IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 15, Issue 2 Ver. X (Feb. 2016), PP 81-84
www.iosrjournals.org

Study of Thyroid Dysfunction in Patients with Rheumatoid Arthritis

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Abstract
Introduction*: The relationship between thyroid disease and rheumatic disorders has been the subject of considerable debate. Thyroid dysfunction and/or autoimmune thyroid disease were observed in patients with rheumatoid arthritis (RA), which could be attributed to the natural feature of autoimmune diseases and their tendency to overlap. Consideration of the fact that autoimmunity plays a role in the pathogenesis of both RA and hypothyroidism has raised the need to study the frequency of thyroid dysfunction and thyroid antibodies in RA patients and their relation to disease activity.*
Material and methods *One hundred RA patients were included in this study. RA patients were subjected to a full assessment of medical and rheumatological history, and examination as well as routine lab tests. Patients underwent thyroid function testing including thyroid antibodies.*
Results *The most common thyroid dysfunction was hypothyroidism, which was found in twenty three (23%) Rheumatoid arthritis patients, followed by subclinical hypothyroidism in three(3%) patients, whereas subclinical hyperthyroidism was present in two (2%) patients. Autoimmune thyroid disease was present in 10 % patients.*
Conclusion *Hypothyroidism was the most common thyroid disorder associated with RA present in 23%.*
Keywords: *autoimmune thyroid disease, hypothyroidism, rheumatoid arthritis, rheumatoid arthritis disease activity.*

I. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune systemic inflammatory multisystem disease of unknown cause that may affect many tissues and organs, but principally attacks synovial joints, primarily affecting the peripheral joints in a symmetrical pattern. The pathology of the disease process often leads to destruction of articular cartilage.

RA affects ˜1% of the adult general population. Constitutional symptoms including fatigue, malaise, and morning stiffness are frequently experienced. Although the cause of RA is unknown, autoimmunity plays a pivotal role in both its chronicity and its progression through the high level of cytokines, especially the tumor necrosis factor α (TNF-α).

Thyroid dysfunction may be broadly classified as hypothyroidism and hyperthyroidism. The most common cause of thyroid disorders worldwide is iodine deficiency, leading to goiter formation and hypothyroidism. However, in noniodine deficiency areas, the cause of hypothyroidism is either autoimmune (Hashimoto's thyroiditis), with a prevalence of 1-2%, and it is 10 times more common in women than in men , or hypothyroidism associated with the destructive treatment for thyrotoxicosis .

The relationship between thyroid dysfunction and RA has been a subject of debate, where several surveys suggested a relation between Hashimoto's thyroiditis and RA. 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.

Moreover, thyroid dysfunction was observed at least three times more often in women with RA than women with similar demographic features with noninflammatory rheumatic diseases such as osteoarthritis and fibromyalgia . This was also confirmed in a more recent study in which thyroid dysfunction 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 overlap . Frequent association with autoimmune diseases of other organs such as systemic lupus erythematosus , Sjogren's syndrome, scleroderma , and vasculitis was observed.

Considering that autoimmunity plays a role in the pathogenesis of both RA and hypothyroidism through TNF-a, with the noticeable improvement in hypothyroidism in RA patients with anti-TNF-a treatment , this raised the need to study hypothyroidism and thyroid antibodies in RA patients and their relation to disease activity.

II. Material And Methods

1) The patient group included 100 adult RA patients who presented to the outpatient clinics and were inpatients of Medicine Departments of Bundelkhand Medical College and associated Hospitals Sagar. 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. Exclusion criteria were as follows:

1. Patients on medication known to cause thyroid dysfunction (e.g. lithium, interferon alpha, etc.).
2. Evidence of malignancy.
3. Concurrent infection.
4. Any collagen disease other than RA.
5. Pregnant women.
6. Chronic liver or renal diseases.
7. Diabetic patients.
8. Patients who had undergone thyroidectomy.

III. Methods

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

Assessment of medical and rheumatological history

Medical and rheumatological history was assessed with a special focus on symptoms of thyroid problems (e.g. palpitation, cold intolerance, weight gain, RA disease duration, morning stiffness, tender joints, swollen joints, etc.).

General and rheumatological examination

Careful general and musculoskeletal examination, thyroid gland examination, and calculation of BMI (weight in kg divided by the patient's height in m^2 ; ≥25 was considered abnormal) were performed. Waist circumference [an abnormal waist circumference was defined according to the International Diabetes Federation (IDF) for men as a circumference ≥94 cm and for women as ≥80 cm (*http:www.idf.org/metabolic-syndrome*) was measured. Medical treatment with methotrexate and/or prednisone was recorded including their current doses.

Laboratory investigations

Routine laboratory investigations were performed including the following:

1. Complete blood count using a Coulter JS (California, USA) cell counter.
2. The ESR in the first hour, estimated using the Westergren method.
3. Quantitative C-reactive protein (CRP) titer assessed using the immunoturbidimetric method.
4. Kidney function tests (serum creatinine, blood urea nitrogen) were performed using the calorimetric method.
5. Liver enzymes (ALT, AST) were assessed using the kinetic method.
6. Fasting blood sugar and 2 h postprandial were determined.
7. The lipid profile including total cholesterol, serum triglycerides, low-density lipoprotein (LDL), and high-density lipoprotein was assessed.
8. Immunological assessment was performed for the rheumatoid factor (RF/IgM) that was measured using a Biotec (San Diego, USA, Genway Biotech) RA factor latex agglutination slide for the qualitative and semiquantitative determination of RF in the serum.
9. Anti-cyclic-citrullinated peptide antibodies were assessed using an enzyme-linked immunosorbent assay. The cut-off value for the anti-cyclic-citrullinated peptide antibody was 5 U/ml .

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 Angeles, California, USA).
2. Free serum triiodothyronin (FT3) level was determined using IMMULITE 2000 FT3, competitive, analog-based immunoassay for quantitative estimation of FT3 in serum on an IMMULITE 2000 system.
3. Free serum thyroxin 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 values were 0.27-4.2 IU/ml for TSH, 2.57-4.43 pg/ml for FT3, and 0.93-1.71 ng/dl for FT4 .

Clinical hypothyroidism and hyperthyroidism

Clinical hypothyroidism and hyperthyroidism were defined on the basis of the criteria of thyroid abnormalities as defined by the Dutch National Healthcare Consensus Committee :

Subclinical hypothyroidism: it was indicated by increased serum TSH in the presence of a normal serum FT4 level.

Clinical hypothyroidism: it was indicated by increased serum TSH with decreased serum FT4 level, at which stage most patients have symptoms and benefit from treatment.
Subclinical hyperthyroidism: it was indicated by normal serum FT4 and FT3 levels, with TSH levels below the normal range, usually undetectable.
Clinical hyperthyroidism: it was indicated by increased serum FT4 and FT3 levels, with TSH levels suppressed below the normal range, usually undetectable.
Antithyreoglobulin (anti-TG) antibodies and antithyroid peroxidase (anti-TPO) antibodies were assayed using an enzyme-linked immunosorbent assay method (Calbiotech Inc. California, USA). The reference values were less than 100 IU/ml for anti-TG antibodies and less than 50 IU/ml for anti-TPO.
The diagnosis of Autoimmune thyroid disese was made on the basis of the presence of antithyroid antibodies (presence of increased anti-TPO antibodies levels) in patients with concomitant thyroid dysfunction and/or goiter. However, Autoimmune thyroid disese (AITD) was suspected if the values of anti-TPO antibodies were close to the reference range with increased levels of anti-TG.
Thyroid ultrasound was performed routinely at the Radiology Unit to indicate the need for a thyroid biopsy. However, biopsy was not performed as ultrasound did not show any indications such as cold nodules. A thyroid scan was performed for the patients who showed subclinical hyperthyroidism (two patients and one control) using 99mTc radionucleid (g-rays emitters) and a gamma camera.

IV. Results;

This study included 100 adult RA patients; 90 (90%) were women and 10(10%) were men, and their ages ranged from 35 to 62 years (mean 45.2 ± 7.8 years), and a disease duration of 1-15 years (mean 7.7 ± 4.3 years). Of the 100 RA patients studied, laboratory thyroid abnormalities were present in 28 (28%) patients.

1. Hypothyroidism was the most common disorder found in 23 (23%) patients
2. Subclinical hypothyroidism was found in three(3%) patients
3. Subclinical hyperthyroidism was found in two (2%) patients
4. None of the patients had hyperthyroidism.

According to the (laboratory thyroid functions) , patients were subdivided into two groups: seventy seven (77%) patients were either normal or had a subclinical thyroid state (group A), whereas 23 (23%) patients were in a hypothyroid state (group B).

On comparing the demographic data between seventy seven (77%) patients with normal or subclinical thyroid disorders (group A) and 23 (23%) patients in a hypothyroid state (group B), there were significant differences in disease duration ($P < 0.05$), BMI ($P < 0.00$), waist circumference ($P < 0.00$),. In addition, there were significant laboratory differences in ESR ($P < 0.05$), levels of cholesterol ($P < 0.05$), TG ($P < 0.05$), LDL ($P < 0.05$), anti-TPO ($P < 0.05$), and anti-Tg ($P < 0.05$) antibodies. Highly significant differences were present in TSH ($P < 0.001$), FT3 ($P < 0.001$), and FT4 ($P < 0.001$).

Current prednisone used (daily dose) and methotrexate (weekly dose) were higher in group B than in group A, with a significant difference ($P < 0.05$). Anti-TPO antibodies were present in nine (9%) RA patients, whereas anti-Tg antibodies were present in three (3%) RA patients. Accordingly, Autoimmune thyroid disease was considered positive in six(6%) patients who showed hypothyroidism together with positive anti-TPO antibodies. Significant positive correlations were also found between TSH levels and BMI, waist circumference, and TG [$r = 0.75$ ($P < 0.32$), $r = 0.83$ ($P < 0.019$), and $r = 0.67$ ($P < 0.049$), respectively].

V. Discussion

The coexistence of thyroid dysfunction/thyroiditis and RA has been a subject of debate [1]. Some workers have suggested that hypothyroidism might exacerbate rheumatoid disease with a destructive arthropathy affecting mainly the proximal interphalangeal joint[2,3], associated with fatigue, anemia, and myalgia, all attributed to the inflammatory state of RA . This study was designed to investigate the association of hypothyroidism and thyroid autoantibodies with RA. The study included 100 adult RA patients, 90 (90%) women and 10 (10%) men. Thyroid abnormalities were present in twenty eight (28%) RA patients. participants, which is not in agreement with the study of Shiroky *et al*. [4], who found that 29 (30%) RA patients had evidence of thyroid dysfunction compared with 10 (11%) of their controls, although another Egyptian study has reported less frequent thyroid dysfunction (8.3%) [5]. Hypothyroidism was the most common disorder in our study, found in twenty three (23%) patients, similar to other authors who showed that clinical hypothyroidism was the most common thyroid disorder associated with RA . Clinical hypothyroidism was observed three times more often in RA female patients than in women of the general population. Anti-TPO and anti-Tg antibodies were present in 14 and five of our RA patients (9.3 and 3.3%, respectively). These results are almost in agreement with the results of Mousa *et al*. [5], who found positive anti-TPO and anti-Tg antibodies in 10 and 6% of Egyptian RA patients. However, our data were different from those of other populations, where these antibodies were present in 15.9 and 12.3% of Turkish RA patients [6]. Also, a higher percentage of thyroid antibodies was recorded in Polish RA patients (15 and 12%, respectively) as well as in Colombian RA patients

(37.8 and 20.8%) [7]. These variations in the percentage of antithyroid antibodies can be attributed to ethnic and environmental differences of the studied populations. AITD was considered positive in 10 RA patients, which was almost in agreement with the results of other studies that found a prevalence of AITD in 9.8% of their studied RA patients; however, others have found a higher prevalence of 16% in their RA patients . 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 [8]. 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 antithyroid activity of one of the antibodies produced in RA . Moreover, a genetic predisposition determined by a certain Human Leucocyte Antigen (HLA) type, most often HLA-DR, is one possible explanation for the presence of two or more autoimmune diseases in one individual . More explanations have been suggested when anti-TNF-α treatment improved thyroid function in hypothyroid patients with RA , also provided evidence that inflammatory cytokines may play a pathogenic role in thyroid dysfunction .

VI. Conclusion

Thyroid dysfunction and Autoimmune thyroid disease are common in RA patients, with hypothyroidism being the most common disorder prevalent in 23% of patients.

Acknowledgement

We sincerely thanks to all members of Department of Medicine of Bundelkhand Medical College Sagar.

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Table-1

Serial no.	variables	Patients(n=100)
1.	Age	35-62
2.	Sex	90 F, 10M
3.	BMI(kg/m2)	32.98-41.91
4.	Waist circumference(cm)	89.74-121.81

Table-2

Serial no.	Variables	patients
1.	Subclinical hypothyroidism	3
2.	Subclinical hyperthyroidism	2
3.	hypothyroidism	23

Table-3

variables	TSH(IU/ml)		Free T3	
	r	P value	r	P value
Disease duration	0.256	0.12	-0.31	0.54
ESR	0.783	0.02	-0.763	0.01
BMI	0.754	0.032	-0.781	0.031
WAIST CIRCUMFERENCE	0.839	0.019	-0.801	0.024
CHOLESTEROL	0.251	0.335	-0.244	0.302
TRIGLYCERIDE	0.677	0.049	-0.705	0.036
LDL	0.211	0.301	-0.302	0.554
PREDNISONE	0.315	0.423	-0.112	0.56
METHOTREXATE	0.7454	0.035	-0.844	0.012