THE PREVALENCE OF THYROID DYSFUNCTION IN RHEUMATOID ARTHRITIS

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M.D. DEGREE IN GENERAL MEDICINE

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CHENNAI

CERTIFICATE

Certified that this dissertation entitled "**THE PREVALENCE OF THYROID DYSFUNCTION IN RHEUMATOID ARTHRITIS"** submitted by **Dr.BINCY.B.K, M.D,** Post Graduate student in Internal Medicine, Govt Rajaji hospital, Madurai-625020, to the faculty of General Medicine ,The Tamil Nadu Dr.M.G.R Medical University, Chennai in partial fulfilment of the requirement for the award of MD degree branch 1 General Medicine, is a bonfide research work carried out by her under our direct supervision and guidance.

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DECLARATION

I , **Dr.BINCY.B.K ,** solemnly declare that the dissertation entitled "**THYROID DYSFUNCTION IN RHEUMATOID ARTHRITIS"** has been prepared by me.

This is submitted to **THE TAMILNADU Dr.M.G.R. MEDICAL UNIVERSITY, CHENNAI** in partial fulfilment of the regulations for the award of MD degree (branch 1) General Medicine.

Place : Madurai

Date: **DR. BINCY. BK**

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CONTENTS

ABSTRACT

AIMS : The aim of the study was to evaluate the the prevalence of thyroid dysfunction and the incidence of autoimmune thyroditis in rheumatoid arthritis

METHODS : The study was a cross sectional observational study involving 50 rheumatoid arthritis patients (8 male and 32 female) .The conditions which can alter thyroid profile were excluded from the study population at the time of selection . 40 age and sex matched healthy subjects were taken as controls . Thyroid function test were done in all patients and controls. In patients who were found to have thyroid dysfunction TPO antibodies were done.

RESULTS : Prevalence of thyroid dysfunction is 14% in patients with rheumatoid arthritis. Prevalence of thyroid dysfunction in control population was 5%. Among patients who had thyroid dysfunction there was no statistically significant difference in gender. Abnormal thyroid function is mainly in the form of both overt and subclinical hypothyroidism. Prevalence of autoimmune hypothyroidism is 22% in our case population.

CONCLUSION : In summary, our study confirms that the prevalence of thyroid dysfunction in rheumatoid arthritis is high and is associated with thyroid autoimmunity and suggest that all rheumatoid arthritis patients should undergo thyroid function testing and those with elevated TSH should go for autoimmune screening with TPO.

INTRODUCTION

Rheumatoid arthritis (RA) is the most common inflammatory arthritis affecting about 0.5-1% of general population (1).RA is a systemic autoimmune disorder characterised by symmetrical, inflammatory, deforming polyarthritis affecting small and large peripheral joints with associated systemic disturbance such as vasculitis and nodules. Being an autoimmune disease it can be associated with other autoantibody mediated diseases like autoimmune thyroididtis (1). The prevalence of thyroid dysfunction in rheumatoid arthritis is 10-15% which is high in previous studies(2)(3). Autoimmune thyroiditis, specifically Hashimoto's thyroiditis, is more prevalent in persons with autoimmune disorders including rheumatoid arthritis.

Boelaert et al (4) investigated the prevalences of and relative risks for coexisting autoimmune diseases in patients with Graves disease (2791 patients) or Hashimoto thyroiditis (495 patients). The authors found coexisting disorders in 9.7% of

patients with Graves disease and in 14.3% of those with Hashimoto thyroiditis, with rheumatoid arthritis being the most common of these (prevalence = 3.15% and 4.24% in Graves disease and Hashimoto thyroiditis, respectively

.

The term autoimmune hypothyroidism identifies situations with insufficient thyroid function caused by an autoimmune thyroid diseases due to autoimmune destruction of the thyroid gland. In its initial stage, chronic autoimmune thyroiditis is characterized by the presence of hallmarks of thyroid autoimmunity and normal thyroid function. As a consequence of the autoimmune attack to the gland, hypothyroidism may develop, usually slowly and insidiously, through a subclinical phase levels and an eventual phase of overt insufficiency.

Etiology and pathogenesis of chronic autoimmune thyroiditis and mechanisms leading to the hypothyroid phase remain elusive. However, some predisposing genetic factors and some triggering environmental factors have been identified. The role of antigen-

presenting cells, of T and B-cell response, and of effector mechanisms in the immuno pathogenesis of chronic autoimmune hypothyroidism has been extensively investigated. Circulating thyroid autoantibodies are the hallmarks of AITD and thyroid peroxidase antibodies is more sensitive than other antibodies in identifying thyroid autoimmunity.(5)

Hypothyroidism is associated with fatigue, anemia, arthritis, and myalgia, and also induces destructive arthropathy, mainly of the proximal interphalangeal joints which would normally be attributed to the inflammatory state of a patient with RA. Since autoimmune thryoiditis in rheumatoid arthritis is usually asymptomatic, any patient who is not responding to conventional treatment of RA or having high levels of TSH should be evaluated for autoimmune thryroiditis. There are studies evidence that RA patient having autoimmune thyroiditis improved symptomatically with thyroid supplementation. (6)

REVIEW OF LITERATURE

The thyroid gland produces two related hormones, thyroxine (T4) and triiodothyronine (T_3).Autoimmune disorders of the thyroid gland can stimulate overproduction of thyroid hormones (*thyrotoxicosis*) or cause glandular destruction and hormone deficiency (*hypothyroidism*).

Prevalence and clinical relevance

In the NHANES III study it was shown that 4.6% of the US population had hypothyroidism (0.3% clinical and 4.3% subclinical) and 1.3% had hyperthyroidism (0.5% clinical and 0.7% subclinical) (7)

Thyroid Hormone Synthesis

Thyroid hormones are derived from Tg, a large iodinated glycoprotein. After secretion into the thyroid follicle, Tg is iodinated on tyrosine residues that are subsequently coupled via an ether linkage. Reuptake of Tg into the thyroid follicular cell allows proteolysis and the release of newly synthesized T4 and T3. (8)

Iodine Metabolism and Transport

Iodide uptake is a critical first step in thyroid hormone synthesis. Ingested iodine is bound to serum proteins, particularly albumin. The thyroid gland extracts iodine from the circulation in a highly efficient manner. Iodide uptake is mediated by NIS, which is expressed at the basolateral membrane of thyroid follicular cells. Low iodine levels increase the amount of NIS and stimulate uptake, whereas high iodine levels suppress NIS expression and uptake (8)

Organification, Coupling, Storage, Release

After iodide enters the thyroid, it is trapped and transported to the apical membrane of thyroid follicular cells, where it is oxidized in an organification reaction that involves TPO and hydrogen peroxide. The reactive iodine atom is added to selected tyrosyl residues within Tg. The iodotyrosines in Tg are then coupled via an ether linkage in a reaction that is also catalyzed by TPO. Either T4 or T_3 can be produced by this reaction, depending on the number of iodine atoms present in the iodotyrosines. After coupling, Tg is taken back into the thyroid cell, where it is processed in lysosomes

to release T_4 and T_3. Uncoupled mono- and diiodotyrosines (MIT, DIT) are deiodinated by the enzyme dehalogenase, thereby recycling any iodide that is not converted into thyroid hormones. (8)

Thyroid Hormone Transport and Metabolism (8)

Serum Binding Proteins

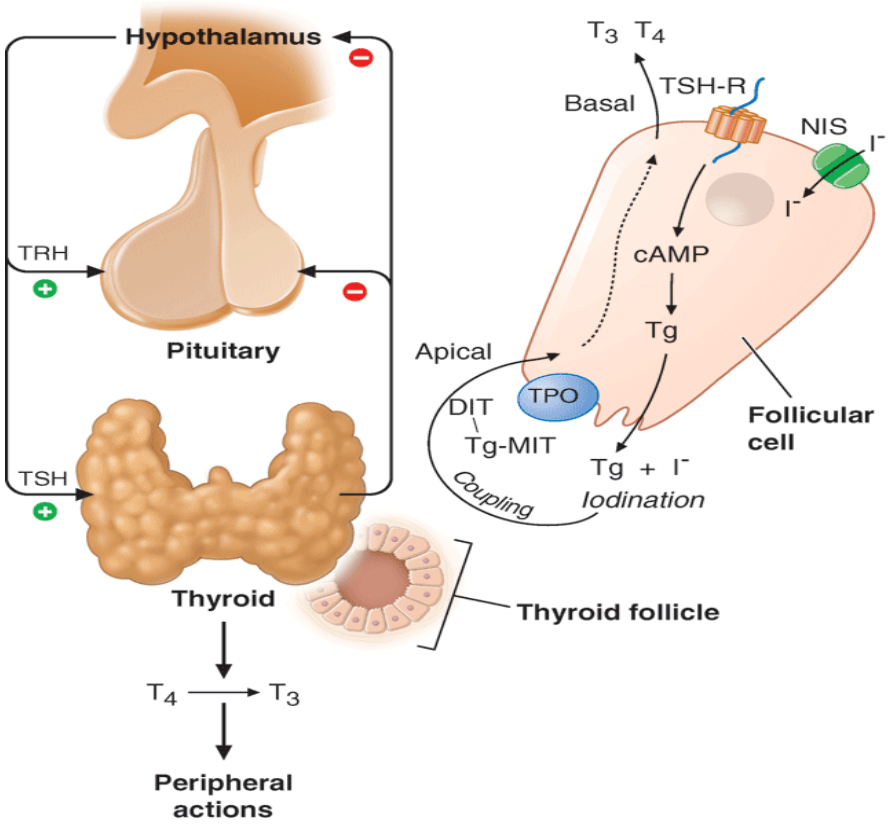
T4 is secreted from the thyroid gland in about twentyfold excess over T_3. Both hormones are bound to plasma proteins, including thyroxine-binding globulin (TBG), transthyretin (TTR, formerly known as thyroxine-binding prealbumin, or TBPA), and albumin. The plasma-binding proteins increase the pool of circulating hormone, delay hormone clearance, and may modulate hormone delivery to selected tissue sites. The concentration of TBG is relatively low (1–2 mg/dL), but because of its high affinity for thyroid hormones ($T_4 > T_3$), it carries about 80% of the bound hormones. Albumin has relatively low affinity for thyroid hormones but has a high plasma concentration (3.5 g/dL), and it binds up to 10% of T_4 and 30% of T_3. TTR carries about 10% of T_4 but little T_3.

Deiodinases

T4 may be thought of as a precursor for the more potent T_3. T_4 is converted to T_3 by the deiodinase enzymes.

Regulation of thyroid hormone synthesis. (8)

Thyroid hormones T_4 and T_3 feed back to inhibit hypothalamic production of thyrotropin-releasing hormone (TRH) and pituitary production of thyroid-stimulating hormone (TSH).The thyroid stimulating hormone (TSH) controls the secretion of T3 and T4, plays a pivotal role in control of the thyroid axis and serves as the most useful physiologic marker of thyroid hormone action. It is secreted in a pulsatile manner with peak secretion at night. Its secretion is stimulated by thyrotropin releasing hormone(TRH). Both TRH and TSH release are under negative feedback of free T3 and T4.



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 18th Edition: www.accessmedicine.com

T_3 is bound with 10–15 times greater affinity and ten times greater efficacy than T_4, which explains its increased hormonal potency. Though T_4 is produced in excess of T_3, receptors are occupied mainly by T_3.T4 is quantitatively secreted at much higher levels, it should be regarded as a pro-hormone that requires deiodination and conversion to T3 to become biologically active (8)

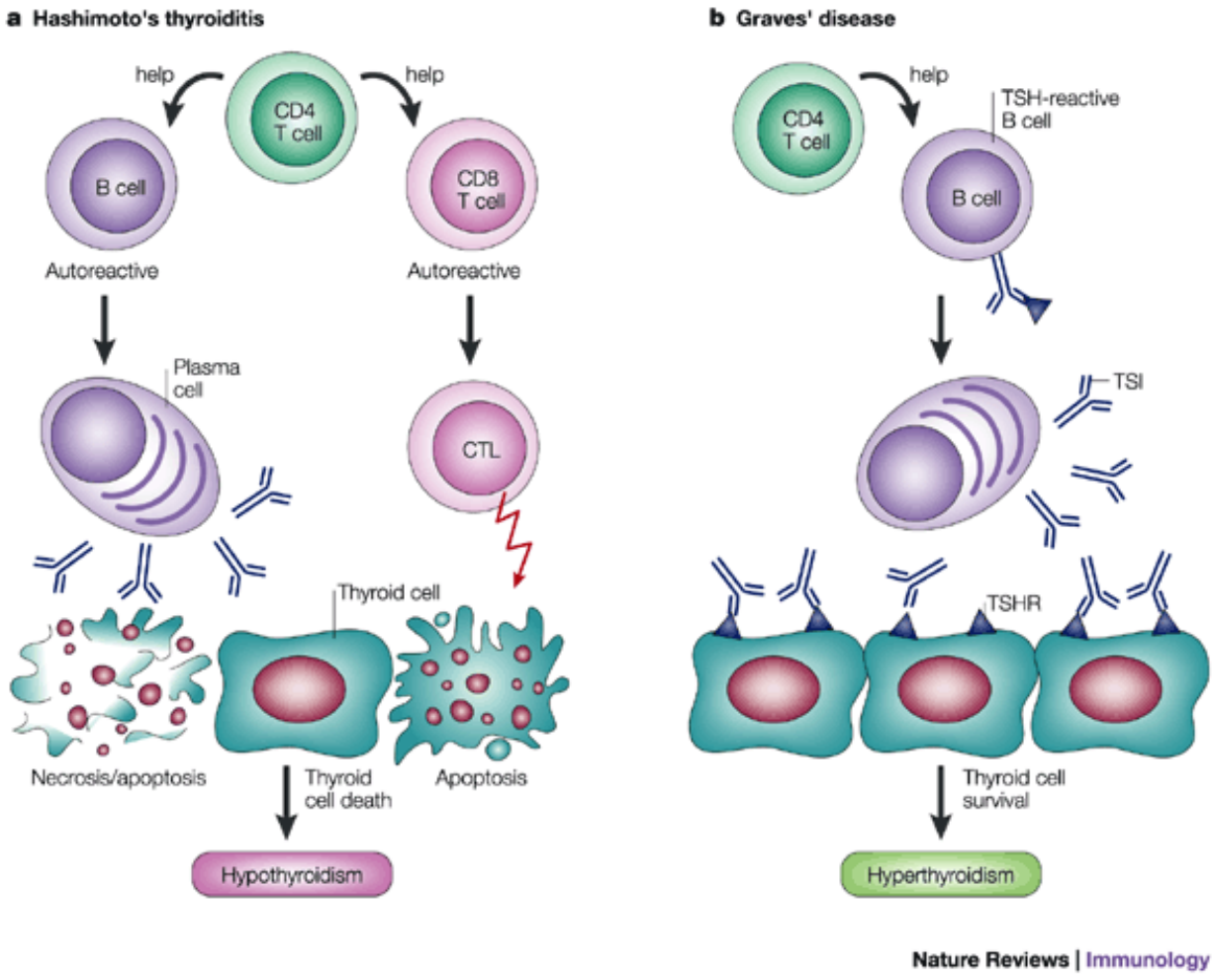
Autoimmune thyroid disease (AITD) :

The term "autoimmune thyroid disease" is used to describe all autoimmune thyroid conditions, including Graves' disease,

Hashimoto's thyroiditis, and various other disorders (eg, postpartum thyroiditis, most cases of silent thyroiditis). The most common presentation is the presence of positive antithyroid antibodies in a euthyroid patient. Hypothyroidism with or without goiter is more common than hyperthyroidism. (8)

Rheumatic complaints start simultaneously with the first symptoms of hypothyroidism and joint pain and swelling usually disappear with thyroxine substitution. A study by Gerster Jean CHence **(6)**, as thyroxine replacement may reverse the rheumatic complaints, thyroid function should be performed as part of the biochemical profile in patients with RA not responding to antirheumatic treatment. Hypothyroidism should be considered in the differential diagnosis of destructive arthropathy (**11).**

PATHOPHYSIOLOGY OF AUTOIMMUNE THYROIDITIS (25)



During Hashimoto's thyroiditis, self-reactive $CD4^+$ T lymphocytes recruit B cells and $CD8^+$ T cells into the thyroid. Disease progression leads to the death of thyroid cells and hypothyroidism. Both autoantibodies and thyroid-specific cytotoxic T lymphocytes (CTLs) have been proposed to be responsible for autoimmune thyrocyte depletion.

In Graves' disease, activated $CD4^+$ T cells induce B cells to secrete thyroid-stimulating immunoglobulin (TSI) against the thyroid-stimulating hormone receptor (TSHR), resulting in unrestrained thyroid hormone production and hyperthyroidism

Prevalence

The mean annual incidence rate of autoimmune hypothyroidism is up to 4 per 1000 women and 1 per 1000 men. The mean age at diagnosis is 60 years, and the prevalence of overt hypothyroidism increases with age. Subclinical hypothyroidism is found in 6–8% of women (10% over the age of 60) and 3% of men. The annual risk of developing clinical hypothyroidism is about 4% when subclinical hypothyroidism is associated with positive TPO antibodies.(8)

The prevalence of thyroid antibody positivity in the general population is 15% to 25% in women and 5% to 10% in men. Graves' disease is less prevalent than Hashimoto's thyroiditis. (9)

The prevalence of thyroid dysfunction and autoimmunity in rheumatoid arthritis according to previous studies were 10-20% (13, 14, 2, 3) and 15-30% respectively.

Subclinical hypothyroidism is defined as mild elevation of serum thyrotropin (TSH) levels and normal circulating thyroid hormone levels. Antithyroid antibodies are positive in 90% of affected patients.(10)

In the Whickham study (15) , in an English town, 8% of women 35 years of age and older had subclinical hypothyroidism. In that study, old age, female sex, and antithyroid antibody positivity were associated with higher risk of progression to overt hypothyroidism, and 40% of patients with subclinical disease developed clinical hypothyroidism after 20 years. The annual rate of progression to overt hypothyroidism was 2.1% in women with positive antithyroid antibody (antithyroperoxidase

antibody or antithyroglobulin antibody) and normal serum TSH, 2.6% in women with mildly elevated TSH and negative antithyroid antibody, and 5% in women with both elevated serum TSH and positive thyroid antibody. (9)

The most common presentation is the presence of positive antithyroid antibodies in a euthyroid patient. In such patients, a palpable thyroid abnormality may or may not be present.

Clinical classification of autoimmune thyroid disease(10)

1. Clinical hypothyroidism with goiter or atrophic thyroid gland
2. Graves' disease (hyperthyroidism with or without extrathyroidal manifestations.
3. Hashimoto's thyroiditis with positive antithyroid antibodies with or without palpable thyroid abnormality
4. Subclinical hypothyroidism with or without goiter
5. Transient thyroiditis
6. Postpartum thyroiditis (transient hyperthyroidism followed by transient hypothyroidism.
7. Silent thyroiditis (transient hyperthyroidism followed by euthyroidism)

Tests to Determine the Etiology of Thyroid Dysfunction

Autoimmune thyroid disease is detected most easily by measuring circulating antibodies against TPO and Tg. As antibodies to Tg alone are uncommon, it is reasonable to measure only TPO antibodies. About 5–15% of euthyroid women and up to 2% of euthyroid men have thyroid antibodies; such individuals are at increased risk of developing thyroid dysfunction. Almost all patients with autoimmune hypothyroidism, and up to 80% of those with Graves' disease, have TPO antibodies, usually at high levels (8)

Thyroid peroxidase antibodies is more sensitive than other antibodies in identifying thyroid autoimmunity, which is present in 90% of those with autoimmune thyroiditis. So screening for TPOA helps in finding out those with AITD (10)

Measurement of Thyroid Hormones

TSH is the most reliable and sensitive screening test for thyroid dysfunction as autoantibodies may persist for many years without thyroid dysfunction and allows both hypothyroidism and hyperthyroidism to be diagnosed with certainty. TSH levels change dynamically in response to alterations of T4 and T_3, a logical approach to thyroid testing is to first determine whether TSH is suppressed, normal, or elevated However, the presence of thyroid autoantibodies increases the risk for thyroid disease and so particularly those with positive TPO antibodies should undergo screening.(8)

HYPOTHYROIDISM

Hypothyroidism is a clinical syndrome caused by decreased levels of thyroid hormones. It can be primary in which there is intrinsic disorder of thyroid gland or it may be secondary in which there is pituitary or hypothalamic defect.

TSH is the single most important parameter for screening hypothyroidism. A normal TSH level rules out primary hypothyroidism but not secondary. To diagnose primary

hypothyroidism TSH level should be above 20 μIU/ml or at least above 10μIU/ml if clinical features strongly suggest. In the presence of elevated TSH, low T4 especially free T4 is necessary to confirm hypothyroidism. Circulatory free T3 is usually reduced. But it may be normal in 25% of hypothyroid patients. So T3 measurements are not reliable indicators of hypothyroidism.(8)

HYPERTHYROIDISM

Hyperthyroidism is a clinical syndrome which results from excessive circulating levels of free thyroid hormones.

Laboratory investigations show TSH levels below normal. Free and total thyroid hormone levels are increased. In 2 to 5% of patients, only T3 is increased and T4 is normal. This condition is called *"T3 thyrotoxicosis"*. Occasionally total and free T4 will be increased with normal T3 level. This condition is called *"T4 thyrotoxicosis"*. (8)

Rheumatoid Arthritis

DEFINITION:

Rheumatoid Arthritis is a chronic multi system inflammatory disorder disease of unknown cause, characterised by symmetrical, inflammatory, deforming polyarthritis(16) affecting small and large peripheral joints with associated systemic disturbance such as vasculitis and nodules.

Rheumatoid arthritis (RA) is the most common inflammatory arthritis affecting about 0.5-1% of general population (1)(16).

EPIDEMIOLOGY:

Incidence

The most recent US data on the incidence of RA is from the Rochester Epidemiology Project (12), a study that has provided the majority of population-based descriptive statistics on RA. In 1995-2007, 41 per 100,000 people were diagnosed with RA each year. Incidence rose with age (e.g., 8.7 per 100,000 people among those aged 18-34 compared with 54 per 100,000 among those aged

≥ 85 years); incidence peaked among people aged 65-74 years (89 per 100,000) (all estimates age- adjusted to 2000 US population). From 1995 to 2007, rates increased by 2.5% each year among women but there was a small decrease (0.5%) among men (12).

Prevalence:

The prevalence of RA is 0.5–1% of the adult population worldwide. RA occurs more commonly in females than in males, with a 2–3:1 ratio.(16) The onset is more frequent during the fourth and fifth decades of life, with 80 % of all patients developing the disease between the ages of 35 and 50. (8)(16)

DIAGNOSIS

The American college of Rheumatology (ACR) has developed and revised criteria for the classification of RA based on a hospital population of patients with established active disease. These criteria distinguish active RA from other forms of inflammatory arthritis with a diagnostic sensitivity and specificity of about 90%.(8)(17).

The 1987 Revised Criteria for the Classification of RA

1. a. Four of seven criteria are required to classify a patient as having rheumatoid arthritis (RA).

b. Patients with two or more clinical diagnoses are not excluded.

2. Criteria[a]

a. Morning stiffness: Stiffness in and around the joints lasting 1 h before maximal improvement.

b. Arthritis of three or more joint areas: At least three joint areas, observed by a physician simultaneously, have soft tissue swelling or joint effusions, not just bony overgrowth. The 14 possible joint areas involved are right or left proximal interphalangeal, metacarpophalangeal, wrist, elbow, knee, ankle, and metatarsophalangeal joints.

c. Arthritis of hand joints: Arthritis of wrist, metacarpophalangeal joint, or proximal interphalangeal joint.

d. Symmetric arthritis: Simultaneous involvement of the same joint areas on both sides of the body.

e. Rheumatoid nodules: Subcutaneous nodules over bony prominences, extensor surfaces, or juxtaarticular regions observed by a physician.

f. Serum rheumatoid factor: Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in less than 5% of normal control subjects. [a]Criteria a–d must be present for at least 6 weeks. Criteria b–e must be observed by a physician. ***Source:*** From Arnett et al.(28)

ETIOLOGY:

The initiating cause of rheumatoid arthritis remains unclear.

1. Genetic factors:-

Genetic studies of the distribution of RA in families and in mono & dizygotic twins show that there is a small but definite contribution of genetic factors to the disease.

In twins studies, there is around 12-15% concordance of disease in identical twins and around 2- 5% in non-identical twins (1).10% of patients with RA will have an affected first degree relatives. Recent studies have shown an association between HLA-DR, (HLADW4 and HLA-DW14) and seropositive disease. In Indians RA is most commonly associated with HLA-DR1.(18)

2. Environmental factors:

It has been suggested that RA might be a manifestation of the response to an infectious agent in a genetically susceptible host .Organism included EBV , CMV , Parovirus B1931, Rubella virus and mycoplasma.

Cigarette smoking was associated with increased risk of RA.(16)

Exposure silica dust, organic solvent, mineral oils were associated with increased risk of RA. The mechanism by which these produce damage is not clear, probably by producing persistent infection of articular structures and by acting as super antigens. Of all the potential environmental structures, the only one clearly associated with the development of RA is cigarette smoking.(1)

3.Host factors.

RA is one of many autoimmune diseases that is predominant in women. Autoantibody-producing B cells exposed to estradiol are more resistant to apoptosis, suggesting that autoreactive B cell clones might escape tolerance. The effect on T lymphocytes is more difficult to reconcile with the female preponderance in RA because estrogen .Estrogen receptors are expressed on fibroblast-like synoviocytes (FLS) and, when stimulated, increase production of metalloproteinases in the synoviums tend to bias T cell differentiation toward the T helper type 2 (Th2) phenotype .

Exposure to oral contraceptive pills confers protection and postpone the onset of RA.(19-20).Pregnancy often is associated with remission of the disease in the last trimester. More than three

quarters of pregnant patients with RA improve in the first or second trimester, but 90% of these experience a flare of disease associated with an increase in RF titers in the weeks or months after delivery.(1) (21-24)

PATHOLOGY:

1.Rheumatoid disease process in the joints is characterized by(1)

a. Synovitis

b. Inflammatory effusion

c. Cellular exudates into the joint space

d. Damage to tendon, ligament and bone in and around articulating surfaces of the joint by the proliferating inflammatory tissue called pannus

2. Extra articular features associated with RA consist of two types of lesion.

• First is fibrointimal hyperplasia without inflammatory changes leading to vascular occlusion.

• Second lead to extravascular lymphocyte macrophage granuloma lesion of RA.

3. Extravascular nodule formation in areas subject to pressure is characteristic granulomatous lesion of RA.

PATHOGENESIS

The inflammatory synovial membrane produces large amount of immunoglobulins mainly as RF. In theory, self-reactive T cells might arise in RA from abnormal central (thymic) selection due to defects in DNA repair leading to an imbalance of T cell death and life, or defects in the cell signaling apparatus lowering the threshold for T cell activation. The inflammatory synovium contains activated T- lymphocyte, act as helper factors for B-cell proliferation, stimulate fibroblast to produce collagen and stimulate macrophage.Activated macrophages produce prostaglandin E2 and enzyme such as collagenase, IgG and IgM rheumatoid factors, elastase and cathepsin, TNF which may play a part in destruction of bone and cartilage. Effusion of synovial fluid into joint space takes place during active phases of the disease. Hypertrophy of the synovial membrane occurs with the formation of lymphoid follicles resembling an immunologically active lymph node.

Inflammatory granulation tissue (Pannus) is formed, spreading over and under the articular cartilage which is progressively eroded and destroyed. Later, fibrous adhesions may form between the layers of pannus across the joint space and fibrous or bony ankylosis may occur. Muscles adjacent to inflamed joints atrophy and there may be focal infiltration with lymphocytes.IL-1 and TNF have potent effects on synovial fibroblast and chondrocyte function that involve stimulation of prostaglandin and collangenase production as well as modulation of synthesis of proteoglycans, collagen and fibronectin. These cytokines may contribute to the local demineralization of bone by activating osteoclasts

Systemic manifestations of RA can be accounted for by release of inflammatory molecules from the synovium. These include IL-1, TNF, IL-6, which account for many of the manifestations of active RA **.(8)**

Evidence suggesting RA as autoimmune disease(1)

As a consequence of the persistence of the Rheumatoid Arthritis Agent and the consequent chronic stimulation of the

immune response, a variety of auto antibodies are formed and in particular rheumatoid factor. These factors and their ability to form immune complexes are thought to be responsible for some of the inflammatory lesions especially the extraarticular features, seen during the course of the disease. Some of the immune complexes formed locally in the joint while others may be formed in the circulation and deposition in the tissues.

Articular Disease:(1)

The most common symptoms are pain and stiffness. The latter frequently exhibit diurnal rhythms, worse on early morning. The affected joints worse as the disease advances, muscle atrophy tendon sheath and joint destruction results in limitation of joint movement, joint instability, subluxation and deformity.

Characteristic deformity include flexion contracture of small joints of hands and feet, the knee, hips and elbow. Axial involvement of cervical spine occurs in 8%, atlantoaxial subluxation upto 25% of patients. Sub axial subluxation present as a series risk of cord compression.

Laboratory Investigations (8)

Anemia of chronic disease is seen in the majority of patients with RA, and the degree of anemia is proportional to the activity of the disease. Therapy that controls the disease results in normalization of the hemoglobin. Thrombocytosis is common, with platelet counts returning to normal as the inflammation is controlled. White blood cell counts may be elevated, normal, or profoundly depressed as in the case of Felty syndrome

Acute phase reactants, erythrocyte sedimentation rate and C-reactive protein levels, also parallel the activity of the disease, and their persistent elevation portends a poor prognosis, both in terms of joint destruction and mortality

Rheumatoid factor, an autoantibody directed against the constant (Fc) region of IgG is positive in about 50% of cases at presentation and an additional 20–35% of cases become positive in the first 6 months after diagnosis. Rheumatoid factor has an unfortunate name because it is not unique to RA and occurs in many other diseases, particularly those characterized by chronic stimulation of the immune system. In RA, the presence of

rheumatoid factor is associated with more severe articular disease, and essentially all patients with the extra-articular features are seropositive for rheumatoid factor.

AIMS AND OBJECTIVES

1. To study the prevalance of thyroid dysfunction in rheumatoid arthritis
2. To study the incidence of autoimmune thyroditis in rheumatoid arthritis

MATERIALS AND METHODS

Study design:

Cross sectional observational study to analyse the prevalence of thyroid dysfunction and thyroid autoimmunity in rheumatoid arthritis .

Setting:

Rheumatology and Medicine OPD,

Govt Rajaji Hospital**,** Madurai**.**

Approval:

The study was approved by the ethical committee of Govt Rajaji Hospital, Madurai.

Study population:

Fifty patients of Rheumatoid arthritis and forty age and sex matched healthy controls , between the age of 17 to 60 years were selected for the study from Rheumatology clinic and outpatient department of Internal Medicine, Government Rajaji Hospital, Madurai between (September 2010 to September 2011) after thorough history taking and clinical examination and by exclusion

criteria. All the RA patients were selected on the basis of 1987 Revised American Rheumatism Association Criteria for the classification of rheumatoid arthritis

INCLUSION CRITERIA:

Diagnosed cases of rheumatoid arthritis according to 1987 Revised American Rheumatism Association Criteria for classification of rheumatoid arthritis.

EXCLUSION CRITERIA:

Patients with rheumatoid arthritis with the following conditions were excluded from the study

1. Nephrotic syndrome
2. Diabetes mellitus
3. Thyroid disorders
4. Liver disorders
5. Drugs like

a. Diuretics

b. Oral contraceptives

Patients suffering from inflammatory diseases, diabetes mellitus, renal disorders, thyroid disorders and diseases known to

affect the hormonal status were excluded from the study. Patients on medications known to alter the hormonal levels, pregnant, postpartum and post menopausal patients were excluded from the study.

Consent:

Patients were informed about the details of the test performed and obtained consent before collecting blood samples. Any patient not willing to cooperate after initially signing the informed consent was allowed to withdraw from the study

Method of testing:

T3,T4, TSH -- Chemiluminescence.

Thyroid peroxidase -- Enzyme Linked Immuno Sorbent Assay.

Normal ranges:

T**3** -- 77-135 ng/dl

T4 --5.4-11.7 μg/dl

TSH –0.34-4.2 μIU/ ml

TPOA upto 75U/ml

Result interpretations:

- Any T3 /T4 value above the upper limit of normal along with a low TSH < 0.34 mIU/ml is considered as hyperthyroidism.
- Any T3 /T4 value below the lower limit of normal along with an elevated TSH > 4.2 μIU/ ml is considered as hypothyroidism.
- TSH > 4.2 μIU/ ml along with normal range T3 , T4 is considered as subclinical hypothyroidism.
- TSH < 0.34 μIU/ ml along with normal range T3 ,T4 is considered as subclinical hyperthyroidism.
- Thyroid autoimmunity is considered to exist if TPOA level is > 75IU/ml and not to exist if it is lesser

Statistical analysis:

Statistical analysis was carried out for 90 participants (50 RA patients, 40 controls) after categorizing each variable. Base line data was collected from patients.RF,T3,T4,TSH and TPO in patients with thyroid dysfunction were analyzed. The significance

of difference in mean between two groups were analyzed by student t test. Statistical significance was taken when p value < 0.05. Statistical analysis was carried out using standard formulae. Microsoft excel 2007 and SPSS (statistical package for social sciences) version 13 software was used for data entry and analysis.

OBSERVATIONS AND RESULTS

TOTAL NUMBER OF PATIENTS : 50

FEMALE : 42

MALE : 8

AGE : 17-60 YEARS

MEAN AGE : 41.82 YRS

TOTAL NO. OF HYPOTHYROID PATIENTS : 7 (14%)

MALE : 1

FEMALE : 6

SUBCLINICAL HYPOTHYROIDISM : 3(6%)

OVERT HYPOTHYROIDISM : 4(8%)

TOTAL NO. OF HYPERTHYROID PATIENTS. : NIL

TOTAL NO. OF HYPOTHYROID PATIENTS

WITH TPOA : 2/7 (22%)

MALE : 0

FEMALE : 2

MEAN AGE OF PATIENTS WITH AITD : 45.5 YRS

TABLE 1

THYROID STATUS IN RELATION TO GENDER.

THYROID STATUS	TOTAL NO. (IN%)	GENDER	
		Male	Female
EUTHYROID	43 (86%)	7 (16.3%)	36 (83.7%)
HYPOTHYROID	7 (14%)	1 (14.3%)	6 (85.7%)
HYPERTHYROID	0	0	0

On comparing the female : male 5.2:1 ratio by **chi square test** , the p value is 1.0 and 0.457.. which is > 0.05 . So, the association between gender and hypothyroidism is not significant indicating that there is no significant gender difference among hypothyroid and euthyroid rheumatoid arthritis as per this study.

CHART 1

THYROID STATUS IN RELATION TO GENDER IN ACTUAL NUMBERS

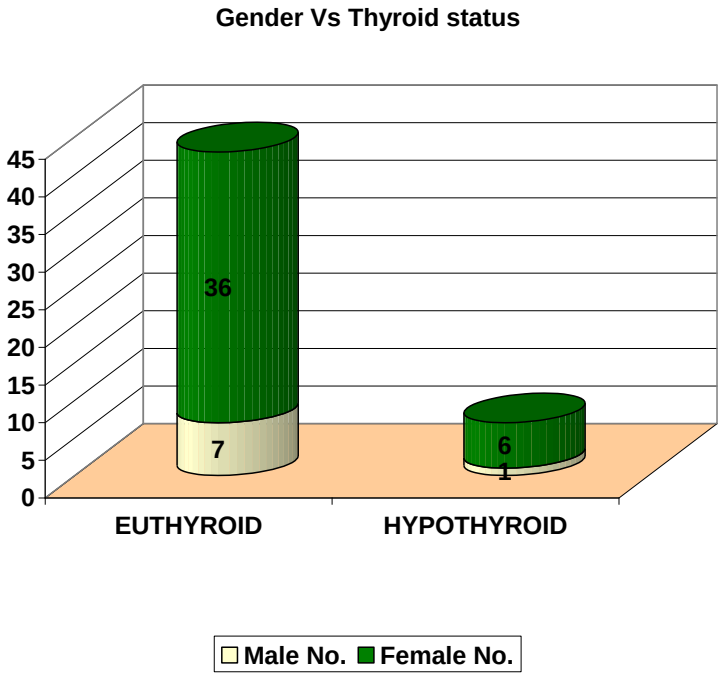


TABLE:2

COMPARISON OF T3 VALUES IN

CASES AND CONTROLS

	CASE	CONTROL
MEAN	99.70	134.8
STANDARD DEVIATION	22.29	31.37
P VALUE	<0.001	

On comparing the T3 by **chi square test** , the p value is 0.001 which is < 0.05 . So,there is significant abnormality in T3 levels in rheumatoid arthritis.

. CHART 2

COMPARISON OF T3 VALUES IN

CASES AND CONTROLS

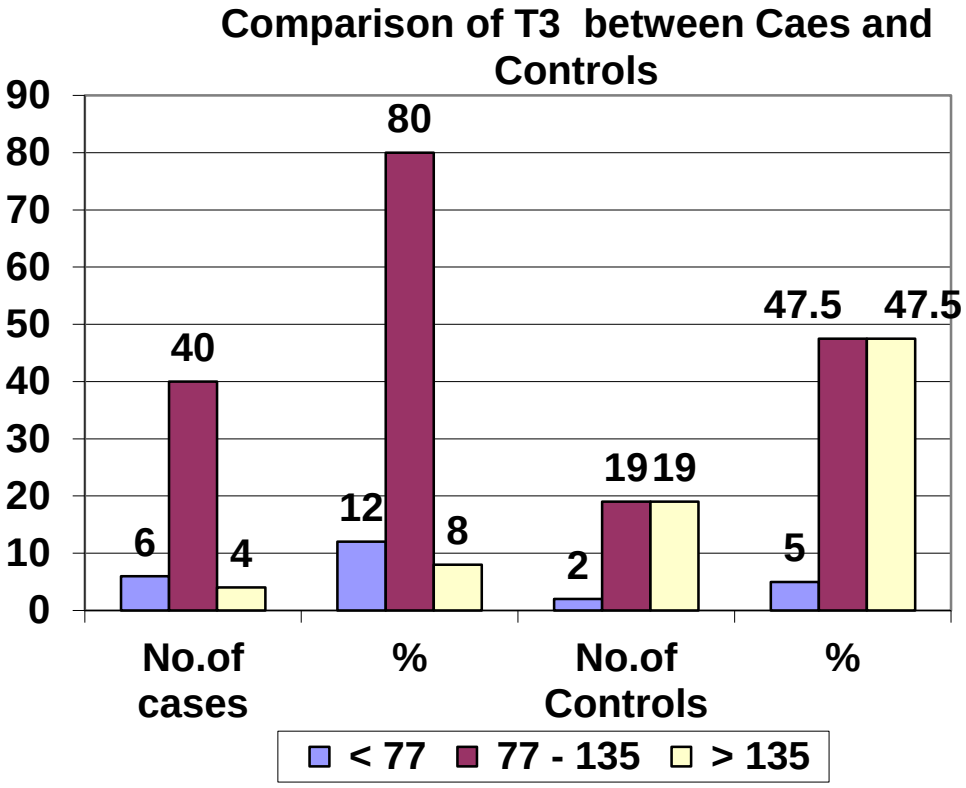


TABLE :3

COMPARISON OF T4 VALUES IN

CASES AND CONTROLS

	CASE	CONTROL
MEAN	6.49	9.2
STANDARD DEVIATION	4.72	3.03
P VALUE	0.002	

On comparing the T4 by **chi square test** , the p value is 0.002 which is < 0.05 . So,there is significant abnormality in T4 levels in rheumatoid arthritis

CHART 3:

COMPARISON OF T4 VALUES IN

CASES AND CONTROLS

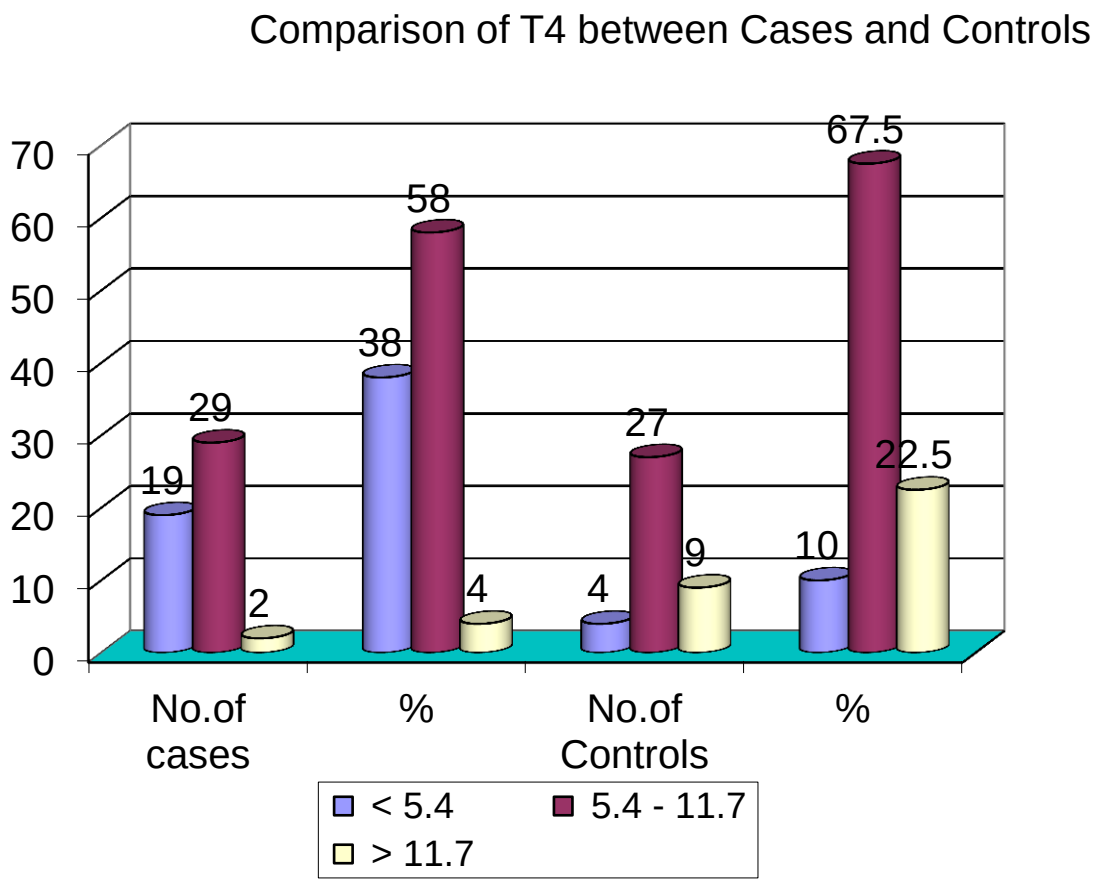


TABLE :4

COMPARISON OF TSH VALUES IN

CASES AND CONTROLS

	CASES	CONTROLS
MEAN	2.75	1.96
STANDARD DEVIATION	1.96	0.96
P VALUE	0.04	

On comparing the TSH by **chi square test** , the p value is 0.04 which is < 0.05 . So,there is significant abnormality in TSH levels in rheumatoid arthritis

CHART :4

COMPARISON OF TSH VALUES IN CASES AND CONTROLS

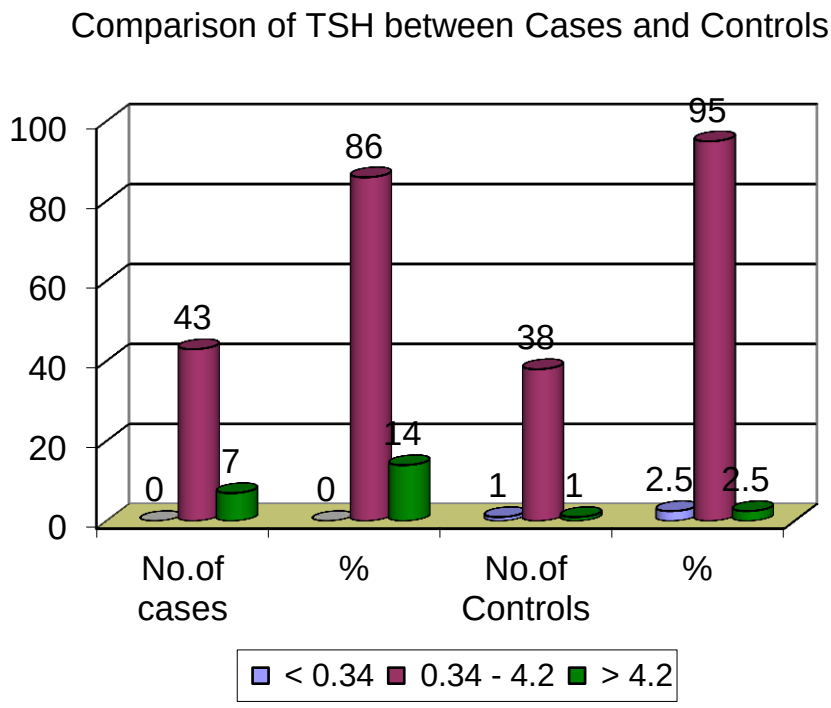


Table - 5

AGE WISE DISTRIBUTION OF THYROID DYSFUNCTION

AGE	TOTAL NO	EUTHYROID	HYPOTHY ROID	SUBCLINICAL HYPOTHYROID	SUBCLINICAL HYPERTHYROIDISM
20-29	3	1	2	0	0
30-39	16	15	0	1	0
40-49	21	19	2	0	0
50-50	7	6	0	1	0
60-69	3	2	0	1	0

In our study thyroid dysfunction in rheumatoid arthritis is common in 20-50 age group.

Chart - 5

PREVALENCE OF THYROID DYSFUNCTION IN

RHEUMATOID ARTHRITIS

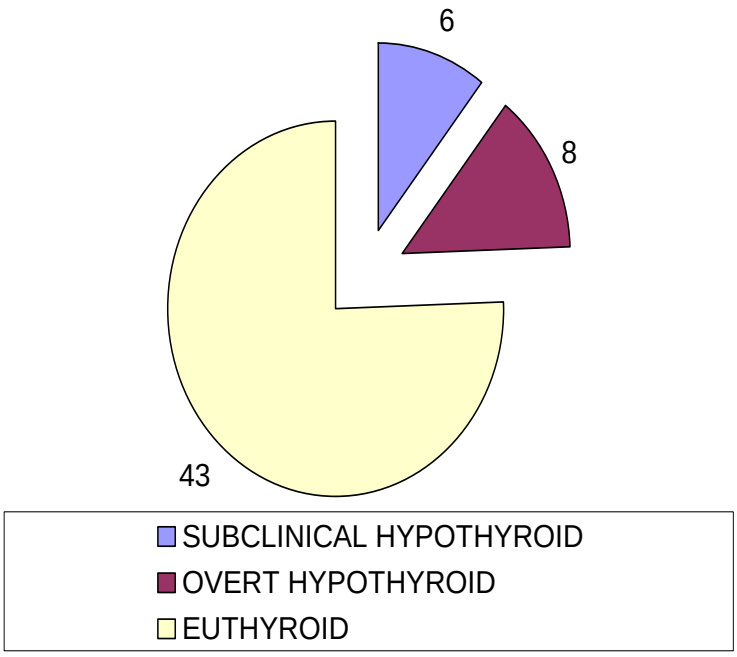


Chart - 6

PREVALENCE OF AUTOIMMUNE HYPOTHYROIDISM

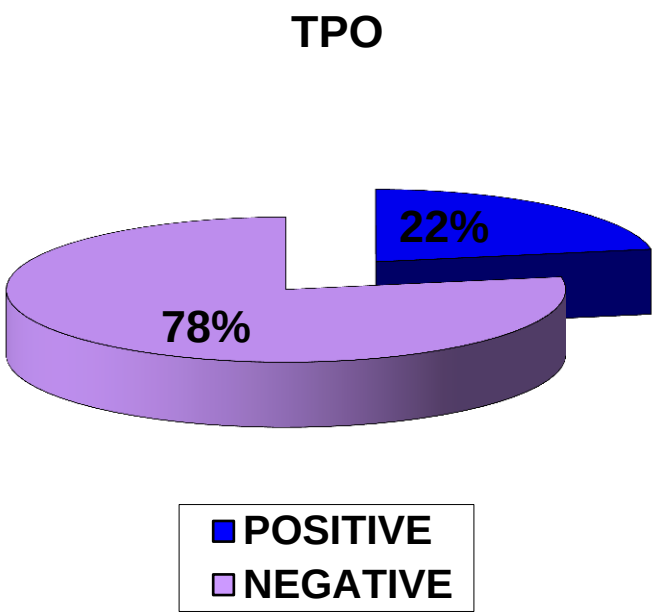
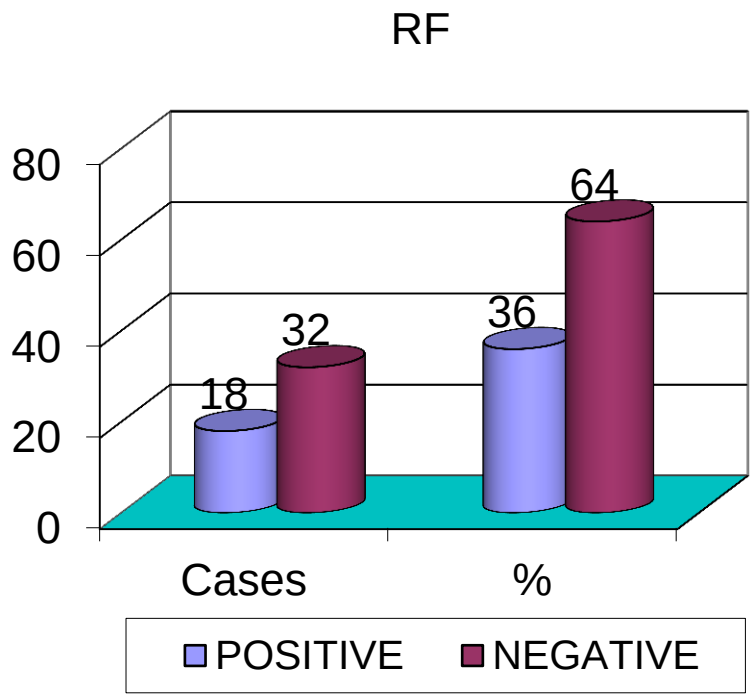


Chart – 7

Rheumatoid Factor



18 cases were RF positive and 32 were RF negative

INTERPRETATION OF RESULTS:

- Among patients with thyroid dysfunction in rheumatoid arthritis there is no statistically significant difference in gender .
- Prevalence of thyroid dysfunction in rheumatoid arthritis is 14%.
- Abnormal thyroid function is mainly in the form of both overt and subclinical hypothyroidism.
- Prevalence of autoimmune Hypothyroidism in rheumatoid arthritis is 22%.

DISCUSSION

Prevalence of Thyroid dysfunction in rheumatoid arthritis:

The reported prevalence of thyroid dysfunction in rheumatoid arthritis populations varies widely between studies. But, thyroid dysfunction is found to be associated with organ specific antibody.

In a study by Fabiola Atzeni (13)to assess thyroid function as well as the prevalence and clinical value of anti-thyroid antibodies in patients with rheumatoid arthritis (RA) done in 70 RA patients , 9 males and 61 females, mean age 47 years (range 15–77) were analyzed. **:** Twenty-six patients (37%) with RA were positive for TPOAb and 16 (23%) for TgAb. In 5 (7.1%) patients TSH level was slightly elevated. The increase of TSH levels was associated with normal FT4 in 3 cases (4.2%) and with reduced FT4 in 2 cases (2.8%). One patient (1.5%) had low TSH serum value along with normal FT4.

Another study by(14). Caron P, Lassoued S, Dromer C, Oksman F, Fournie A to find the prevalence of thyroid abnormalities in patients with rheumatoid arthritis. Prevalence of hypothyroidism and autoimmune thyroiditis and was 19.1% and 16.2% respectively.

In study by (2)Przygodzka M, Filipowicz-Sosnowska regarding prevalence of thyroid diseases and antithyroid antibodies in women with rheumatoid arthritis done among 100 patients with RA thyroid function and antithyroid antibodies were assessed. ATD was more prevalent (16%) in patients with RA than in the control group (9%). The difference was no statistically significant. Antithyroglobulin (anti-TG) and antithyroid peroxidase (anti-TPO) antibodies were (12% and 15%, respectively) in patients with RA and (9% and 18%, respectively) in the control group . The most common thyroid dysfunction observed in both groups was subclinical hypothyroidism.

A study by (3) El-Sherif WT El Gendi SS, Ashmawy MM, Ahmed HM Salama MM thyroid disorders and autoantibodies in systemic lupus erythematosus and rheumatoid arthritis done among

20 patients with SLE and 20 with RA were studied. The results were compared with 20 healthy age and sex matched controls. This study revealed that thyroid disorders in RA, 10% had hypothyroidism (subclinical) and 5% had subclinical hyperthyroidism. TPOAb was found in 5% of RA patients and 10% of controls.

A study by Gonçalves, Fabrícia Torres MD et al, (26) autoimmune thyroiditis and rheumatoid arthritis :is there really an association? done in 189 patients and 117 with nonautoimmune rheumatic diseases. Thyroid dysfunction was found in 11, and thyroid autoantibodies in 15 RA patients, compared with 18 and 13 of the control group, respectively. The conclusion was there is no association between thyroid disease and RA.

On the whole, in agreement with many similar reports, we observed a higher prevalence of thyroid dysfunction in our study and hypothyroidism was the thyroid dysfunction found ,none of the patients had hyperthyroidism.

Prevalence of Thyroid autoimmunity in ra:

In study by(2) Przygodzka M, Filipowicz-Sosnowska A regarding prevalence of thyroid diseases and antithyroid antibodies in women with rheumatoid arthritis done among 100 patients with RA thyroid function and antithyroid antibodies were assessed. ATD was more prevalent (16%) in patients with RA than in the control group (9%). The difference was no statistically significant. Antithyroglobulin (anti-TG) and antithyroid peroxidase (anti-TPO) antibodies were present in similar percentage of patients with RA (12% and 15%, respectively) and in the control group (9% and 18%, respectively.

(3) El-Sherif WT El Gendi SS, Ashmawy MM, Ahmed HM Salama MM Thyroid disorders and autoantibodies in systemic lupus erythematosus and rheumatoid arthritis done among 20 patients with SLE and 20 with RA were studied. The results were compared with 20 healthy age- and sex- matched controls. TPOAb was found in 5% of RA patients and 10% of controls, and ATGAb 30% of RA patients and 10% of controls.

In a study by(13) Fabiola Atzeni to assess thyroid function as well as the prevalence and clinical value of anti-thyroid

antibodies in patients with rheumatoid arthritis (RA) done in 70 RA patients , 9 males and 61 females, mean age 47 years (range 15–77) were analyzed. **:** Twenty-six patients (37%) with RA were positive for TPOAb and 16 (23%) for TgAb. In 5 (7.1%) patients TSH level was slightly elevated, this study shows an increased prevalence of anti-thyroid antibodies in RA patients with a low prevalence of hormonal alterations

On analysing TPO antibodies in those with thyroid dysfunction prevalence was 22 % which was also comparable with the previous studies.

CONCLUSION

- Prevalence of hypothyroidism in RA is more than that seen among general population.
- Some patients develop subclinical form of the disease thus reducing the possibility of clinical suspicion.
- There is an association of thyroid autoimmunity and thyroid dysfunction in RA.

In summary, our study confirms that the prevalence of thyroid dysfunction in rheumatoid arthritis is high and is associated with thyroid autoimmunity and suggest that all rheumatoid arthritis patients should undergo thyroid function

testing and those with elevated TSH should go for autoimmune screening with TPO.

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PROFORMA

STUDY OF THYROID DYSFUNCTION IN RHEUMATOID ARTHRITIS

Name :

Age :

Sex :

Ip no :

Address :

Phone no :

C/F

Hyperthyroidism:

Hyperactivity, irritability

Heat intolerance

Palpitation

Weakness

Wt loss

Diarrhoea

Polyuria

Hypothyroidism:

Fatigue

Puffy face

Wt gain

Constipation

dry coarse skin

Hoarse voice

Cold intolerance

PAST HISTORY :

HTN / DM / TB / BA /ATT /CAD /

CVA / RHD/

Hypothyroidism

Hyperthyroidism

On thyroxine

Antithyroid drugs

PERSONAL HISTORY

Smoking , alcoholism

GENERAL EXAMINATION

PR

BP

Jaundice

Pallor/odema/cyanosis

Hypothyroidism

Thyroid swelling

Alopecia

Carpel tunnel syndrome

Serous cavity effusion

Bradycardia

Pseudomyotonia

Peripheral odema

Hyperthyroidism

Tachycardia,AF

Tremor

Goiter

INVESTIGATIONS: FOR THYROID DYSFN

T4

T3

TSH

Anti-TPO

Investigations for RA

RA factor

ABBREVIATIONS

T4	-	Tetraiodothyronine
T3	-	Triiodothyronine
TSH	-	Thyroid stimulating hormone
Tg	-	Thyroid globulin
TPO	-	Thyroid peroxidase
AITD	-	Autoimmune thyroid disease
RA	-	Rheumatoid Arthritis

MASTER CHART-CASES

S.No	name	age	sex	RF	T3	T4	TSH	TPO
1	lexmi	40	F	y	110.54	10.9	2.7	
2	ravi	40	M	y	91.86	6.4	3.3	
3	ibrhim	51	M	n	125.37	8.9	2.4	
4	mariama	53	F	y	96.8	8.8	5.26	14.4
5	alagamma	30	f	y	123.72	9.2	4.65	16.2
6	paramesh	27	f	y	90.8	1.13	8	124
7	subalexmi	59	f	n	63.68	6.8	5.46	150
8	velmani	30	f	n	116.83	10.3	2.6	
9	muthumar	36	f	y	96.97	10.7	0.9	
10	mathai	60	m	n	89.59	7.1	2.5	
11	alagu	48	m	n	104.6	9.7	2.4	
12	jayamala	30	f	n	98.41	18.3	0.84	
13	muthurak	48	f	n	131.78	11.5	2.48	
14	adakala	45	f	n	144.77	7.6	2.87	
15	muthu.k	48	m	n	114.65	10.5	2.8	
16	lexmi	34	f	y	65.22	6.4	2.7	
17	nagalexm	44	f	n	122.89	11.6	4.15	
18	dhanam	55	f	n	56.35	8	2.4	
19	kavitha	35	f	n	99.03	9.2	2.3	
20	muthulex	60	f	n	98.67	11.1	0.49	
21	muthurak	40	f	y	136.22	9.4	1.6	
22	rabith	43	f	y	89	9.6	0.66	
23	raja	43	m	y	89.49	9.6	2.3	
24	kalavathi	43	f	n	87.94	8.3	2.13	
25	thenmozhi	45	f	n	109.4	9.4	2.2	
26	pushpa	49	f	n	99.32	10.3	2.77	
27	jothimani	44	f	y	78.56	8.9	1.95	
28	sivakami	25	f	n	92.67	10.6	2.7	
29	panchavar	34	f	y	91.32	9.3	4.12	
30	manimala	33	f	n	160	1.19	2.5	
31	rajathi	40	f	n	33	1.3	7.8	68
32	kamala	55	f	n	78	1.16	2.4	
33	sankar	56	m	n	90	1.07	1.6	
34	arumugm	59	m	n	80.6	0.81	0.6	
35	santhi	35	f	n	87.8	0.99	2.9	
36	kripavathi	39	f	n	80	1.03	1.8	
37	kavitha	18	f	n	120	0.92	1.7	
38	vasanthy	35	f	y	140	1.68	0.76	
39	valarmath	49	f	y	130	1.51	2.5	
40	meena	45	f	n	120	1.5	0.72	
41	shamala	32	f	y	80	1.57	2.7	
42	kanimozhi	33	f	y	120	0.98	3.8	
43	sumathy	28	f	n	130	1.2	8.9	64
44	rama	40	f	y	50	0.31	6.7	48
45	veena	38	f	n	128	0.97	2.4	
46	lalitha	45	f	n	90.2	2.4	3.4	
47	mari	50	f	y	74	0.44	4.1	
48	thangam	42	f	n	88	8.4	2.4	
49	leelavathi	36	f	n	90.6	7.6	1.56	
50	jayamala	30	f	n	98.41	18.3	1.4	

S.No.	name	age	sex	T3	T4S	TSH
1	kala	28	f	130	12.62	1.36
2	Raman	51	m	126	8.6	1.22
3	ramany	53	f	114	8.8	2.2
4	kalavathy	30	f	128	12.6	2.4
5	parvathy	27	f	110	7.6	2.34
6	kalyani	60	f	90	5.5	0.72
7	Ramesh	40	m	136	2	2.6
8	nithya	33	f	75	4.4	1.3
9	muthulexmi	40	f	128	13.2	0.02
10	rasiya	32	f	140	9.7	2
11	meena	49	f	240	12.3	1.8
12	mariya	45	f	111	11.6	1.6
13	meenakshi	35	f	128	10	2.2
14	kavitha	18	f	147	10.2	4.1
15	suhasini	39	f	128	12.4	2.57
16	subalexmi	35	f	142	7.1	0.58
17	Senthil	59	m	155	8.4	5.2
18	padma	55	f	140	5.4	2.1
19	revathi	40	f	136	16.3	1.2
20	sumathy	33	f	168	5.7	2.2
21	panchu	34	f	178	8.2	2.9
22	amritha	25	f	136	7.6	2.4
23	chandra	48	f	87	4.6	1.6
24	indira	49	f	196	7.1	1.8
25	umavathy	45	f	135	8.9	2.6
26	rakku	42	f	160	9.5	0.44
27	Murugan	43	m	116	5.6	2.6
28	sormam	43	f	126	10.7	2.1
29	gandhimathy	40	f	130	13	2.6
30	yamini	60	f	170	10.8	2.5
31	deepa	35	f	136	9.2	1.5
32	muthuraku	55	f	148	10	2.8
33	ramany	45	f	163	12.1	2.4
34	radha	34	f	128	10.7	2.2
35	Selvan	48	m	168	7	2.4
36	jannet	45	f	98	9.9	0.8
37	indhumathi	45	f	110	11.5	2.4
38	sandhya	30	f	122	11	3
39	Mariappan	48	m	138	11.9	3.3
40	susheela	33	f	75	4.4	1.3