Hypothyroidism and Thyroid Antibodies in Egyptian Patients with Rheumatoid Arthritis and it's Relation to Disease Activity

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Abstract: Introduction: Autoimmune thyroid disease (AITD) is the most common organ specific autoimmune condition, affecting approximately 2% of the female population and 0.2 % of the male population. Thyroid dysfunction and autoantibodies have been frequently associated with rheumatoid arthritis (RA).Objective: To determine the association between hypothyroidism, thyroid autoantibodies with rheumatoid arthritis, and to evaluate any deviation of RA course with presence of thyroid antibodies. Methods: This study included 100 subjects, 70 of them were patients with rheumatoid arthritis diagnosed according to the EULAR/ARC 2010 revised criteria and 30 healthy controls. RA patients were subjected to a full assessment of medical and rheumatological history, and examination as well as routine laboratory tests. Patients and controls underwent thyroid function testing including thyroid antibodies. Patients disease activity was determined using the Modified Disease Activity Score and their functional status was assessed using the Modified Health Assessment Questionnaire. Results: Nineteen (27.1%) RA patients were found to have thyroid dysfunction. The most common thyroid dysfunction was hypothyroidism which was found in 15 (21.4%) RA patients; followed by subclinical hypothyroidism in 3 (4.3%) patients, whereas subclinical hyperthyroidism was present in one (1.4%) patient. Whereas among the control group one (3.33%) showed clinical hypothyroidism and one (3.33%) showed subclinical hypothyroidism. As regard thyroid autoantibodies; this study demonstrated that 25 (35.7%) of RA patients were positive for anti-TPO and 16 (22.9%) were positive for anti-TG. Three patients (10%) of the control group were positive for anti-TPO and two (6.66%) were positive for anti-TG. Conclusion: Thyroid dysfunctions are common in RA patients, with hypothyroidism being the most prevalent one. TSH has shown an evident positive correlation with RA disease activity as well as clinical and laboratory disease parameters.

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1. Introduction:

Autoimmune thyroid disease (AITD) is the most common organ specific autoimmune condition, affecting approximately 2% of the female population and 0.2% of the male population (33).

Autoimmune thyroid disease arises due to complex interaction between environmental and genetic factors, that are yet to be completely defined. AITD is multifactorial in that a genetic predisposition combines with environmental risk factors to promote disease. Early evidence that AITD has a hereditary component stems from studies of familial aggregation. Several studies of young people with AITD showed a definite genetic propensity for thyroid autoimmunity to run in families (31).

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that affects all population around the world. Women are affected 2.5 – 3 times more than men with the peak age of onset is fourth to fifth decade of life. The classic symptoms are arthritis particularly of small joints of hands and sparing the distal interphalangeal joints, and mostly in a bilateral symmetrical pattern. Systemic symptoms include fever, weight loss, malaise and fatigue which can antedate or occur with the flare of joint symptoms. Extra-articular manifestations are present in 50% of the patients, and the most common extra-articular manifestation is secondary Sjorgen's syndrome which is present in 30-40% of cases (15).

The relationship between thyroid dysfunction and rheumatoid arthritis (RA) has been a subject of debate, where several surveys suggest a relation between Hashimoto's thyroiditis and RA (32). Other studies showed that abnormal or changing thyroid status may precipitate or exacerbate musculoskeletal disease, especially when common features and symptoms for hypothyroidism such as fatigue,

malaise, dyslipidemia, and increased weight could be masked by the original RA symptoms (19).

Moreover, thyroid dysfunction was observed at least three times more often in women with RA than women with similar demographic features with non-inflammatory rheumatic diseases such as osteoarthritis and fibromyalgia (13). This was also confirmed in a more recent study in which thyroid abnormal function and/or autoimmune thyroid disease (AITD) was observed in 6-33.8 % of patients with RA, which can be attributed to the natural feature of autoimmune diseases and their tendency to ovelap (21). Frequent association with autoimmune diseases of other organs such as systemic lupus erythematosus (24), Sjogren's syndrome, scleroderma (12), and vasculitis (17) was observed. The purpose of the present study was to determine the association between hypothyroidism, thyroid auto-antibodies with rheumatoid arthritis and to evaluate any deviation of rheumatoid arthritis course with presence of thyroid antibodies.

Patients and Methods

This study was carried out on 100 subjects in the period between January 2015 to January 2016.

The subjects were divided into:

The patient group: included 70 adult rheumatoid arthritis Egyptian patients who presented to the outpatient clinics and were inpatients of the Rheumatology and Rehabilitation and Internal Medicine Departments of El Husien hospital and El Sahel Teaching hospital. These patients were either newly diagnosed according to the 2010 American College of Rheumatology (ACR)/EULAR RA classification criteria (1) or had been diagnosed previously according to the ACR revised criteria of RA 1987 (3). Exclusion criteria for our patients include: patients on medication known to cause thyroid dysfunction (e.g. lithium, amiodarone, sulfonamides, ketoconazole, Ethionamide, cytokines (as interferon alpha, tyrosine kinase inhibitors), evidence of malignancy, concurrent infection, any collagen disease other than RA, pregnant women, chronic renal diseases, diabetic patients, and patients who had undergone thyroidectomy.

The control group: included 30 healthy individuals their age and sex matched with the patient group.

Methods:

The nature of this study was explained to all participants and a verbal consent was obtained. All patients were subjected to the following:

1. **Medical and rheumatological history:**

Medical and rheumatological history was assessed with a special focus on symptoms of thyroid dysfunction (e.g. palpitation, cold intolerance, weight gain, RA disease duration, morning stiffness, tender joints, swollen joints, etc.) and history of similar conditions in the family. Medical treatment with methotrexate and/or prednisone was recorded including their current doses.

2. **General and rheumatological examination:**

Careful general and musculoskletal examination, thyroid gland examination was assessed.

3. **Assessment of disease activity:**

The disease activity was performed using the Modified Disease Activity Score (MDAS28) including 28 tender and swollen joint count scores, ESR, and the patient's subjective assessment (SA) of RA disease activity in the last 7 days record on a scale between 0 and 10, where 0 indicated 'no activity' and 10 indicated 'highest activity possible'. MDAS28 is calculated using the following formula (20):

$DAS28=0.56 \times \sqrt{(28TJC)}+0.28x \sqrt{(28SJC)} + [0.70xIn (ESR)] +0.014XPGA$

The activity score of patients is graded as follows: A score of ≤2.6 was considered to indicate remission, >2.6 and ≤3.2 as low activity, >3.2 and ≤ 5.1 as moderate activity and >5.1 as high activity (2).

4. **Assessment of disability index:**

Using the modified health assessment questionnaire (MHAQ) (18):

Each question is given a score 0-3 as shown: 0= without difficulty, 1=with some difficulty, 2=with much difficulty, and 3= unable to do.

The highest score in each item is the score for that item; the sum of the scores for the eight items is divided by eight to get the MHAQ score. MHAQ scores <0.3 are considered normal, although the average MHAQ in the general population increases with age (18).

1. Dress yourself, including trying shoelaces and doing buttons?
2. Get in and out of bed?
3. Lift a full cup or glass to your mouth?
4. Walk outdoors on flat ground?
5. Wash and dry your entire body?
6. Bend down to pick up clothing from the floor?
7. Turn taps on and off?
8. Get in and out of a car?

5. **Laboratory investigations:**

The following laboratory examinations were performed to all patients and controls:

A- Routine laboratory tests: including complete blood count (CBC), ESR in 1st hour estimated using the westergren method, quantitative C-reactive protein (CRP) titer, kidney function tests (serum creatinine), liver enzymes (ALT, AST), serum albumin, fasting blood sugar (FBS), and immunological assessment was performed for the rheumatoid factor (RF/IgM). Rheumatoid factor latex agglutination slide for the

qualitative and semiquantitative determination of RF in the serum.

B- Assessment of thyroid function was performed using the following:

1. Thyroid stimulating hormone (TSH): was measured using immunometric assays (IMMULITE 2000 Third Generation; Diagnostic Products Corporation, Los Angles, California, USA), Reference value was 0.27-4.2 IU/ml.

2. Free serum tri-iodothyronine (FT3) level was determined using IMMULITE 2000FT3, competitive, analog-based immunoassay for quantitative estimation of FT3 in serum on an IMMULITE 2000 system, Reference value was 2.57-4.43 pg/ml.

3. Free serum thyroxine level (FT4) was measured using IMMULITE 2000 FT4, solid phase chemiluminescent competitive immunoassay method for the quantitative determination of FT4 in serum on an IMMULITE 2000 system, Reference value was 0.93-1.71 ng/ml.

4. Anti-thyreoglobulin (anti-TG) antibodies and anti-thyroid peroxidase (anti-TPO) were assayed using an Immunoradiometric Assay. The reference values were less than 20 IU/ml for anti-TG antibodies and less than 35 IU/ml for anti-TPO (7).

Statistical Analysis:

All data were collected, tabulated, and statistically analysed.

Data were analyzed using the software, statistical package for social science (SPSS) version 17 as follows:

1) Description of quantitative variables as mean, SD, and range.

2) Description of qualitative variables as number and percentage.

3) The x^2-test was used to compare groups in terms of qualitative variables.

4) The Fisher exact test was used instead of x^2-test if one of the compared items (cell on excel) is less than digit 5.

5) An unpaired t-test was used to compare two groups in terms of quantitative variable.

6) P value more than 0.05 was considered insignificant, P value less than 0.05 was considered significant, and P value less than 0.001 was considered highly significant.

7) Relationship between parameters was analyzed using the Pearson correlation coefficients (r).

3. Results

This study focused on patients with RA and hypothyroidism, hence we excluded hyperthyroid patients; resulting in three subgroups: subclinical hypothyroidism, clinical hypothyroidism, and euthyroidism.

1. Clinical hypothyroidism: was defined by a documented medical history of hypothyroidism. Clinical hypothyroidism it was indicated by increased serum TSH (more than 4.2 IU/ml) with decreased serum FT4 level (less than 0.9 ng/dl), at which stage most patients have symptoms and benefit from treatment (21).

2. Subclinical hypothyroidism: it was indicated by increased serum TSH (more than 4.2 IU/ml) in the presence of a normal serum FT4 level.

3. Euthyroidism: (normal TSH, FT3, and FT4) with positive antibodies (anti-TG or anti-TPO or both).

Table 1: Demographic data for patients and controls:

Demographic data	Patients	Controls	P value
Age (years) Mean ± SD	39.3 ± 7.61	41.23 ± 9.82	0.228
Sex [No. (%)] Male Female	 8(11.4%) 62(88.6%)	 3(10%) 27(90%)	0.570

This table shows no statistically significant difference between patients and controls as regard age and sex.

A. Clinical findings:

1) Constitutional and articular manifestations:

Table 2: Constitutional and articular manifestations of RA patients:

	Frequency	Percent
Fatigue	33/70	47.1%
Weight loss	6/70	8.6%
Fatigue and weight loss	4/70	5.7%
Bilateral symmetrical arthritis	70/70	100%
Morning stiffness	53/70	75.7%
Deformities	20/70	28.6%

2) Disease duration and functional ability:

Table 3: Disease duration and descriptive statistics for RA patients according to functional state parameters (MHAQ=Modified Stanford Health Assessment Questionnaire):

	Mean	SD
Disease duration (years)	9.371	7.193
MHAQ	1.0577	0.8375

3) RA patients suffering from hypothyroidism according to their activity state:

Table 4: Classification of RA patients suffering from hypothyroidism (n=18) according to their activity state:

Activity state	Frequency	Percent
Inactive state	1/18	5.6%
Mild activity state	4/18	22.2%
Moderate activity state	11/18	61.1%
Severe activity	2/18	11.1%

4) Symptoms suggestive of thyroid disease:

Table 5: Comparison between patients and controls as regard most common symptoms that suggest hypothyroidism:

Symptoms	RA cases		Controls		P value
	No	Percent (%)	No	Percent (%)	
Weight gain	4/70	5.7	1/30	3.3	0.003
Intolerance to cold	6/70	8.6	1/30	3.3	
Hoarseness of voice	2/70	2.9	0	0	
Muscle pain	8/70	11.4	1/30	3.3	
Total	20/70	28.6	3/30	10	

There was a statistical significant difference between the RA patients and the control group in the reported symptoms suggestive of hypothyroidism with a P value of 0.003.

B. Laboratory investigations:

Table 6: Pattern of thyroid abnormalities among RA patients and controls:

Variables	Patient		Controls		P value	
	No	Percent	No	Percent		
Hypothyroidism	15/70	21.4%	1	3.33%	<0.05	S
Subclinical hypothyroidism	3/70	4.3%	1	3.33%	>0.05	NS
Subclinical hyperthyroidism	1/70	1.4%	0	0	>0.05	NS
Total	19/70	27.1%	2/30	6.7%		

Laboratory thyroid abnormalities were present in 19/70 (27.1%) patients versus two (6.66%) control participants. This table shows significant differences between both groups in hypothyroidism.

Table 7: Positive thyroid auto-antibodies of the RA patients and control:

Antibody	Patient		Control		P value	
	No	Percent	No	Percent		
Anti-TPO	25/70	35.7%	3/30	10%	<0.05	S
Anti-TG	16/70	22.9%	2/30	6.7%	<0.05	S

Table 8: Correlation between rheumatoid factor and thyroid antibodies:

	Anti-TPO		Anti-TG	
	r	P value	r	P value
RF	0.288	0.01	0.234	0.051
DAS	0.318	0.007	0.300	0.012

There was a statistically significant positive correlation between RF and anti-TPO among all RA patients (r=0.288, P <0.05), whereas there was no statistically significant correlation between RF and anti-TG (r=0.234, P >0.05).

Also, there was a statistically significant positive correlation between DAS with both anti-TPO and anti-TG levels.

Table 9: Comparison between demographic and laboratory data of rheumatoid arthritis patients (group A) and rheumatoid arthritis patients with abnormal thyroid state (group B):

Demographic and laboratory data	Group A (51/70) Mean ± SD	Group B (19/70) Mean ± SD	P value	
Age	38 ± 8.02	40 ± 6.35	>0.05	NS
Sex	6 male 45 female	2 male 17 female	>0.05 >0.05	NS NS
Disease duration	8.2 ±6.8	12.5 ± 7.5	<0.05	S
DAS28	4.3 ± 1.2	6.9 ± 1.9	<0.05	S
ESR	35.84 ± 9.57	52.25 ± 10.53	<0.05	S
CRP	28.82 ± 15.16	23.26 ± 13.15	>0.05	NS
Creatinine	0.99 ± 0.28	1.03 ± 0.27	>0.05	NS
Prednisone (mg/day)	3.2 ± 1.8	7.8 ± 9.2	<0.05	S
Methotrexate (mg/week)	8.5 ± 1.2	12.7 ± 6.5	0.005	S
Anti-TPO	28.61 ± 14.86	50.42 ± 35.76	0.000	HS
Anti-TG	25.88 ± 22.16	25.47 ± 22.06	>0.05	NS

According to the laboratory thyroid functions, patients were subdivided into two groups:
Group A: 51/70 (72.8%) patients were normal thyroid state.
Group B: 19/70 (27.1%) patients were in abnormal thyroid state.
On comparing the demographic and laboratory data between group A and group B, there were significant differences in disease duration (P < 0.05), disease activity (P < 0.05), ESR (P < 0.05), dose of prednisone and methotrexate (P < 0.05) and anti-TPO (P < 0.001) as shown in table 9.

Table 10: Correlation between levels of thyroid stimulating hormone with disease duration, activity score and drug intake in rheumatoid arthritis patients:

Variables	TSH		
	r	P value	
Disease duration	0.256	0.12	NS
ESR	0.783	0.02	S
DAS28	0.888	0.01	S
MHAQ	0.854	0.014	S
Prednisone (mg/day)	0.315	0.42	NS
Methotrexate (mg/week)	0.745	0.03	S

There were significant positive correlation between TSH levels and the RA disease activity parameters (ESR, DAS28, MHAQ, and dose of methotrexate).

4. Discussion

AITD is a term used to bring together a group of pathologies that involve thyroid dysfunction and an autoimmune response against this endocrine organ as its hallmark (10, 30).

The coexistence of thyroid dysfunction/thyroiditis and rheumatoid arthritis (RA) has been a subject of debate. Some workers have suggested that hypothyroidism might exacerbate rheumatoid disease with a destructive arthropathy affecting mainly the proximal interphalangeal joints, associated with fatigue, anemia, and myalgia all attributed to the inflammatory state of RA (9).

The relationship between RA and the thyroid gland has been studied extensively, with several studies demonstrating the autoimmune nature of thyroid dysfunctions in RA; however, the exact pathogenic mechanism is still unclear (11).

There is evidence that the thyroid gland is impaired in RA patients and that joint features are associated with thyroid gland diseases. Thyroid gland dysfunction in RA are most often of autoimmune character proved by the presence of different autoantibodies against the thyroid gland antigens and may have eu-, hypo-, or even hyperthyroid manifestations (25,28).

This study was designed to investigate the association of hypothyroidism and thyroid autoantibodies with RA and to study their correlation with RA disease activity.

Hypothyroidism was reported to be the most frequent pattern of thyroid dysfunction among patient with RA (24). In this study hypothyroidism constitute 21.4 % of our patient which consider significant in comparison with control group. The second pattern of thyroid dysfunction in this study is subclinical hypothyroidism (SCH) which constitutes 4.3% of our RA patients. In contrast to other study by Chan et al which showed that the prevalence of SCH was more than that of clinical cases (5). The lower incidence of subclinical cases might be explained by the pyramid hypothesis. This hypothesis is based on the observation that subclinical hypothyroidism will develop into clinically manifest hypothyroidism in approximately one quarter of the cases. Facilitating factors for this development are old age, female gender, and higher titers of antibodies for thyroid peroxidase (TPOab). This progression into a clinical hypothyroidism is also called the 'disease pyramid' theory (24). It has been shown that; abnormal or changing thyroid status may precipitate or exacerbate musculoskletal disease, especially when common features and symptoms of different disease are the same and even the symptoms of new disease masked by the original one (9).

Fatigue, anemia, arthritis, and myalgia are cardinal manifestations of hypothyroidism and in the time all these symptoms are common in patient with RA. There was a statistical significant difference between the RA patients and the control group in these symptoms (P=0.003). In another hand, when we focus on a symptom as fatigue, results showed that patients with fatigue had a significantly higher DAS (P= 0.03).

It was worthy noted that, patient with RA had significant prevalence of anti-TPO and anti-TG (35.7% and 22.9%, respectively), in comparison with controls (P<0.05). Mousa et al, has been found positive anti-TPO and anti-TG antibodies in 10 and 6% of Egyptian RA patients (17). Also, a different percentage of thyroid antibodies were recorded in Colombian RA patients (37.8 and 20.8%) (20). The variations in the percentage of antithyroid antibodies can be attributed to ethnic and environmental differences of the studied populations. An increased prevalence of antithyroid antibodies has been documented in patients with RA but a limited studies focusing on the relationship of these antibodies with arthritis activity (14) and a number of studies did not confirm the association between AITD and RA activity (4).

The results of this study not only show a high prevalence of antithyroid antibodies in RA but also provide evidence for a significant association between antithyroid antibody titers and RA activity parameters such as DAS 28 (Since DAS28 remains the main tool in the evaluation of RA activity). A study done by Koszarny et al showed that a potential significant association between antithyroid antibody titers and the parameters of RA activity such as DAS28, ESR and CRP (14).

The results of present study showed also positive significant correlation between RF and anti-TPO among all RA patients, whereas there was no statistically significant correlation between RF and anti-TG.

On the other hand, in non-autoimmune hypothyroidism however, it was found in this study that patients with RA and clinical hypothyroidism had a higher DAS28 score compared to RA patients without clinical hypothyroidism which also found by Cojocaru-Gofita et al (6). Also, Delamere et al found that thyroid dysfunction is associated with increased mean duration and incidence of morning stiffness (8).

Current prednisone used (daily dose) and methotrexate (weekly dose) were higher in hypothyroid patient than in other subjects. The results showed positive significant correlation between serum levels of TSH and dose of methotrexate, indicating that higher levels of TSH are associated with higher dose of methotrexate (MTX), therefore higher grades of RA disease activity.

The results showed positive significant correlations between serum levels of TSH and RA activity parameters (ESR, MDAS28 and MHAQ), indicating that higher levels of TSH are associated with higher grades of RA disease activity. On the other hand, on classification of RA patients suffering from hypothyroidism according to their activity state found that most of patients (94.4%) were in active state (moderate activity followed by mild activity then severe activity), and only one (5.6%) was in inactive state. Some authors found that hypothyroidism correlated with the number of swollen joints in RA patients (24), whereas others found higher levels of CRP in RA patients with hypothyroidism (17). However, other studies by Punzi et al and Singh et al (22,27) could not find a correlation between hypothyroidism and RA disease activity state and concluded that thyroid hormonal defects were related to the disease duration and not the disease activity.

Through numerous studies (5,19) have focused on the functional and immune thyroid gland abnormalities in patients with previous history of RA and the joint changes in patients with previous autoimmune thyroid diseases. Women are significantly more likely to develop RA than men and hormones are known to affect the disease status in patients with RA (13,16). Common etiological factors

for RA and hypothyroidism have been discussed such as the use of salicylates and many other NSAIDs or corticosteroids in treating RA, which have been shown to alter thyroid gland function (3,22,26). Therefore, the pathogenesis of thyroid disease in patients with RA may have a common pathway and it was speculated that thyroid disorders are the result of the anti-thyroid activity of one of the antibodies produced in RA (9). Moreover, a genetic predisposition determined by a certain human Leukocyte Antigen (HLA) most often HLA-DR, is one possible explanation for the presence of two or more autoimmune diseases in one individual (28). More explanations have been suggested when anti-TNF-α treatment improved thyroid function in hypothyroid patients with RA (23), also provided evidence that inflammatory cytokines may play a pathogenic role in thyroid dysfunction (29).

In conclusion, thyroid dysfunctions are common in RA patients, with hypothyroidism being the most common disorder prevalent in 21.4% of patients. TSH has shown an evident positive correlation with RA disease activity as well as clinical and laboratory disease parameters. We recommend to do thyroid function and anti-thyroid antibody tests as a part of the biochemical and immunological profile in RA patients; to treat both clinical and subclinical hypothyroidism in RA patients; and clinical follow- up is needed to clarify the effect of thyroid dysfunction treatment on RA activity and vice versa.

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