimic each other [3]. Most of the researchers evaluated the occurrence of thyroid disorders in the context of RA showing high prevalence [4–6]. Furthermore, patients with RA were found to be at three times higher risk of having thyroid autoantibodies than healthy controls [7].

In the other direction, a few studies have been designed to probe the prevalence of RA in patients with AITD [8,9].

In general, the concept of polyautoimmunity has been widely accepted, and the 'preclinical screening' of patients with AITD for secondary AID is highly recommended [10,11].

The aim of this study was to estimate the frequency of RA in patients with AITD in relation to the healthy control.

Patients and methods

This cross-sectional, case–control study was conducted over a year on 103 patients with AITD attending the outpatient clinic at Al-Azhar University Hospital, New Damietta, Egypt for a routine follow-up. Of these, 79 patients had Hashimoto's thyroiditis, and 24 had Graves' disease. Well-controlled (or with borderline biochemical

control) patients already diagnosed to have Graves' or hypothyroidism with positive antithyroid peroxidase antibodies (TPOAb) (measured by chemiluminscence, Siemens Healthcare Products Ltd, Surrey, UK) were included in the study. Conversely, those who had undergone thyroidectomy were excluded. A group of 100 volunteers, matched for age and sex, with normal thyroid function and without a history of AID, were tested for the prevalence of RA in the general population.

All included patients completed a structured questionnaire seeking a personal and family history of common AID, including RA, as well as history of thyroid disorders. A full clinical examination stressing on the signs of RA was performed. The Disease Activity Score 28 was calculated for patients diagnosed to have RA.

The participants of the study were tested for the serum levels of thyroid stimulating hormone, free triiodothyronine, free thyroxine, and rheumatoid factor (RF; Omega Diagnostic, Alva, Scotland, UK), in addition to erythrocyte sedimentation rate and C-reactive protein (CRP; Omega Diagnostic).

Anticitrullinated peptide antibody (Diametra, Spello PG, Italy) was done only for suspicious rheumatoid cases who showed negativity for RF. Levels above 10 IU/ml were considered positive. Diagnosis of RA was achieved by a specialist based on the 2010 ACR/EULAR classification criteria [12].

All statistical calculations were performed using SPSS, version 19 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as the mean±SD, and analyzed by the independent sample paired *t*-test. In contrast, qualitative data were expressed as number and percentage, and analyzed by χ^2-test. The correlation was done using Pearson's correlation test. *P* value was considered significant if less than 0.05.

Ethical approval

The study was approved by the Local Research Ethics Committee of the Faculty of Medicine, Al-Azhar University. A written informed consent was provided by all the participants, and the study was conducted according to the Declaration of Helsinki.

Results

The study enrolled 103 patients (86 women and 17 men) with an AITD of either Hashimoto's thyroiditis (*n*=79) or Graves' disease (*n*=24) and 100 volunteers. The mean age of the thyroid group was 39.29±10.09 years, and the duration of the thyroid disease ranged from 3 months to 9 years (Tables 1 and 2).

Eleven (10.7%) patients with AITD were found to have RA. This was significantly higher than that of the control group (3%). The Disease Activity Score 28-CRP was nearly comparable (4.95 and 3.85, respectively). Three rheumatoid cases in Hashimoto' subgroup were negative for RF, but they revealed anticitrullinated peptide antibody positivity with the following titers: 86, 68, and 76 IU/ml. Conversely, positive RF was the role in all Graves' patients with RA.

The occurrence of RA arthritis was associated with a longer thyroid illness duration, higher erythrocyte sedimentation rate, higher TPOAb, RF, and CRP titers, and with the existence of positive RF, type 2 diabetes mellitus (T2DM), other AID, and family history of RA (Tables 2 and 3). In that context,

Table 1 Comparison between cases with autoimmune thyroid diseases and control group

	Cases with AITD (*n*=103) (mean±SD)	Control group (*n*=100) (mean±SD)	*t* (χ^2)	*P*
Age (years)	39.29±10.09	41.51±8.78	1.673	0.096
Sex (male/female)	17/86	18/82	0.079	0.778
Cases of RA [*n* (%)]	11 (10.7)	3 (3)	4.660	0.031*
T2DM (*n*)	13	8	1.168	0.28
HTN (*n*)	10	14	0.896	0.344
Other autoimmune diseases (*n*)	9	4	1.9	0.168
Family history of thyroid disease (*n*)	48	13	27.25	<0.001*
Family history of RA (*n*)	7	2	2.755	0.097
Positive RF (*n*)	10	4	2.575	0.109
ESR – first hour (mm)	22.71±20.45	20.28±16.51	0.929	0.354
Total CRP	11.13±10.61	4.55±2.26	2.612	<0.001*
Positive CRP (*n*)	70	11	68.65	<0.001*
TSH	5.60±5.96	2.08±0.86	5.931	<0.001*

AITD, autoimmune thyroid diseases; CRP, C-reactive protein (N: 6 mg/dl); ESR, erythrocyte sedimentation rate; HTN, hypertension; RA, rheumatoid arthritis; RF, rheumatoid factor (N<8 IU/l); T2DM, type 2 diabetes mellitus; TSH, thyroid stimulating hormone (N: 0.3–5.0 mIU/l).
*Significant *P*<0.05.

however, there was no significant difference between Graves' disease and Hashimoto's thyroiditis (Table 4).

Out of nine thyroid patients who experienced the coexistence of another AID, vitiligo was present in six cases. The other three patients had a documented premature ovarian failure, idiopathic thrombocytopenic purpura, or bullous pemphigoid.

On testing the correlation between the titers of both RF and TPOAb in a cohort of thyroid population, we found a significant positive correlation (r=0.474, P<0.001) (Fig. 1). Similar correlations were found in the subgroups of Hashimoto's thyroiditis and Graves' disease (r=0.363, P<0.001, r=0.766, P<0.001, respectively).

Discussion

In this study, the prevalence of RA in patients with AITD was 10.7%, and this was significantly higher than that found in healthy control. The coexistence of both disorders may imply their tendency to overlap due to similar immunological mechanisms and genetic susceptibility [13].

Although the close association between AITD and RA has been well acknowledged, the prevalence of RA among patients with AITD varies considerably. In a study of Boelaert *et al.* [11], RA was prevalent in 3.15% of patients with Graves' disease and 4.24% of patients with Hashimoto's thyroiditis. In a Colombian study, however, AITD was coexisting with RA in as high as 21% of cases [14]. This suggests the role of environmental factors or ethnic variability.

It has previously been proposed that the link between AITD and RA may be attributed to the underlying thyroid dysfunction. In our results, however, there were no significant differences concerning the levels of thyroid stimulating hormone, free triiodothyronine, and free thyroxine between rheumatoid and nonrheumatoid thyroid patients. Thus, it seems likely that autoimmunity, rather than a direct action of the thyroid hormones, is responsible for that link [15].

Table 2 Demographic and clinical features of thyroid patients with and without rheumatoid arthritis

	Rheumatoid arthritis (mean±SD)		t (χ^2)	P
	Positive (n=11)	Negative (n=92)		
Age (years)	42.27±9.30	38.93±10.17	1.037	0.302
Total small joint arthritis	5.73±1.85	0.11±0.52	10.031	<0.001*
Total big joint arthritis	3.00±1.00	0.26±0.74	11.164	<0.001*
Duration of thyroid disease (months)	78.09±63.88	42.73±39.54	2.603	0.011*
Duration of RA (months)	21.50±8.60	–	–	–
Hashimoto'/Graves' (n)	8/3	71/21	0.109	0.742
Sex (male/female)	1/10	16/76	0.491	0.483
Goiter [n (%)]	9 (81.8)	70 (76.1)	0.181	0.671
Other autoimmune diseases [n (%)]	3 (27.3)	6 (6.5)	5.305	0.02*
HTN [n (%)]	2 (18.2)	8 (8.7)	1.009	0.315
T2DM [n (%)]	5 (45.5)	8 (8.7)	12.038	0.001*
Family history of thyroid disease [n (%)]	3 (27.3)	45 (48.9)	1.849	0.174
Family history of RA [n (%)]	6 (54.5)	1 (1.1)	44.328	<0.001*

HTN, hypertension; RA, rheumatoid arthritis; T2DM, type 2 diabetes mellitus. *Significant P<0.05.

Table 3 Laboratory findings of thyroid patients with and without rheumatoid arthritis

	Rheumatoid arthritis (mean±SD)		t (χ^2)	P
	Positive (n=11)	Negative (n=92)		
TSH	7.89±7.60	5.33±5.72	1.354	0.179
FT3	4.53±2.52	4.19±1.78	0.577	0.565
FT4	13.93±9.12	13.59±7.57	0.137	0.892
TPOAb	317.55±66.75	119.67±81.76	7.715	<0.001*
Total RF	87.75±12.26	4.51±1.68	19.2	<0.001*
Positive RF [n (%)]	8 (72.7)	2 (2.17)	55.79	<0.001*
ESR – first hour (mm)	73.73±20.75	16.61±8.32	9.045	<0.001*
Total CRP	32.82±15.36	8.53±6.04	5.194	<0.001*

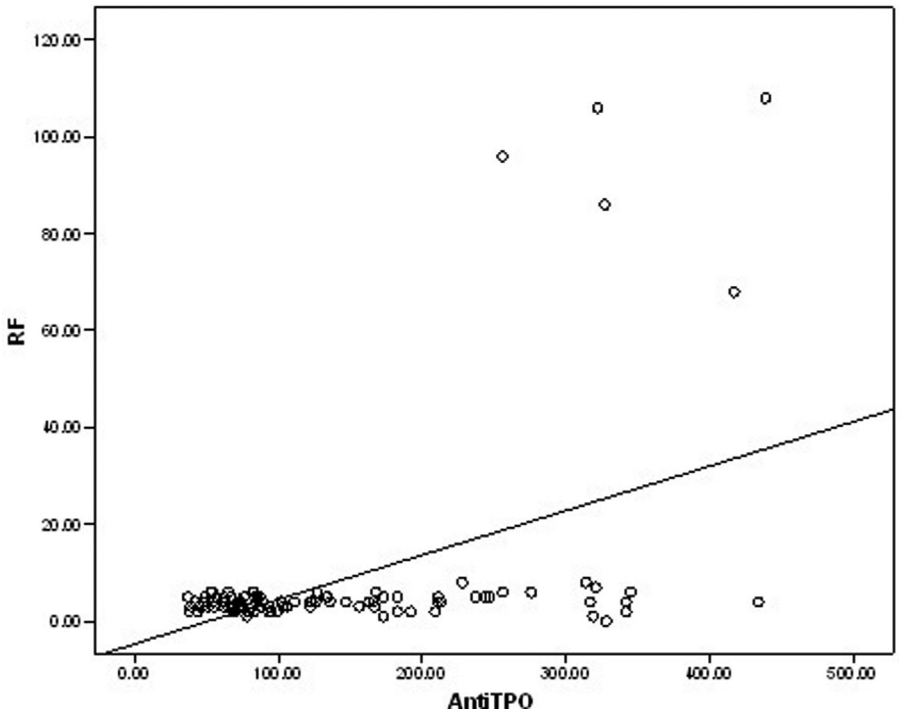
CRP; C-reactive protein (N<6 mg/dl); ESR, erythrocyte sedimentation rate; FT3, free triiodothyronine (N: 3.5–6.5 pmol/l); FT4, free thyroxine (N: 10–23 pmol/l); RF; rheumatoid factor (N<8 IU/l); TPOAb, thyroid peroxidase antibodies (N<35 UI/ml); TSH, thyroid stimulating hormone (N: 0.3–5.0 mIU/l). *Significant P<0.05.

Table 4 Characteristics and comparison of thyroid subgroups

	Hashimoto' (*n*=79) (mean±SD)	Graves' (*n*=24) (mean±SD)	*t* (χ^2)	*P*
Age (years)	39.49±10.28	38.63±9.65	0.368	0.714
Cases of RA [*n* (%)]	8 (10.12)	3 (12.5)	0.109	0.742
RF-positive RA (*n*)	5	3	0.126	0.938
Total small joint arthritis	0.67±1.95	0.83±1.76	–0.365	0.716
Total big joint arthritis	0.56±1.16	0.54±1.10	0.057	0.955
Duration of thyroid (months)	47.46±43.93	43.38±44.03	0.399	0.691
Duration of RA (months)	1.39±5.73	1.45±5.18	–0.044	0.965
TPOAb	142.27±101.66	136.00±100.16	0.265	0.791
Total RF	6.75±15.54	13.04±28.99	–1.020	0.317
ESR – first hour (mm)	21.68±18.30	26.08±26.52	–0.922	0.358
Total CRP	10.87±10.83	11.98±10.00	–0.447	0.656
Positive CRP (*n*)	54	16	0.024	0.877

CRP, C-reactive protein (N<6 mg/dl); ESR, erythrocyte sedimentation rate; RA, rheumatoid arthritis; RF, rheumatoid factor (N<8 IU/l); TPOAb, thyroid peroxidase antibodies (N<35 UI/ml).

Figure 1



Correlation between rheumatoid factor (RF) and thyroid peroxidase (TPO) antibody titers in patients with autoimmune thyroid disease (r=0.474, P<0.001).

The above explanation is supported by evidence denoting the occurrence of rheumatic diseases even in 'euthyroid AITD', or that they are more frequent in 'autoimmune' thyroid patients rather than those having other thyroid etiologies [16–18].

From the pathological point of view, it has been suggested that a polyclonally accelerated production of autoantibodies by both thyroid and immune cells may be the mechanism responsible for the coexistence of non-organ-specific autoantibodies with AITD [19]. In other words, the overlap of autoantibodies may be clarified by a malfunctioning T-cell and B-cell regulation causing reactions against autoantigens producing RF and thyroid autoimmunity [1].

In that context, we observed a positive correlation between titers of both RF and TPOAb in thyroid patients (r=0.474, P<0.001). This correlation continued in Hashimoto's and Graves' subgroups (r=0.363, P<0.001, r=0.766. P<0.001, respectively). In addition, patients with RA showed higher TPOAb titers than those without rheumatoid (P<0.001, respectively).

Supportive data for this close association came from the study of Cárdenas Roldán *et al.* [20], who studied

patients with RA, and observed that 37.8% were positive for TPOAb and 20.8% for antithyroglobulin antibodies. Similar findings were reported in the study of Atzeni *et al.* [21]. Furthermore, a significant positive correlation between TPOAb and even rheumatoid activity has been observed [22].

In our results, more than half of the thyroid patients diagnosed to have RA had told a positive family history of RA ($P<0.001$). Also, they showed a higher frequency of other AID than non-RA patients ($P=0.021$).

In the study of Rojas-Villarraga *et al.* [14], familial autoimmunity was a risk factor for polyautoimmunity. Moreover, Trbojević *et al.* [23] reported the co-occurrence of AID in family groups and the transition from one clinical picture to another within the same individual over time. Also, the results of Boelaert *et al.* [11] were in agreement of that.

On comparing Graves' disease with Hashimoto's thyroiditis in our study, there was no significant difference regarding the prevalence of RA. Conversely, the study of Wiebolt *et al.* [24] reported a markedly higher clustering of additional autoimmunity in Hashimoto's rather than Graves' disease. However, this study targeted a wide scale of AID such as celiac disease, adrenal, β-cell, gastric, and adrenal autoimmunity.

Another important point in our results to be addressed is the high prevalence of T2DM in patients having both thyroid and RA diseases (45%). Actually, the relationship between T2DM and either RA or AITD has also been extensively studied. In a recent Danish study, the prevalence of diabetes mellitus in patients with RA was significantly increased versus that expected from the general population. The risk increased for those having rheumatoid for more than 4 years [25]. Interestingly, the risk seems to be extended to both types of diabetes mellitus [26,27].

In contrast, there is also evidence to suggest an association between AITD and T2DM [28,29]. Sarfo-Kantanka *et al.* [30] observed a high prevalence of thyroid autoimmunity in Ghanaian patients with T2DM. He added that thyroid autoimmunity in T2DM patients was significantly associated with poor glycemic control.

Conclusion

Patients with AITD had an increased risk of developing RA than the general population. The absence of a significant biochemical difference between thyroid patients with and without RA regarding the thyroid profile, together with the positive correlations between their autoantibodies, indicates an underlying immune mechanism. The risk of coexistence of RA with thyroid autoimmunity was augmented with higher titers of RF, CRP, and TPOAb, and was associated with the presence of T2DM, another AID, and a family history of RA.

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Conflicts of interest

There are no conflicts of interest.

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