Prevalence of Auto Immune Thyroid Diseases in Rheumatoid Arthritis Patients

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Abstract*:* **Background:** The coexistence of thyroid autoimmunity and rheumatoid arthritis has been evaluated by many researches. RA patients had a three times higher risk of having thyroid autoantibodies than healthy population. *Objective:* To determine whether autoimmune thyroid disease is more prevalent in patients with rheumatoid arthritis compared to the control group. *Methods*: Forty patients diagnosed with RA and forty healthy control were included. They were subjected to full history taking, complete physical examination, laboratory investigations, and Radiological investigations. Bivariate, and multivariate analysis were used to evaluate the association between thyroid dysfunction, AITD and RA. **Results**: In our population AITDs was more prevalent in RA patients compared to the control group (7.5*vs* 2.5%). Subclinical hypothyroidism was the most common disorder found in (7.5%) patients. The presence of anti-TPO antibodies was 6 (15%), and anti-TG antibodies was 8 (20%) in RA patients compared to only one (2.5%) in control participants, ($P < 0.05$). However, thyroid function between studied groups showed significant high TSH in RA group compared to control. **Conclusions***:* Thyroid dysfunction and AITD are common in RA patients, with subclinical hypothyroidism being the most common disorder prevalent in 7.5% of patients. In addition the AITD prevalence in RA patients was 7.5% (n=3) in the present study. Higher prevalence of autoimmune thyroid disorder between RA patients in comparison with controls indicates the need for screening not only of thyroid hormone function, but also of the presence of autoimmune thyroid disorder marker (ATPO and ATG antibodies).

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Introduction

Recently, rheumatic diseases are reported to be the second greatest cause of disability in the world and the fourth greatest impact on the overall health[1]. Rheumatoid arthritis (RA) is a chronic multisystem autoimmune disorder of unknown etiology. In Europe, it has an incidence of approximately 1%. It is more common in women[2]**.** Abnormal autoimmune response, genetic susceptibility, biological factors such as hormonal changes or viral infection and some environmental are known to trigger RA[3, 4]. The synovial membrane is the primary target of the inflammatory process which lead to cartilage and bone destruction[5]. However, the corresponding systemic inflammation may result in disorders of multiple organ systems evolving extra-articular manifestations[6]. The evolution of RA is highly variable. Some patients may have only a short-term process oligoarticular with minimum lesion, while others suffers a polyarthritis evolving with progressive and continuous involvement of other organ systems[7]**.** Rheumatoid arthritis is commonly seen with thyroid hormone autoantibodies and thyroid dysfunction[8, 9]**.** Joint symptoms can be a manifestation of hypothyroidism; physicians might consider whether it could be an early manifestation of RA [10]**.**

Autoimmune thyroid disease (AITD) is a term referred to who has thyroid dysfunction and an autoimmune response against this endocrine organ as its hallmark[11, 12]. Thyroid autoimmunity, which is the most common immune-mediated disease, is frequently together with other organ as well as non organ-specific autoimmune disorders. Meanwhile, rheumatoid arthritis (RA) is a chronic immune-mediated inflammatory disorder that mainly results in cartilage destruction as well as synovial joint inflammation, both the adaptive and innate immune responses involve in the progression of this disease. Considering that autoimmune elements may be common characteristics of thyroid autoimmunity and RA, it is likely that both disorders may coexist within some patients[13]. Thyroid abnormal function and /or autoimmune thyroid disease (ATD) are observed in 6% to 33.8% patients with rheumatoid arthritis (RA)[14]**.**

The two leading types of autoimmune thyroid disease are Hashimoto's type autoimmune thyroiditis (AIT), including the atrophic form, which presents as primary myxedema, and autoimmune thyroiditis, which is also known as Graves' disease (or Basedow's disease in a number of European countries)[15, 16].

As organ specific ADs, this group of pathologies exhibits an autoantibody profile that may be composed of (1) antibodies directed against the thyroperoxidase enzyme (TPOAb), (2) antibodies directed against thyroglobulin protein (TgAb), and (3) antibodies directed against thyrotropin receptor (TSHrAb). The antibodies can either block or enhance the receptor's activity. Furthermore, there is a T or B lymphocytic response that prevails and, ultimately, this will define the pathology that becomes manifest. In general terms, those diseases where the clinical presentation is mainly a hypothyroid state include Hashimoto's thyroiditis[17].

For several decades, the link between rheumatoid arthritis (RA) and autoimmune thyroid disease (AITD) has been an area of interest[18, 19]. The prevalence of AITD in patients suffering from RA has been evaluated and described rheumatologic and non-rheumatologic manifestations. The most common symptoms within manifestations are polyarthralgia and unclassified arthritis, which the main features of RA[20, 21]. The inverse relationship also holds true, and the incidence and prevalence of ATD is clearly increased when patients with differentiated autoimmune and connective tissue diseases are studied[22]. Therefore, the current study aim to determine whether auto immune thyroid disease is more prevalent in patients with rheumatoid arthritis compared to the control group involving age and sex-matched subjects without RA.

Subjects and Methods

Study Population

Forty consecutive patients with RA were enrolled in this study. These patients were either newly diagnosed according to the 2010 American College of Rheumatology (ACR)/EULAR RA classification criteria or had been diagnosed previously according to the ACR revised criteria of RA 1987. The study also included 40 (30 females and 10 males) apparently healthy individuals as a control group.

Clinical assessment

Assessment of medical and rheumatological history with special focus on thyroid dysfunction manifestation. General history was collected according to the sheet of rheumatology and endocrinology departments, faculty of medicine, Al-Azhar University, Damietta. Thyroid examinations, assessment of RA functional status, general and musculoskeletal System examination were also done.

Biochemical assays

Routine laboratory investigations (CBC, ESR, CRP, serum creatinine, and liver enzymes) were assessed. Immunological assessment of the rheumatoid factor was performed by using a Biotec (San Diego, USA, Genway Biotech). In addition, TSH, FT3, FT4, Anti-TG antibodies, and Anti-TPO antibodies were assayed using Enzyme-linked Immunosorbent Assays (ELISAs) method by SUNRISE TECAN device.

Radiological assessment

Colored Doppler ultrasound study of the thyroid gland for positive autoimmune thyroid antibodies cases using TOSHIBA XARIO 200 ultrasound machine. In addition, Plain x-ray, both hands AP of rheumatoid arthritis patients.

Statistical analysis

Data entry and statistical analyses were performed using SPSS (statistical package of social sciences) version 21 ***(SPSS Inc., Chicago, IL, USA by baron and Kenny 1086)***. Categorical data were expressed in number and percentage. Continuous normally distributed data were expressed in mean and standard deviation while none-normally distributed data were expressed in median and rang. The quantitative data were examined by Kolmogrov Smirnov test for normality of data. Student T test was used for continuous normally distributed data and Mann-whitney U test for none-normally distributed data. Comparing of categorical data was done using chi square test or fisher exact test used whenever appropriate. Statistical significance was set at $p<0.05$.

Results

The average age of RA patients was 45.3±11.2 years while in control participants was 40.7 ±10.9 years. Regards the sex distribution, no significant difference were found. Female: male ratio is 8: 2 in RA and 7.5: 2.5 in control group. Positive family history of RA was observed in 9.6% of participants with RA and duration of RA was ranged from 1 to 22 years (table 1).

Our results demonstrate the clinical manifestations suspecting thyroid dysfunction in RA patients (table 2), we found that menstrual dysfunction was the most common manifestations in RA patients (32.5%) while in control participants was (12.5%) with statistical difference between both groups ($p=0.028$). Weight gain was the second common manifestations in RA patients (17.5%). Clinical thyroid examination of participants indicated that RA patients compared with controls had goiter (15% vs. 5%), Cold intolerance (17.5% vs. 7.5%), and heat intolerance (7.5% vs. 2.5%).

The present study estimated significant increased TSH titre in RA group compared control group.

Whereas, T3, T4 do not show any significant difference between both groups, Fig 1. Prevalence of thyroid antibodies is shown in table 3, anti-TPO antibodies and anti-TG antibodies showed significant increased in RA patients (15% and 20% respectively) compared to only (2.5% and 2.5%) in control participants. Moreover, AITDs was more prevalent in patients with RA compared to the control group (7.5*vs* 2.5%), Fig 2. Subclinical hypothyroidism was the most common disorder found in 3 (7.5%) patients versus two (5%) control participant, graphically represented by Fig 3.

Regarding colored doppler ultrasound study of the thyroid gland show nodules for cases which have positive autoimmune thyroid antibody (Fig 4), the current study revealed in RA patients group, 4(10%) were solitary nodule, 2(5%) were multiple nodules and only one thyroid cyst as well as one show hypoechogenicity. While in control group, there is one participant have positive anti thyroid ab, with evaluation by Colored Doppler ultrasound study, there is insignificant thyroid cyst, table 4.

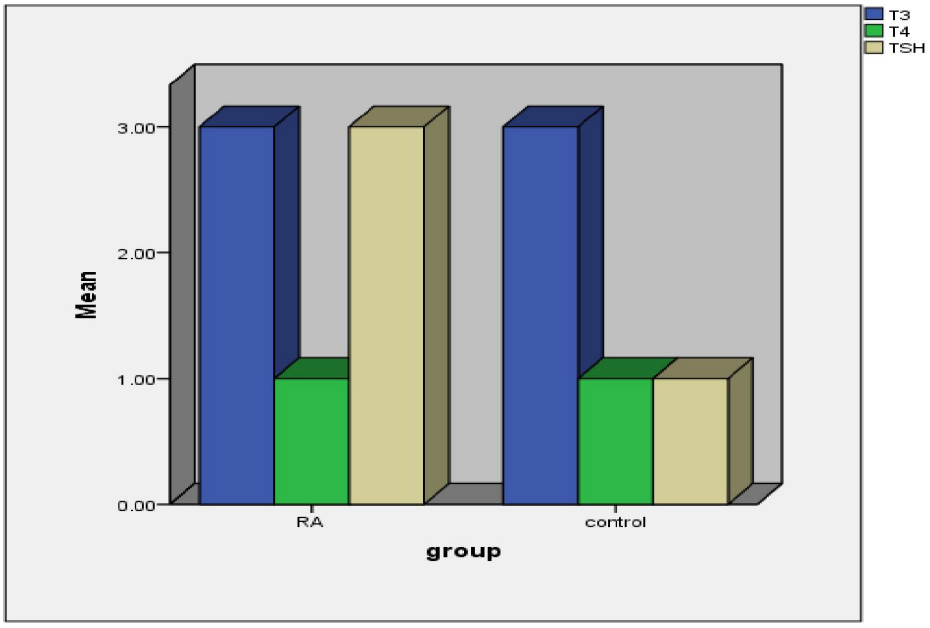

Figure 1. Mean of thyroid hormones between the studied groups

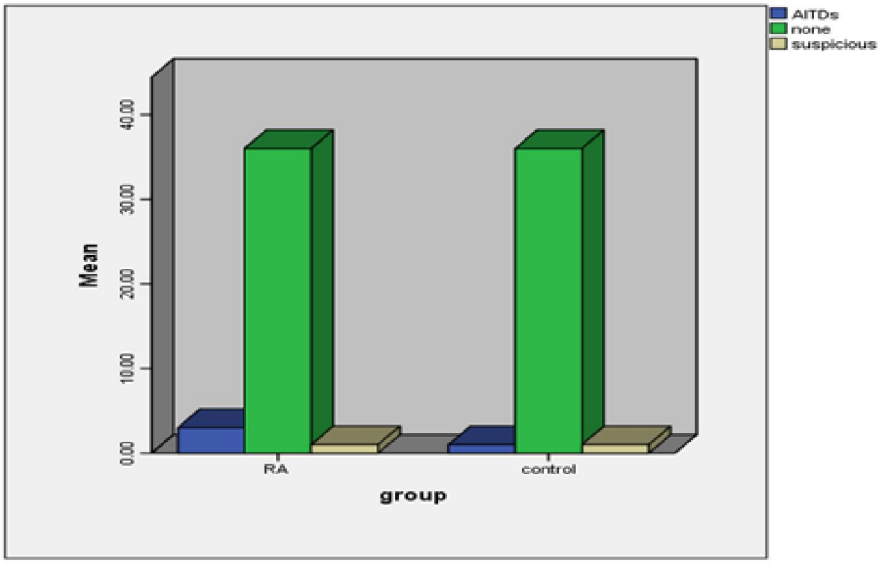

Figure 2. ATIDs prevalence in studied groups

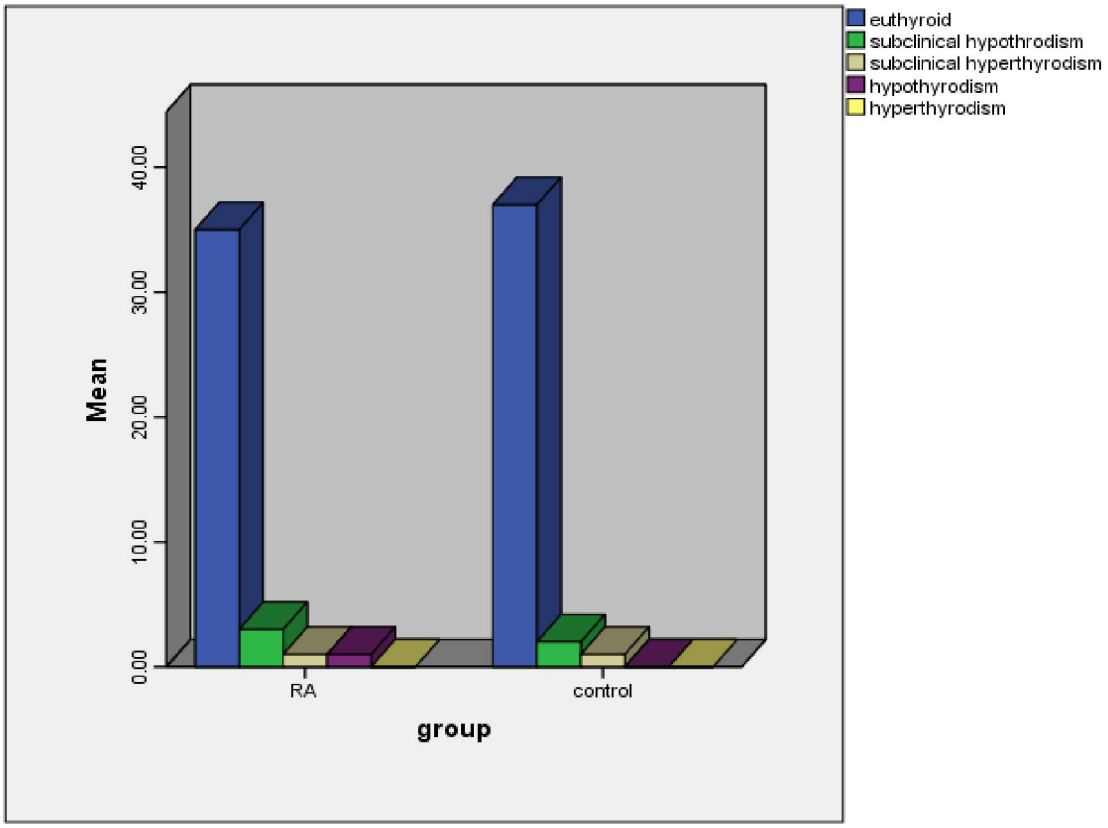

Figure 3. Mean of Thyroid function in RA patients and control groups

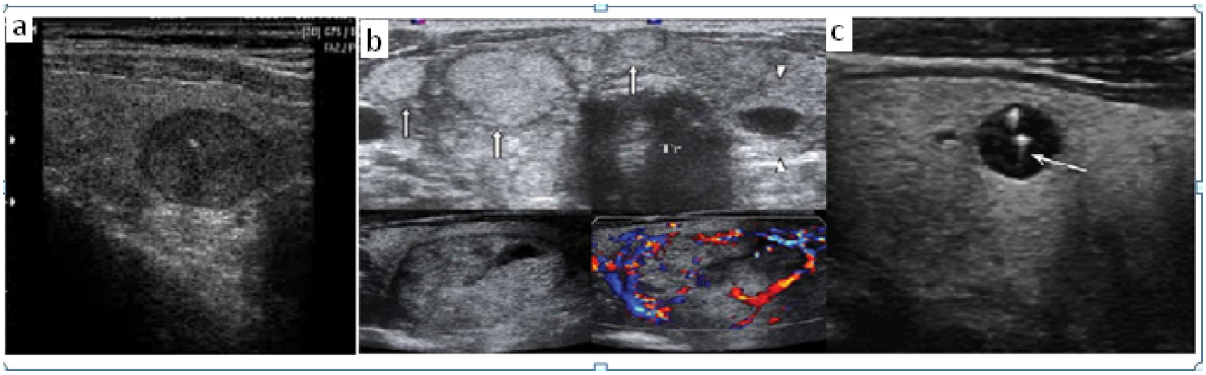

Figure 4. a)- 35 years old RA female patient shows solitary hypoechoic solid thyroid nodule. b)- 52 years RA female patient shows multiple thyroid nodules. c)- 30 years control group female shows solitary colloid Cyst.

Table (1) Demographic characteristics of the studied groups

Variable		Group1 RA (N=40)	Group2Control (N=40)	P value
Age (mean± SD)		45.3±11.2	40.7±10.9	0.068
Sex N (%)	**Female**	32(80)	30(75)	0.79
	Male	8(20)	10(25)	
Age of onset (mean± SD)		33.7±9.6	--	--
Duration of disease (mean± SD)		6.3±4.6	--	--
Positive Family history N (%)		4(9.6)	--	--

RA: rheumatoid arthritis; SD: standard deviation.

Table (2) Clinical manifestations suspecting thyroid dysfunction in both groups

Variable		RA N=40	Control N=40	P value
Goiter N (%)	Yes	6(15)	2(5)	0.079
	No	34 (85)	38(95)	
Palpitation N (%)	Yes	3 (7.5)	1(2.5)	0.721
	No	37(92.5)	39(97.5)	
Heat intolerance N (%)	Yes	3(7.5)	1(2.5)	0.069
	No	37(92.5)	39(97.5)	
Cold intolerance N (%)	Yes	7(17.5)	3(7.5)	0.721
	No	33(82.5)	37(92.5)	
Menstrual dysfunction N (%)	Yes	**13(32.5)**	5(12.5)	**0.028***
	No	27(67.5)	35(87.5)	
Tachycardia N (%)	Yes	4(10)	2(5)	0.219
	No	36(90)	38(95)	
Pregnancy loss N (%)	Yes	2(5)	0	0.701
	No	38(95)	40(100)	
Irritability N (%)	Yes	3(7.5)	1(2.5)	0.721
	No	37(92.5)	39(97.5)	
Weight gain N (%)	Yes	7(17.5)	4(10)	0.177
	No	33(82.5)	36(90)	
BMI mean±SD		35.3±4.3	37.2±2.3	0.092
Morning stiffness mean±SD		42±23.8	--	--
Tender joint count mean±SD		16±3.9	--	--
Swollen joint count mean±SD		13.2±4.8	--	--

*, significant value

Table (3) thyroid auto antibodies

Variable		RA (N=40)	Control (N=40)	P value
ATG	Positive	**8(20)**	1(2.5)	**0.016***
	Negative	32(80)	39(37.5)	
ATPO	Positive	**6(15)**	1(2.5)	**0.038***
	Negative	34(85)	39(37.5)	

Table (4) Colored Doppler ultrasound study of the thyroid gland nodule

Goiter	RA (N=40)	Control (N=40)	P value
Solitary nodule	4(10%)	0(0%)	0.131
Multiple nodules	2(5%)	0(0%)	
Cyst	1(2.5%)	1(2.5%)	
Hypoecchogenecity	1(2.5%)	0(0%)	

Discussion

Autoimmune diseases (AD) represent a spectrum of disorders caused by inflammation of organs due to production of antibodies against self-structures and cytotoxic action of T cells. Data from Europe, North America, Australia, New Zealand (defined as area 1) and Asia, Middle East, Caribbean, South America (defined as area 2) differ in the reported prevalence (cases/100,000 individuals) of rheumatoid arthritis (RA, area 1: 310–810, area 2: 120–550)[23]. RA is three times more frequent in women than men, the prevalence rises with age and is highest in women older than 65 years[24].

For several decades, an increased occurrence of thyroid disorders in patients suffering from RA has been documented—both autoimmune and non-autoimmune in nature[25]. In addition, rheumatologic and non rheumatologic manifestations of AITD have been described[21]. In addition, shared environmental factors such as smoking have been implicated in numerous studies as risk factors for AITD and for RA[12, 26].

In our cohort, forty consecutive patients (32 females and 8 males) with RA and 40 healthy individuals (30 females and 10 males) were enrolled in this study. Evaluation of clinical manifestations suspecting thyroid dysfunction in both groups showed only significant association between menstrual irregularities and RA patients. According to thyroid function tests, RA patients expresses high TSH titre while T3, T4 did not show any significant difference. This is in harmony with ***Atzeni et al., (2008)*** who detected significant elevation of TSH in RA patients when compared with control group [8]. Thyroid function test should be included in clinical evaluation of RA patients[27].

Interestingly, the current study revealed a significant high level of thyroid autoantibodies (ATG, ATPO) when compared to control group. And clarified that 15 % with RA were positive for TPOAb and 20% for TgAb This is constituted with an Italian study concluded that 37% with RA were positive for TPOAb and 23% for TgAb[8]. Moreover, ***Anoop, J., et al. (2017)*** found 32% of patients were anti TPO positive [28]. TPOAb and TgAb are known to predict AITD [29]. The different actions of the anti-thyroid antibodies resulted from differences in cellular location of the antigens, duration of antibody exposure, titers of the circulating antibodies, and immunological mechanisms in GD and Hashimoto's thyroiditis [23]. Therefore, careful estimation of specific antibodies presence should be done in patients with normal TSH.

In line with our results, Rold´an and his coworkers who determine a prevalence of 9.8% of AITD in RA subjects, a TPOAb prevalence of 37.78%, and a TgAb prevalence of 20%. Tronconi, E., et al. (2017) who subject adolescents to the studied group determined eight patients (10.1%) suffered from autoimmune thyroid disease (AITD)[30]. Although the prevalence of those autoantibodies was variable among studies but it confirm the same concept regarding the overlap relation between autoimmune diseases.

Our participants who had positive anti thyroid antibodies (ATPO, ATG) were enrolled into Colored Doppler ultrasound study. They showed nodules in both groups. In RA group, 4(10%) were solitary nodule, 2(5%) were multiple nodules and only one (2.5%) thyroid cyst as well as one (2.5%) show hypoechogenicity. While in control group, there is one participant have positive anti thyroid ab, with evaluation by Colored Doppler ultrasound study, there is insignificant thyroid cyst. This is agree with ultrasonographic features of thyroiditis were significantly evident in RA patients versus controls[31]. Thyroid abnormalities were also evaluated recently by Tekaya and his co-workers in Tunisia. They detected Thyroid abnormalities in 40% of RA patients. The mean abnormality seen was asymptomatic nodules without biological dysfunction [32].

Conclusions

Thyroid dysfunction and AITD are common in RA patients, with subclinical hypothyroidism being the most common disorder prevalent in 7.5% of patients. In addition the AITD prevalence in RA patients was 7.5% (n=3) in the present study. Higher prevalence of autoimmune thyroid disorder between RA patients in comparison with controls indicates the need for screening not only of thyroid hormone function, but also of the presence of autoimmune thyroid disorder marker (anti-TPO and ATG antibodies).

Recommendations

Thyroid dysfunction and AITD are frequent among cases with RA. We suggest that Thyroid function and antithyroid antibodies tests should be performed as part of the biochemical and immunological profile in RA patients. Treatment of both clinical and subclinical hypothyroidism should be considered in RA patients.

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