AN OBSERVATIONAL STUDY TO COMPARE CRP LEVEL WITH HDL LEVEL IN RHEUMATOID ARTHRITIS PATIENTS

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MD DEGREE (BRANCH 1) GENERAL MEDICINE

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CHENNAI, TAMILNADU

CERTIFICATE FROM THE DEAN

This is to certify that the dissertation entitled "**AN OBSERVATIONAL STUDY TO COMPARE CRP LEVEL WITH HDL LEVEL IN RHEUMATOID ARTHRITIS PATIENTS"** is the bonafide work of **DR. S.KARTHIKEYAN** in partial fulfillment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for **M.D General medicine Branch I** examination to be held in **April 2017.**

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DECLARATION

I, **Dr. S. KARTHIKEYAN,** solemnly declare that this dissertation titled **"AN OBSERVATIONAL STUDY TO COMPARE CRP LEVEL WITH HDL LEVEL IN RHEUMATOID ARTHRITIS PATIENTS**" is a bonafide record of work done by me at the Department Of General Medicine, Government Rajaji Hospital, Madurai, under the guidance of **Dr.J.SANGUMANI M.D**, **D.DIAB.,** Professor, Department of General Medicine, Madurai Medical College, Madurai. This dissertation is submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai in partial fulfilment of the rules and regulations for the award of M.D Degree General Medicine Branch- I examination to be held in April 2017.

Place: Madurai **Dr. S. KARTHIKEYAN**

Date:

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CONTENTS

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic disease that primarily targets the synovium, leading to synovial inflammation and proliferation, loss of articular cartilage, and erosion of juxtarticular bone. The natural history of the disease is one of progressive joint damage and deformity and, in a sizeable minority, the development of extra-articular manifestations. Over the last few decades it has become increasingly apparent that chronic activation of the immune system, as observed in the pathogenesis of RA, is associated with changes in intermediary metabolism, potentially leading to increased risk of cardiovascular disease. There is evidence of association of multiple immune regulatory components (including tumour necrosis factor and interleukin-6) in RA.

Dyslipidemia is a major risk factor for atherosclerosis and cardiovascular disease. In RA patients significant decrease levels of HDL cholesterol along with hypercholesterolemia is seen compared with controls. It is found that dyslipidemia can manifest in RA patients with both early and advanced disease. Thus altered lipoproteins along with an increase in lipid peroxidation products suggests that RA patients are at a high risk for the development of coronary heart disease. LDL is associated with the risk of coronary heart disease and also has been shown to undergo oxidation forming oxidized LDL, which leads to

phospholipid release, activating endothelial cells, thereby initiating an inflammatory process which leads to the formation of foam cells and subsequent fatty streaks. Under normal condition HDL exerts its anti atherogenic role by protecting LDL from oxidation. The present study showed that RA patients exhibited high TC and low HDL serum levels. The increment in TC was directly correlated with the increment of CRP level and ESR values. The decrement in HDL-C was inversely correlated with the increment of CRP level and ESR values. It suggested that inflammation is an important determinant for the reduced HDL-C levels observed in RA patients and the correlation between TC and ESR and CRP in active RA patients raises the possibility that cholesterol behave like an activity marker. C-reactive protein and ESR are acute phase reactants for RA which increase in active disease may contribute to atherosclerosis because it stimulates macrophage to produce tissue factor, a pro coagulant that is found in atherosclerotic plaque and significantly associated with risk of CVD in RA. The present study showed as well there is a significant correlation between HDL and duration of the disease, and inversely significant correlation between LDL and disease duration. These results are in agreement with other studies which found that effective treatment of an inflammatory process may prove beneficial for dyslipoproteinemia and possibly the risk of cardiovascular disease and related mortality. Active RA was associated with an adverse lipid

profile that improved significantly upon effective treatment of RA with disease-modifying anti-rheumatic drugs (DMARD) suggesting it was the decrease in RA disease activity that reversed the altered lipid profiles. The present study concluded that patients with RA were characterized by an atherogenic lipid profile, which improves after therapy. Thus, early intervention to control disease activity may reduce the risk of the atherosclerotic process and cardiovascular events in RA patients.

AIMS AND OBJECTIVES

- To compare CRP level with HDL level in rheumatoid arthritis patients
- To improve the long term survival of Rheumatoid arthritis patients by early detection of dyslipidemia and timely institution of treatment

REVIEW OF LITERATURE

RHEUMATOID ARTHRITIS

Most common form of chronic inflammatory arthritis is Rheumatoid arthritis which is idiopathic in nature. It commonly presents with peripheral polyarthritis which is symmetric in nature. Rheumatoid arthritis can present with extra articular manifestations because of systemic nature of disease. Rheumatoid arthritis cause significant mortality and morbidity. Compared with general population, patients with Rheumatoid arthritis has short life expectancy. Mortality rate is two times higher than general population. Leading cause of death in patients with Rheumatoid arthritis is cardio vascular disease. Because of chronic activation inflammation in Rheumatoid arthritis leads to changes in the lipid profile.it accelerates atherosclerosis which leads to increased cardiovascular mortality and morbidity in rheumatoid arthritis patients.

EPIDEMIOLOGY

It affects 0.5 - 1% of adult population. In African and American countries it is around 0.2 - 0.4%. It has highest prevalence in Native Americans which is around 7%.

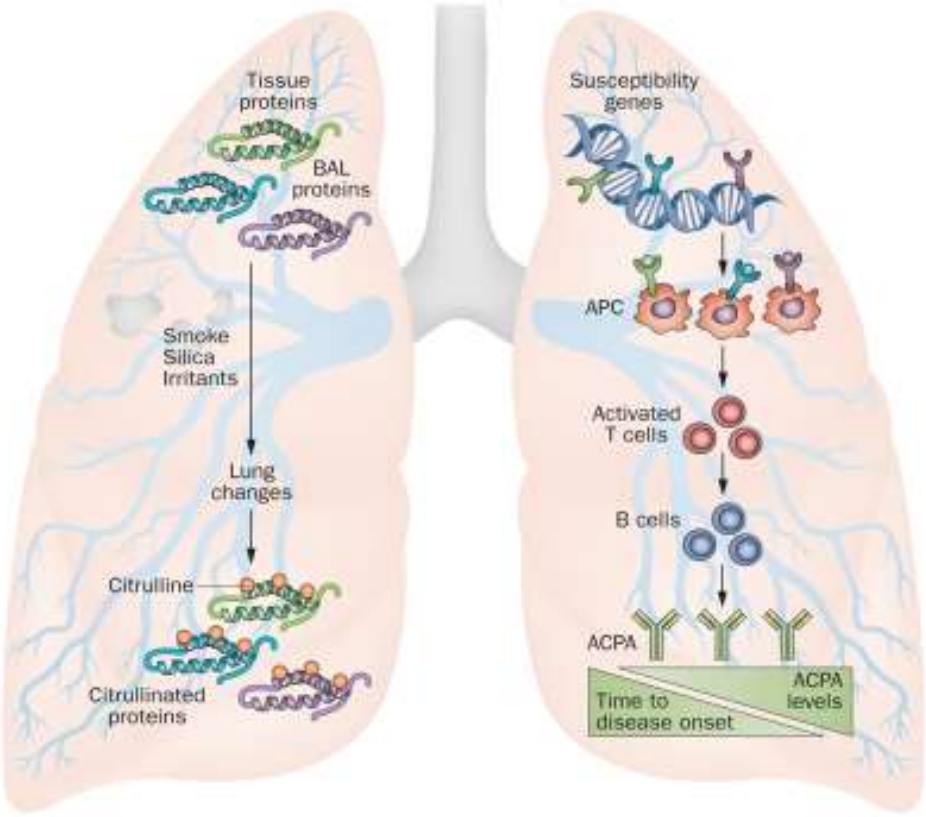
It affects adults between 25 to 55 years with increasing incidence. Incidence decreases after 75 years of age. Females are more commonly affected than males. Female to male ratio is 3:1. Highest female to male ratio is seen in Latin American and African. It is 6-8:1.

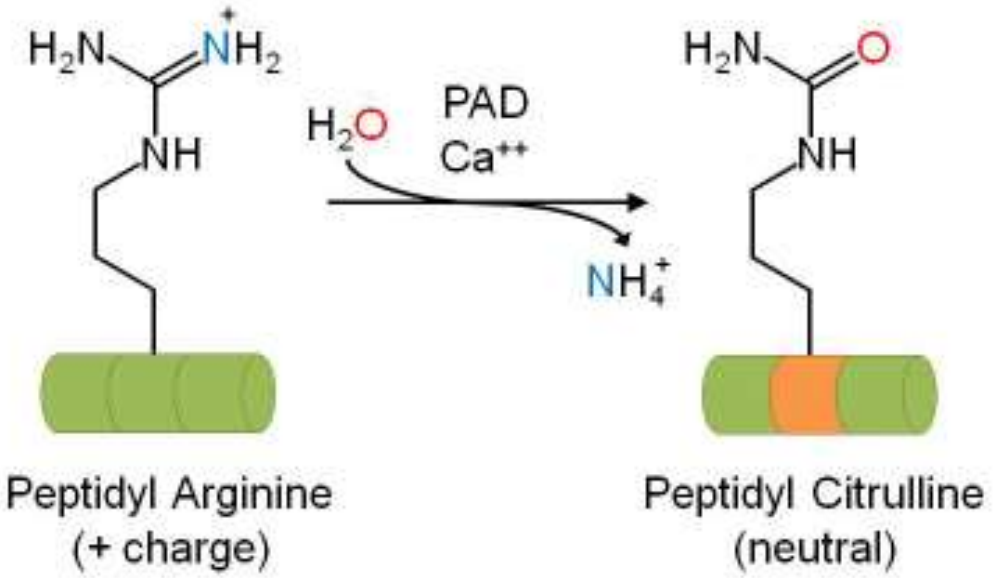
Tumor necrosis factor production is enhanced by estrogen, which may be reason behind increased female prevalence.

GENETIC CONSIDERATIONS

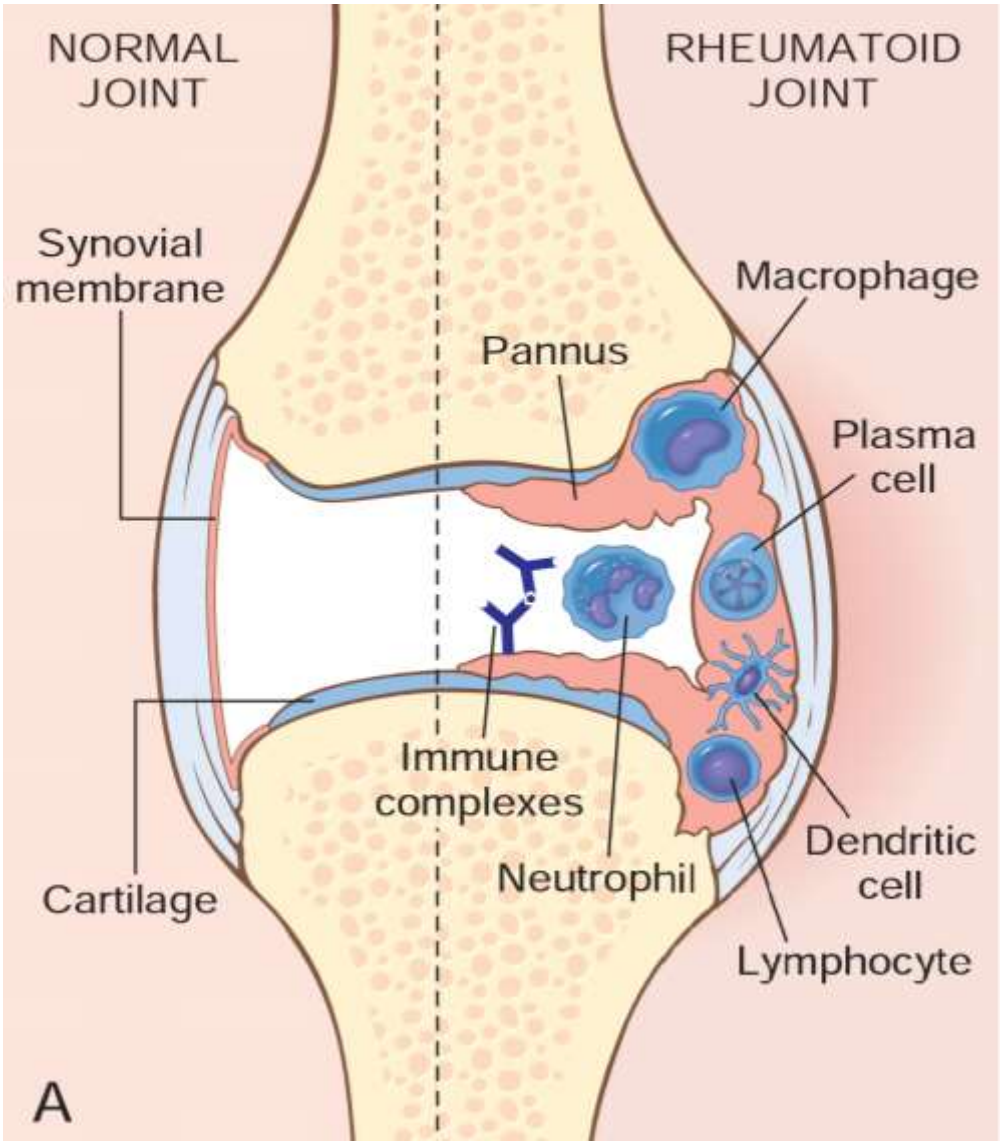
First-degree relative of a patient have risk of 2-10 times greater than general population. Most important alleles are located within the major histocompatibility complex. One-third of genetic risk resides within this locus. Most of this risk is associated with allelic variation in the HLA-DRB1 gene. HLA-DRB1*0401 is associated with high risk of disease. Alleles associated with moderate risk are *0101, *0404, *0901 and *1001. Most common alleles in Asians are *0405, and *0901. Several non-MHC- related genes also contribute like PTPN22/CTLA4.

The peptidyl arginine deiminase type IV (*PADI4*) gene is another risk allele that encodes an enzyme involved in the conversion of arginine to citrulline and is postulated to play a role in the development of antibodies to citrullinated antigens. A polymorphism in *PADI4* has been associated with RA only in Asian populations.

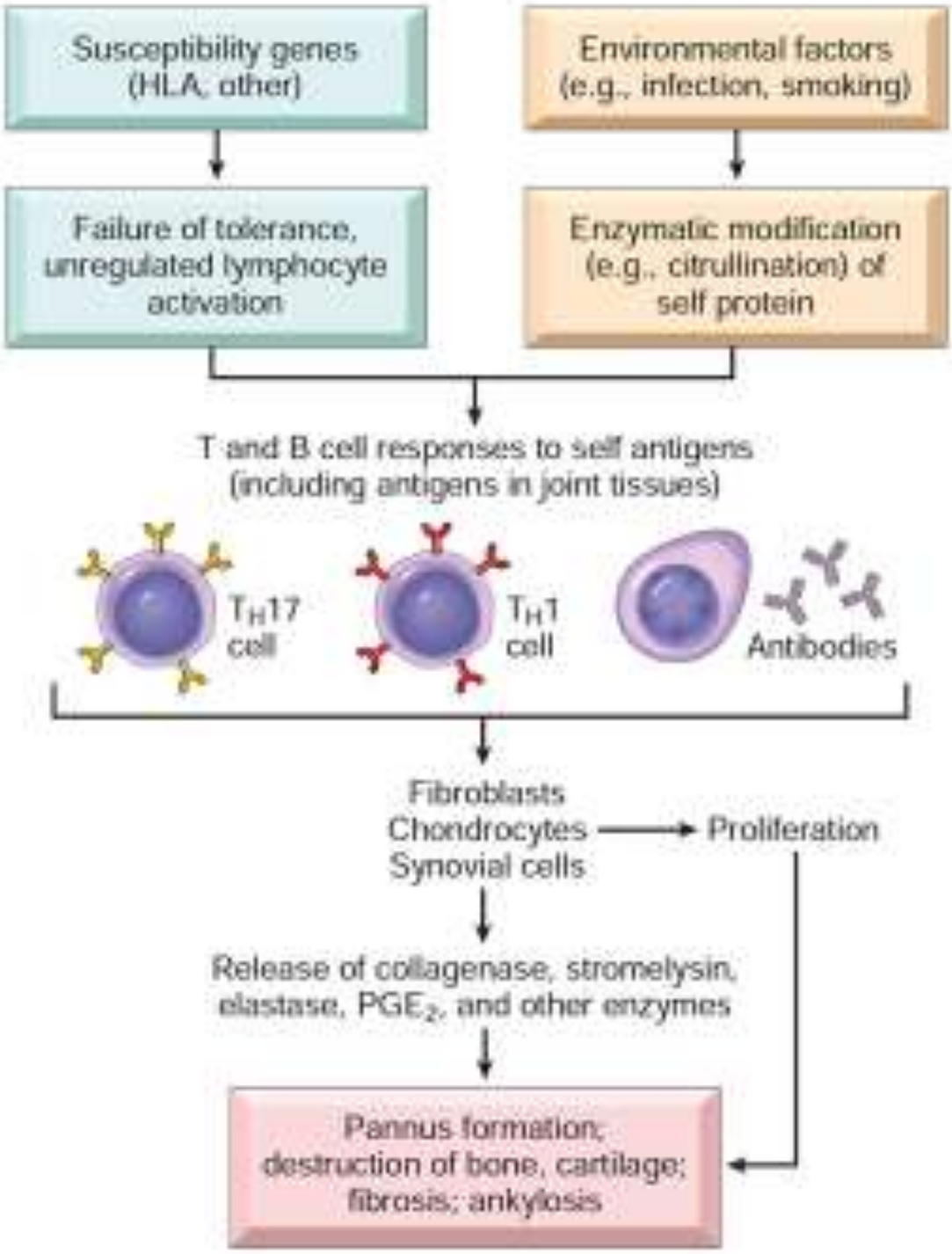

Tissue proteins
BAL proteins
Smoke
Silica
Irritants
Lung changes
Citrulline
Citrullinated proteins
Susceptibility genes
APC
Activated T cells
B cells
ACPA
ACPA levels
Time to disease onset


H_2N
NH_2^+
NH
H_2O
PAD
Ca^{++}
NH_4^+
H_2N
O
NH
Peptidyl Arginine
(+ charge)
Peptidyl Citrulline
(neutral)

The most reproducible of these environmental links is cigarette smoking. Numerous cohort and case control studies have demonstrated that smoking confers a relative risk for developing RA of 1.5–3.5. In particular, women who smoke cigarettes have a nearly 2.5 times greater risk of RA, a risk that persists even 15 years after smoking cessation. A twin who smokes will have a significantly higher risk for RA than his or her monozygotic co-twin, theoretically with the same genetic risk, who does not smoke. Interestingly, the risk from smoking is almost exclusively related to RF and anti-CCP antibody-positive disease. People who are smoking, will be having more circulating level of antibody against CCP(cyclic citrullinated peptide). Normally airways are devoid of citrulline. When a person smokes, it will change the airway epithelium to have citrulline from arginine. Now our immune system will recognize this as foreign antigen, will produce antibody called as anti-CCP antibody.



This image represents normal joint & Rheumatoid joint In rheumatoid joint, there will be a long standing synovitis which leads to pannus formation. Pannus is nothing but hypertrophied synovium. It will start eroding the underlying cartilage & bone. Finally patients with synovitis will land up in erosive arthritis. That erosion will be classically seen in margin of joint (marginal erosion) there only bone is devoid of articular cartilage. Synovial fluid is filled with inflammatory cells and immune complex.



PATHOGENESIS OF RA

CLINICAL FEATURES ARE CLASSIFIED INTO

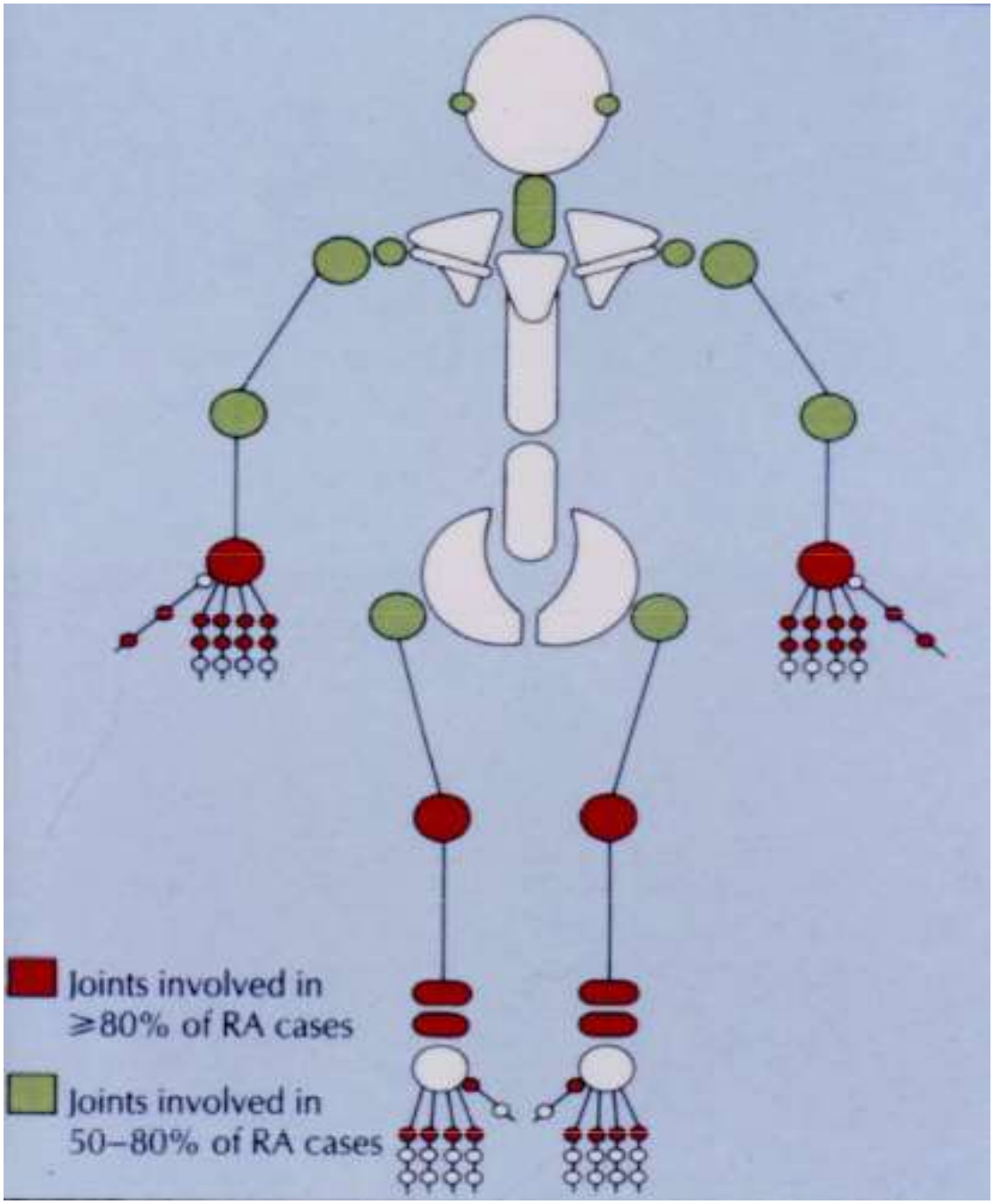
1. ARTICULAR (most common)

2. EXTRA ARTICULAR (30-40%)

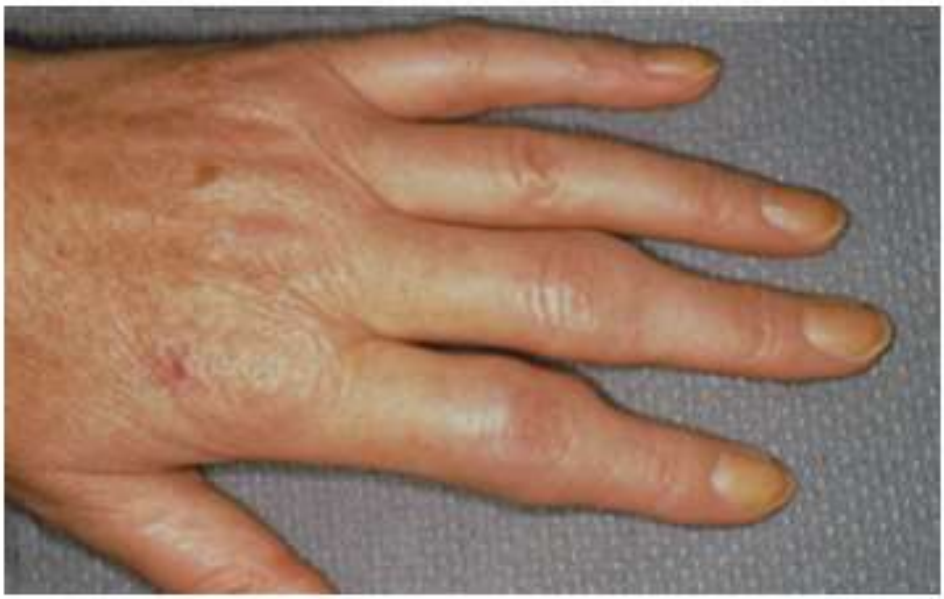
JOINT INVOLVEMENT:

Joint pain/swelling/stiffness is common presenting symptom, which is more in early morning lasts around 1 hour and improves with physical activity. It affects small joints of hand and feet. It is symmetric in nature. Initially it can present as

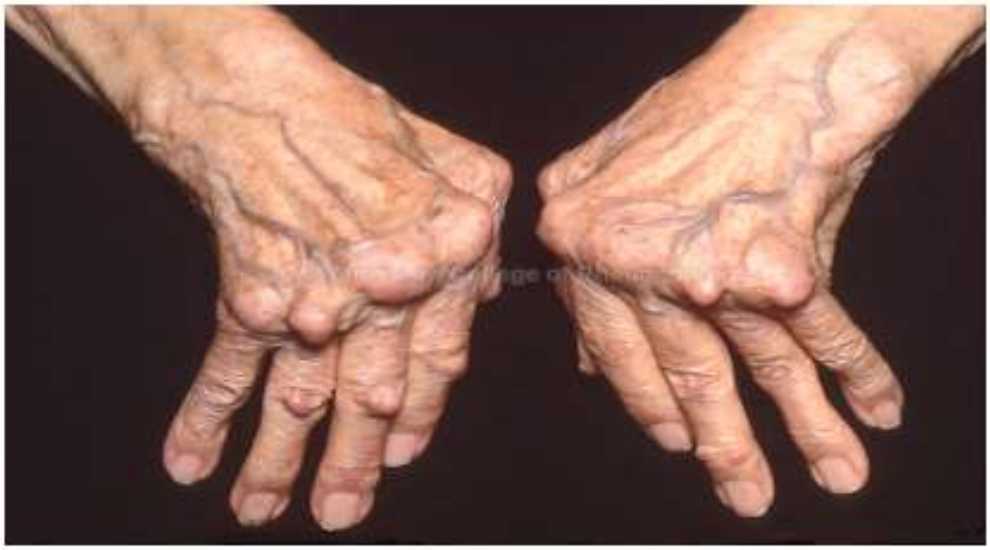
1. Mono articular
2. Oligo articular or
3. Poly articular

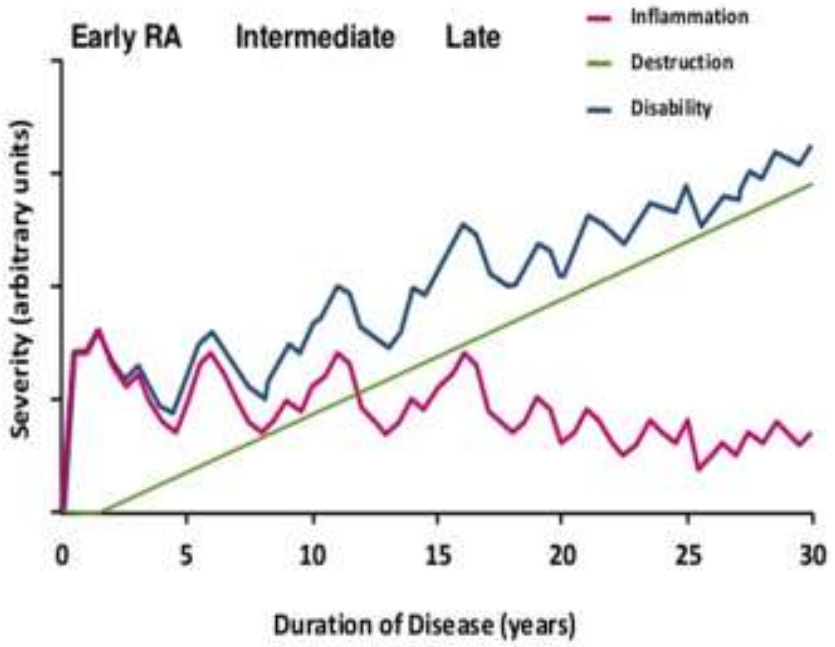

Joints involved in
≥80% of RA cases
Joints involved in
50–80% of RA cases

EARLY INFLAMMATORY STAGE



ADVANCED DEFORMITY STAGE





CONSTITUTIONAL SYMPTOMS

These signs and symptoms include weight loss, fever, fatigue, malaise, depression, and in the most severe cases, cachexia; they generally reflect a high degree of inflammation and may even precede the onset of joint symptoms. In general, the presence of a fever of >38.3°C (101°F) at any time during the clinical course should raise suspicion of systemic vasculitis or infection.

Commonly affected joints are

1. Metacarpo phalangeal (MCP) joint
2. Proximal interphalangeal (PIP) joint
3. Wrist
4. Metatarso phalangeal joint

Radiological evidence of temporo mandibular joint involvement is common. But it does not cause any functional significance. Usually axial skeleton involvement uncommon in RA. It is classical of spondyloarthropathy Thoracic and lumbar spines, sacroiliitis are usually not involved in RA. Rarely C1/C2 cervical segment can be affected. It will lead to atlanto-axial subluxation, that leads to cervical cord compressive myelopathy. Damage to joint and soft tissues leads to chronic irreversible deformity.

1. Swan neck deformity – Hyperextension of PIP
   Flexion of DIP
2. Boutonniere deformity – Flexion of PIP
   Hyperextension of DIP
3. Z line deformity – Subluxation of first MCP
   Hyperextension of first inter phalangeal joint
4. Ulnar deviation - Subluxation of MCP
   Subluxation of PIP to volar side of hand
5. Piano-key movement of Ulnar styloid – Subluxation of distal ulna
6. Trigger finger - due to tenosynovitis of flexor tendon sheath
7. Flat foot – Pes planovalgus due to involvement of mid tarsal joints.

GEODES BONE CYST can be seen in RA affected joints.

SUBCUTANEOUS NODULES

Subcutaneous nodules occur in 20–35% of patients with RA and are usually nontender, firm, and 1 cm or less in diameter. Subcutaneous nodules can be fixed or mobile and occur most frequently over pressure point areas such as the extensor aspect of the elbows, within the olecranon bursa, and over the Achilles tendon but also can overlie joints. Nodulosis over the sacrum, ischial tuberosities, occipital region of the scalp, or borders of the scapulae may develop in bedridden patients. Rarely, nodules develop within organ systems including the scleral layer of the eye, heart valves, lung, on the dural surface of the brain, or in the larynx.

Rheumatoid nodules are strongly associated with rheumatoid factor (positive in >95% of cases). Recent epidemiologic studies demonstrate that patients with RA who smoke have a higher risk of developing nodules. Strongly seropositive individuals with nodulosis tend to carry a worse prognosis, with a higher propensity toward erosive and destructive rheumatoid disease. The mimics of subcutaneous rheumatoid nodules include tophi, xanthomas, Garrod knuckle pads (fibrous nodules on the dorsal surfaces of the PIP joints of patients with Dupuytren contractures), the nodules of multicentric reticulohistiocytosis and, in children, the nodules of acute rheumatic fever. On clinical grounds alone, even

experienced rheumatologists may be unable to distinguish RA with olecranon nodulosis from polyarticular gout with olecranon tophi. Excisional biopsy is sometimes necessary to establish the correct diagnosis. Rheumatoid nodules have characteristic—but not specific—histologic findings of central fibrinoid necrosis with a rim of palisading fibroblasts. Histologically, rheumatoid nodules are indistinguishable from granuloma annulare (dermal or subcutaneous nodules not associated with arthritis) or from “benign nodules” which occur exclusively in children <18 years of age and are not associated with arthritis or with rheumatoid factor.

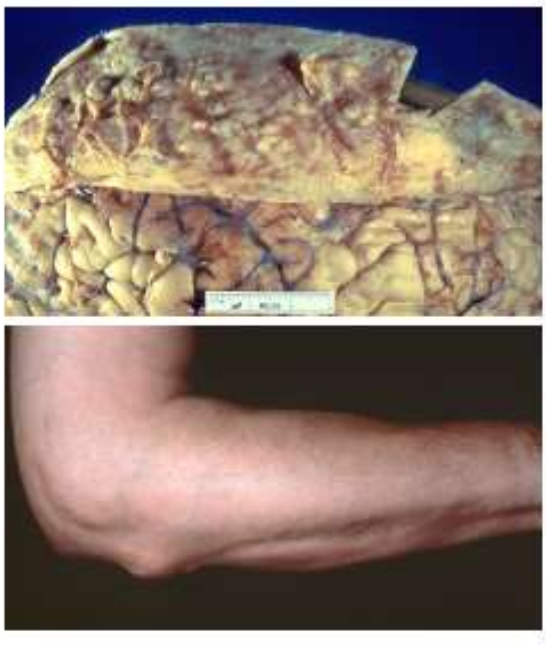
Subcutaneous rheumatoid nodules may resolve with effective therapy of the associated articular disease. A subset of rheumatoid patients, however, experience paradoxical accelerated nodulosis with methotrexate therapy . Nodules in these patients are often found over the extensor aspect of the MCP and PIP joints of the fingers. Methotrexate should be discontinued when there is extensive proliferation of nodules, particularly with ulceration of overlying skin.

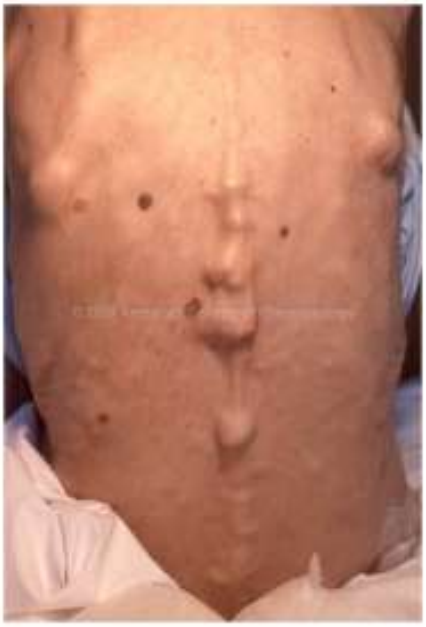
Unfortunately, there is no effective therapy for this situation. Most alternative DMARDs have been tried in these cases but with only ccasional success. Symptomatic subcutaneous nodules located over pressure points can be surgically removed. The effectiveness of this

surgical approach, however, is limited by high rates of recurrence of nodules, poor wound healing, and secondary infection at the operative site, often with S aureus. Rheumatoid nodules in the lung may be solitary or multiple, and some are necrotic. Isolated reports suggest a possible link between leflunomide therapy and necrotic pulmonary nodules. Distinguishing rheumatoid pulmonary nodules from carcinoma can be a particularly difficult problem, even after extensive imaging evaluation with computed tomography (CT) and positron emission tomographic scans.

CT-guided biopsy is usually the only certain means of differentiating between these possibilities.

RHEUMATOID NODULE





SJOGREN'S SYNDROME

Dryness of eyes and mouth is the most common ocular manifestation of RA.

Approximately 30% of patients with RA have sicca symptoms due to secondary Sjögren syndrome. Mucosal dryness most commonly affects the mouth, the conjunctival surfaces of the eyes, and vagina. Dental caries, gingivitis, and accelerated tooth loss may occur due to the lack of adequate salivary lubrication. Patients frequently experience chronic "foreign body" sensations in their eyes, and women often develop recurrent monilial infections of the vaginal mucosa.

Care must be exercised in distinguishing typical Sjögren symptoms from xerostomia due to medications, particularly antidepressants. Chronic hepatitis C infection, which can cause polyarthritis, sicca symptoms, and rheumatoid factor, also can mimic RA with secondary Sjögren syndrome. Occasionally, it is difficult to distinguish RA with secondary Sjögren syndrome from primary Sjögren syndrome with polyarthritis.

The diagnostic evaluations to establish xerophthalmia and xerostomia are those used for primary Sjögren syndrome. In contrast to primary Sjögren syndrome, antibodies to SS-A/Ro and to SS-B/La are not prevalent in the secondary Sjögren syndrome associated with RA. Compared to patients with primary Sjögren syndrome, hypergammaglobulinemia, interstitial nephritis, and distal renal tubular acidosis uncommonly develop in patients with RA and secondary Sjögren syndrome. Additional rare complications include the development of non-Hodgkin large B cell lymphomas or mucosal associated lymphoid tumors (MALT).

Treatment of secondary Sjögren syndrome is symptomatic. Artificial tears or cyclosporine 0.05% emulsion drops twice daily can ease ocular symptoms. Pilocarpine hydrochloride 5 mg orally three to four times daily or cevimeline 30 mg three times daily may be effective in promoting increased salivary production but can cause hyperhidrosis.

PULMONARY MANIFESTATION

1. **PLEURAL DISEASE –**

   Most common pulmonary manifestation. It presents as pleuritic chest pain, pleural effusion.

   Pleural effusions are exudative in nature and characteristically pleural sugar will be very low(<30 mg%).

2. PULMONARY NODULES –Solitary or multiple.
3. RESPIRATORY BRONCHIOLITIS
4. BRONCHIECTASIS
5. CAPLAN'S SYNDROME – A variant of rheumatoid pulmonary nodulosis is Caplan syndrome . In 1953, Caplan described multiple rheumatoid nodules, some with cavitation, in the lungs of Welsh coal miners with RA. This pattern has also been reported in RA patients exposed to silica dust and asbestos, raising the question of whether Caplan syndrome is a combined "pneumoconiosis—RA" entity.
6. ILD –

   Interstitial fibrosis of the lungs is one of the most dreaded complications of RA and often carries a guarded prognosis. The prevalence of clinically evident pulmonary fibrosis among RA patients is approximately 2–3%, and the prevalence of

asymptomatic pulmonary fibrosis detected by high-resolution CT (HRCT) is substantially higher. The cumulative incidence of clinical pulmonary fibrosis approaches 10%.

Common in smokers & male

Presents as dry cough and progressive dyspnea.

Associated with anti CCP positivity

Carries poor prognosis.

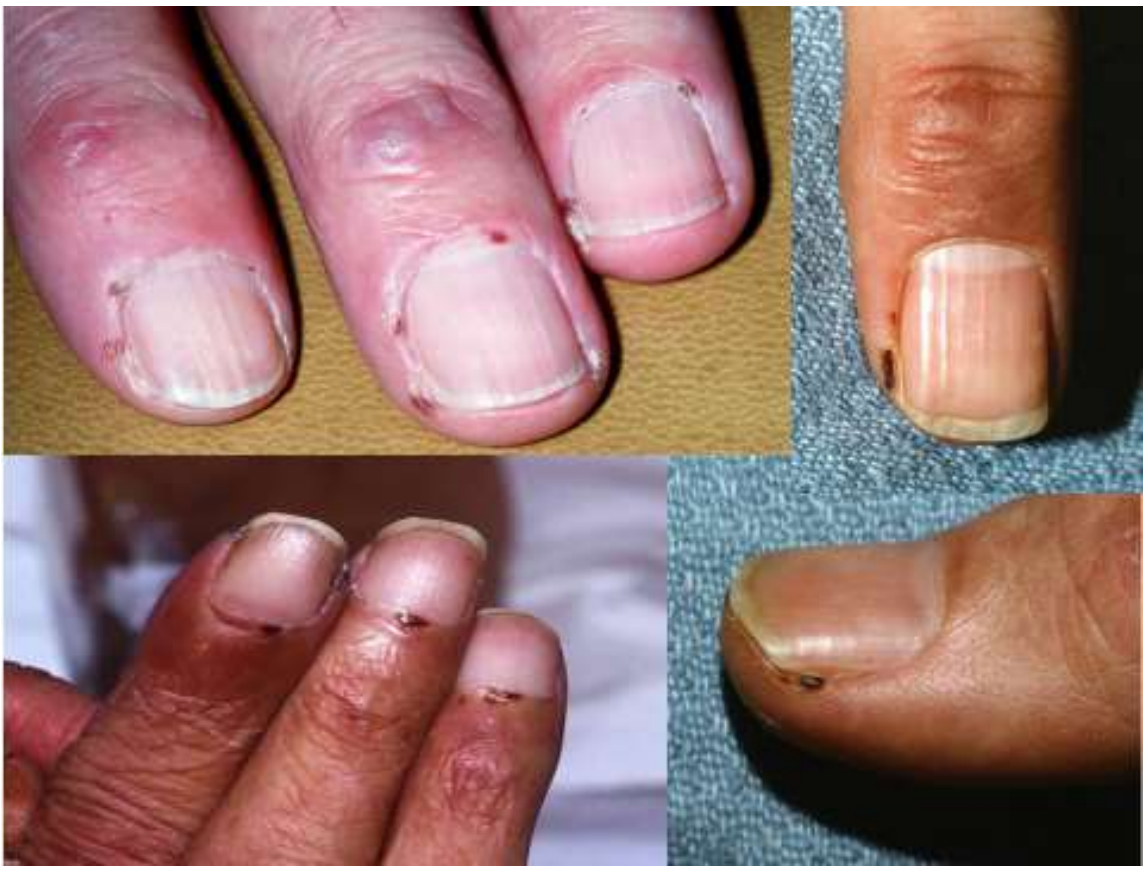
7. CRICOARYTENOID ARTHRITIS can lead to hoarseness of voice

CARDIAC MANIFESTATIONS

It can involve pericardium, myocardium and endocardium. Though pericardium (pericarditis) is the most common site of involvement clinically manifests in less than 10 % of patients. RA patients are highly prone to have constrictive pericarditis .Commonest valvular abnormality is mitral regurgitation. Restrictive cardiomyopathy can result from deposition of amyloid by secondary amyloidosis. Cardiomyopathy can result from myocarditis or coronary artery disease. The most common cause of death in RA is CAD. Patients with high disease activity are highly prone to have adverse cardiac events. Low HDL is the most consistent finding in a background of high disease activity in RA.

VASCULITIS

It occurs in patients with long standing disease. Affects less than 1% of patients. Cutaneous signs are petechiae, purpura, digital infarcts, gangrene, livedo reticularis and vasculitic ulcer. Most common type of vasculitis is leukocytoclastic vasculitis. It will lead to classical small necrotic skin ulcer in hand it is called as Bywaters lesion. RA patients are uncommon to have RAYNAUD'S PHENOMENON. Rheumatoid Vasculitis rarely presents as multiple peripheral nerve palsy.



BYWATERS LESION

PYODERMA GANGRENOSUM

Pyoderma gangrenosum is an ulcerative neutrophilic dermatitis of unknown cause. It occurs in less than 1% of patients with RA and usually manifests a lower-extremity, deep ulcer with purplish, overhanging borders. Initial therapy most commonly involves glucocorticoids; there are some reports of success with anti-TNF agents and with cyclosporine.

HEMATOLOGIC MANIFESTATIONS

1. Normocytic normochromic anemia- severity of anemia correlate with degree of inflammation.
2. Total and differential WBC count will be normal. If any patient having leukopenia in early stage of disease we have to think of drug induced rather than disease per se.
3. Platelet- usually elevated because of acute phase reaction. Rarely immune-mediated thrombocytopenia will be present.
4. Felty's syndrome – rare. Presents as triad of neutropenia, splenomegaly and nodular RA. It occurs in late stages of disease.
5. T cell large granular lymphocyte leukemia- due to indolent growth of LGL cells. It occurs in early stages of rheumatoid arthritis.
6. Lymphoma- fourfold risk of lymphoma. Diffuse large B-cell lymphoma is most common histologic type.

NEUROLOGIC MANIFESTATIONS

The most common neurologic complications of RA are compression neuropathies, particularly compression of the median nerve at the wrist (carpal tunnel syndrome) and compression of the ulnar nerve at the elbow or wrist. Rheumatoid vasculitis can cause mononeuritis multiplex and a mixed motor-sensory peripheral neuropathy. Atlantoaxial subluxation and basilar invagination can produce cervical myelopathy and brainstem compression. An unusual complication of RA is pachymeningitis-inflammation and thickening of dura mater-which presents as a clouded sensorium, cranial nerve abnormalities, and retardation of motor activity. Once an infectious etiology has been excluded, pachymeningitis is treated vigorously with glucocorticoids and appropriate DMARDs.

OSTEOPOROSIS

Inflammatory mediated activation of osteoclasts leads to generalized osteoporosis. Other factors contributing to osteoporosis are immobility and steroid abuse. FRAX algorithm is used to assess the fracture risk in future due to osteoporosis.

RENAL INVOLVEMENT

Kidney involvement is interestingly absent in RA by disease per se. drugs are commonly linked to kidney involvement. Gold and penicillamine were used they are responsible for membranous nephropathy.no more they are used nowadays. Most important complication of rheumatoid arthritis is secondary amyloidosis, it can affect the kidney.

EYE INVOLVEMENT

Keratoconjunctivitis sicca due to secondary Sjögren syndrome is the most common ocular manifestation of RA. However, RA also can cause ocular inflammation, leading to episcleritis, scleritis, and peripheral ulcerative keratitis. Episcleritis , or inflammation of the episclera, manifests as a red eye due to hyperemia of this superficial ocular layer. Episcleritis produces irritation more than pain; it is not a vision-threatening condition. Episcleritis may be self-limited but is often treated with topical corticosteroid drops. Of greater concern is inflammation of the sclera, the deeper, poorly vascularized layer of the eye. Scleritis is most commonly seen in patients who have had RA for 10 years or longer. Patients who are both rheumatoid factor and anti-CCP positive tend to have more intense ocular disease. Scleritis is a painful, persistent

condition. The eye typically is deep red. With time, thinning of the sclera can occur, imparting a bluish hue from the underlying choroid.

Scleritis can be complicated by rheumatoid nodules forming and enlarging within the scleral layer. Unchecked, scleritis can produce scleromalacia perforans and can threaten the structural integrity of the globe. Inadequate or unsuccessful treatment can lead to irreversible blindness. Nodular scleritis is an urgent ophthalmologic problem that requires initiation of immunosuppressive therapy, most often with cyclophosphamide in combination with high-dose oral prednisone (eg, 1 mg/kg/d).

An additional serious ocular complication of RA is peripheral ulcerative keratitis with “melting” of the corneal epithelial layers. Again, this is seen in long-standing RA, often accompanied by rheumatoid vasculitis or other serious extra-articular manifestations. Peripheral ulcerative keratitis must be aggressively treated with immunosuppression using high-dose glucocorticoids and often cyclophosphamide. If the inflammation is successfully ameliorated, a corneal transplant can be performed to salvage vision.

Scleritis, episcleritis are common. Scleromalacia perforans is the severe complication of RA. Uveitis is uncommon.

HYPOANDROGENISM

Testosterone, Dehydroepiandrosterone and Luteinizing hormone levels are lower in postmenopausal women and men with Ra. Chronic inflammation leads to low testosterone level. Controlling of inflammation improves testosterone level.

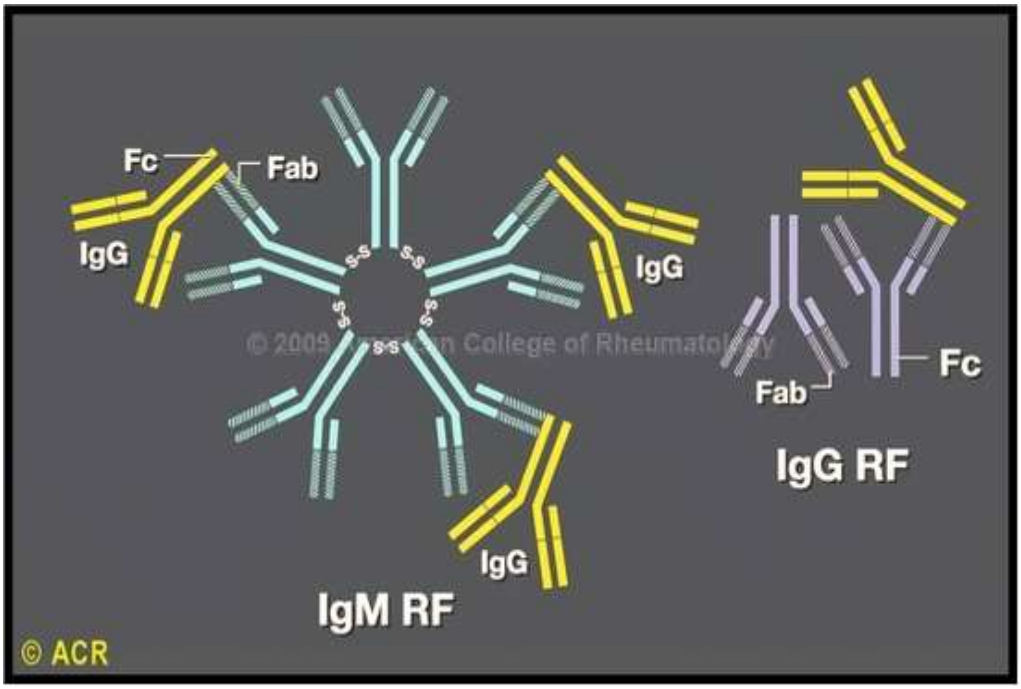
RHEUMATOID FACTOR

Seronegative patients have less extra-articular manifestations and better prognosis compared to seropositive patients. RF is nothing but antibody formed against Fc portion of IgG. Three isoforms of RF is occurring in serum of RA patients IgM, IgG and IgA. Commonly measured in laboratories is IgM isotype. Sensitivity of RF is 75 – 80 %. RA can't be excluded by negative RF. RF positive patients are highly prone for severe erosive arthritis, extra articular manifestations. Patient who are positive for RF have poor prognosis

About 1-5 % of health population is positive for RF. RF is also positive in other connective tissue diseases and chronic infections like

1. Sjogren's syndrome
2. SLE,
3. Mixed essential cryoglobulinemia
4. Subacute bacterial endocarditis,

5. Chronic hepatitis B and C.



ANTI-CCP

It is more specific than RF.

Sensitivity is 75-80%

Specificity is 95%.

It is helpful to differentiate RA from other inflammatory arthritis in early stages. Patients who are negative for one test (RF or Anti-CCP) may be positive for other test so it is complementary to go with both tests. Anti CCP positive patients are highly prone for severe erosive arthritis, extra articular manifestations most important is ILD. Patient who are positive for Anti-CCP have poor prognosis

SYNOVIAL FLUID ANALYSIS

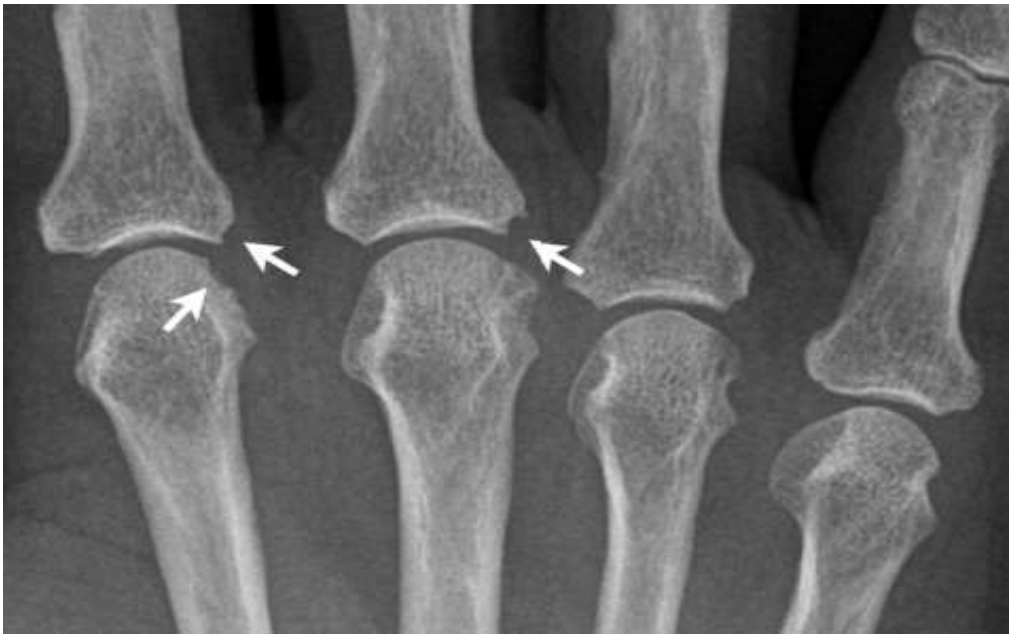
It is inflammatory in nature with WBC count between 5000 to 50,000 per cubic micro liter. Predominant cell type is neutrophil. RF, anti-CCP antibodies and immune complexes is also found in synovial fluid.

JOINT IMAGING

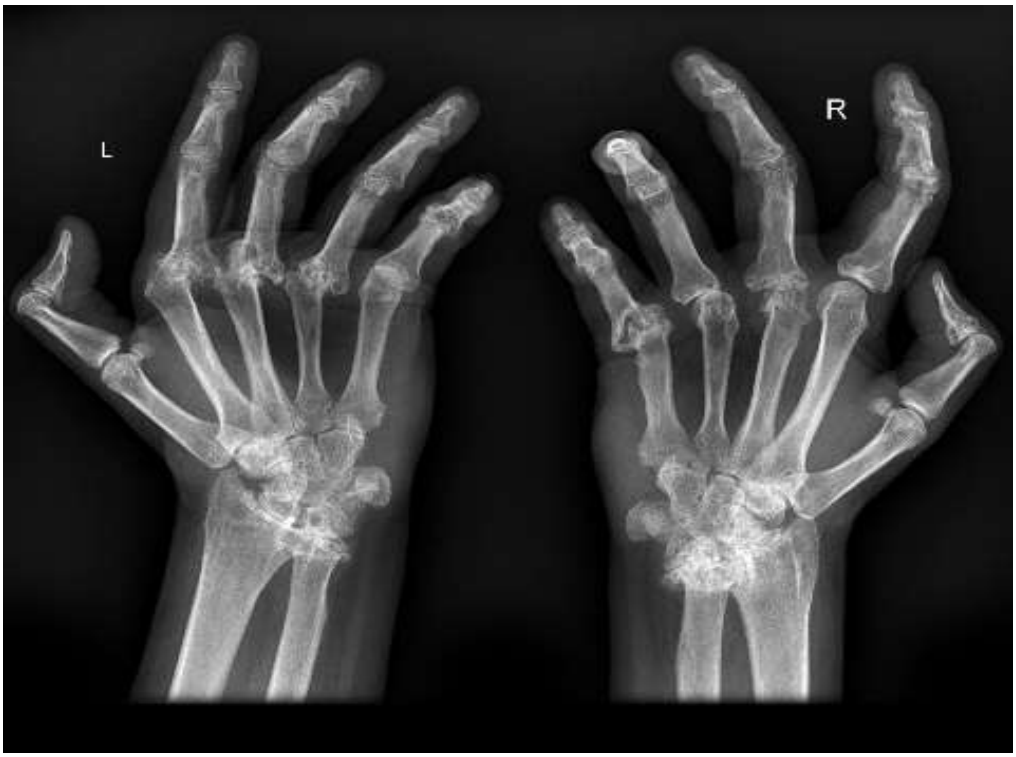
Plain x-ray is commonly used but MRI is sensitive than Pain X-ray in early stages. Common X-ray findings are

1. Juxta articular osteopenia,
2. Soft tissue swelling ,
3. Symmetric joint space loss
4. Subchondral bone erosions
5. Joint subluxation.

Earliest Finding in X Ray is Marginal Erosion of Small Joints.



MARGINAL EROSION OF SMALL JOINTS



CLASSICAL JOINT INVOLVEMENT IN RHEUMATOID ARTHRITIS

MRI- has greater sensitivity to early bone and bone marrow changes as well as synovitis and joint effusions. One of the early sign of inflammatory joint disease is bone marrow edema which can be easily picked up by MRI. Limiting factors are availability and cost.

USG can be used to detect bony erosions in accessible joints. Synovitis is also reliably detected by USG. It has advantages of lack of radiation, portability and low cost.

DIAGNOSIS

ACR-EULAR 2010 classification criteria now is used for diagnose RA. Main of aim revising older 1987 ACR classification criteria is to diagnose RA patients at early stages and introduction of disease modifying therapy at early stages. Serum anti-cyclic citrullinated antibodies is included in newer criteria which is more specific for RA than RF. Rheumatoid nodules and radiographic joint damage is not included in newer criteria because both of changes occurring in late stages of RA. This criteria is applicable to newly presenting patients. They must have at least one joint involvement with definite clinical synovitis.

CLASSIFICATION CRITERIA FOR RHEUMATOID ARTHRITIS

		SCORE
JOINT INVOLVEMENT	1 large joint	0
	2-10 large joints	1
	1-3 small joints	2
	4-10 small joints	3
	>10 joints (at least 1 small joint)	5
SEROLOGY	Negative RF and negative ACPA	0
	Low positive RF or anti-CCP (≤3 times)	2
	High positive RF or anti-CCP (>3times)	3
ACUTE-PHASE RECTANTS	Normal CRP and ESR	0
	Abnormal CRP and ESR	1
DURATION OF SYMPTOMS	<6 Weeks	0
	≥6 Weeks	1

Score 6/10 is diagnosis of Rheumatoid arthritis.

DAS28 (Disease Activity Scoring – 28)

DAS28 to assess improvement and progression of RA. It is a composite measure. It includes four parameters

1. Number of joints showing tenderness

2. Number of joints showing swelling

3. ESR or CRP

4. Subjective assessment of disease activity

Joints to be assessed

1. MCP
2. PIP
3. Wrist
4. Elbow
5. Shoulder
6. Knee

Ankle and MTP is not included.

Values range from 2.0 to 10.0

SCORE	DISEASE ACTIVITY
>5.1	High disease activity
5.1 to 3.2	Moderate disease activity
3.2 to 2.6	Low disease activity
<2.6	Remission

TREATMENT OF RHEUMATOID ARTHRITIS

Drugs used in the treatment of RA are together called as DMARDs

DMARDs are so named because of their ability to slow or prevent structural progression of RA.

1. **Non-biological agents**

NSAIDs,

Glucocorticoids

Glucocorticoids in low doses (eg, prednisone 5–10 mg daily) can provide rapid, symptomatic improvement of articular disease and significantly slow the radiographic progression of RA. Glucocorticoids should be used rarely, if ever, as monotherapy for RA but can help control synovial inflammation while initiating therapy with the slow-acting synthetic DMARDs or when the response to DMARDs is suboptimal.

The toxicities of long-term glucocorticoid therapy are considerable and are dose-dependent. Therefore, prednisone, the most commonly used glucocorticoid, generally should not be used in doses higher than 10 mg daily to treat articular disease and, after initiation of DMARD therapy, should be slowly tapered off or to the lowest effective dose. Long-term therapy with prednisone in doses of ≥7.5 mg/d orally is associated with an increased risk of both vertebral and hip fractures.

Nonsteroidal anti-inflammatory drugs (NSAIDs) play only a minor role, if any, in slowing progression of RA and, therefore , should not be used as the sole therapy for RA. The role of NSAIDs in RA is limited to symptomatic relief. The gastrointestinal toxicity of NSAIDs is a major issue for RA patients, who often have multiple risk factors for gastrointestinal toxicity. The use of protein pump inhibitors reduces the incidence of clinically significant gastrointestinal side effects. Intra-articular injections of glucocorticoids can suppress joint inflammation for several months and can be a useful addition to DMARD therapy, especially when there is residual activity in large joints (eg, wrists, knees). In many cases, patients benefit from consultation with physical and occupational therapists regarding range of motion exercises, joint protection, and assistive devices.

CONVENTIONAL DMARDS

a. Methotrexate (DRUG OF CHOICE)

Methotrexate is the preferred synthetic DMARD of most rheumatologists. Many patients with RA have a durable, clinically meaningful response to methotrexate, which also slows radiographic progression of the disease. While effective as monotherapy, methotrexate also is the anchor drug in most successful combinations of synthetic DMARDs, and biologic agents are more effective when used concomitantly with methotrexate.

Methotrexate is administered as a single dose once a week , never on a daily basis (toxicity is substantially greater when the same amount of drug is administered on a daily basis rather than as a weekly pulse). The typical starting dose is 7.5 mg orally once a week; the dose then is increased by 2.5 mg to 7.5 mg increments as needed to a maximum of 20–25 mg. Oral absorption of methotrexate is variable; therefore, subcutaneous methotrexate may be effective if the response to oral methotrexate is suboptimal. Oral folate (1–4 mg daily) reduces side effects and should be administered concomitantly. Monitoring of blood cell counts, liver transaminase levels, and serum creatinine should be done every 12 weeks (every 2–4 weeks during initiation or after dose adjustments) for the duration of methotrexate therapy.

Contraindications to methotrexate

a. Preexisting liver disease

b. infection with hepatitis B or C

c. ongoing alcohol use

d. renal impairment

Oral ulcers, nausea, hepatotoxicity, bone marrow suppression, and pneumonitis are the most commonly encountered toxicities. With the exception of pneumonitis (which is a hypersensitivity reaction), these toxicities respond to dose adjustments and are reduced by the concomitant use of folic acid. Renal function is critical for clearance of methotrexate and its active metabolites; previously stable patients may experience severe toxicities when renal function deteriorates. Pneumonitis, while rare, is unpredictable and may be fatal, particularly if the methotrexate is not stopped or is restarted.

b. Hydroxychloroquine

Hydroxychloroquine is frequently used for the treatment of RA, usually in combination with other synthetic DMARDs, particularly methotrexate. It has the least toxicity of any of the DMARDs but also is the least effective as monotherapy. Hydroxychloroquine is given orally at

a dose of 200–400 mg daily. An uncommon but serious complication is retinal toxicity, which correlates with cumulative dose and can be prevented by regular screening. The risk of retinal toxicity increases substantially after 5–7 years of use or a cumulative dose of 1000 g. At a minimum, patients should have a baseline ophthalmologic examination within 1 year of initiation of hydroxychloroquine and annual screening examinations after 5 years of therapy. Earlier, more frequent screenings are indicated for patients with risk factors (daily dose >400 mg or >6.5 mg/kg ideal body weight for patients of short stature, kidney or liver dysfunction, other retinal disease, age >60 years).

c. Sulfasalsazine

Sulfasalazine is an effective treatment when given in doses of 1–3 g daily, often in combination with methotrexate, hydroxychloroquine, or both. Recommendations for laboratory monitoring are the same as for methotrexate.

d. Leflunomide

Leflunomide, a pyrimidine antagonist, appears comparable in effectiveness to methotrexate. It is given daily in an oral dose of 10–20 mg and has a very long half-life. The most common toxicity is diarrhea, which may respond to dose reduction. Like methotrexate, leflunomide

has hepatotoxicity, and recommendations for laboratory monitoring are the same as for methotrexate. Because leflunomide is teratogenic and has an exceptionally long half-life, women who have previously received leflunomide (even if therapy was years ago) should have blood levels drawn if they wish to become pregnant. Oral cholestyramine can rapidly eliminate leflunomide if toxicity occurs or if pregnancy is being considered.

2. **Biological DMARDs**

TNF BLOCKERS

ETANERCEPT

INFIXIMAB

ADALIMUMAB

CERTOLIZUMAB

GOLIMUMAB

Anti-TNF agents should be avoided in patients with active infection or a history of hypersensitivity to these agents and are contraindicated in patients with chronic hepatitis B infection or class III/IV congestive heart failure. The major concern is the increased risk for infection, including serious bacterial infections, opportunistic fungal

infection, and reactivation of latent tuberculosis. For this reason, all patients are screened for latent tuberculosis according to national guidelines prior to starting anti-TNF therapy. In the United States, patients are skin tested using an intradermal injection of purified protein derivative (PPD); individuals with skin reactions of more than 5 mm are presumed to have had previous exposure to tuberculosis and are evaluated for active disease and treated accordingly. The QuantiFERON IFN-γ release assay may also be used in selected circumstances to screen for previous exposure to tuberculosis.

IL 1 ANTAGONIST

ANAKINRA

CD 20 ANTAGONIST

RITUXIMAB

- It carries risk of progressive multifocal leukoencephalopathy.

SIGNAL 2 INHIBITOR (CO-STIMULATION INHIBITOR)

ABATACEPT

IL 6 RECEPTOR ANTAGONIST

- TOCILIZUMAB
- Newly approved drug by FDA

- Humanized monoclonal antibody directed against soluble and membrane forms of IL-6 receptor.
- Dyslipidemia is one of the adverse effect the drug

JANUS KINASE PATHWAY INHIBITOR

TOFACITINIB:

- Newly approved drug by FDA
- Oral JAK inhibitor
- Small-molecule inhibitor that primarily inhibits JAK1 & JAK3 pathway.
- Dyslipidemia is one of the adverse effect the drug
- Tofacitinib can be used as monotherapy or in combination with methotrexate.

As mentioned earlier, methotrexate is the DMARD of first choice for initial treatment of moderate to severe RA. Failure to achieve adequate improvement with methotrexate therapy calls for a change in DMARD therapy, usually transition to an effective combination regimen. Effective combinations include: methotrexate, sulfasalazine, and hydroxychloroquine (oral triple therapy); methotrexate and leflunomide; and methotrexate plus a biological. The combination of methotrexate and an anti-TNF agent, for example, has been shown in randomized,

controlled trials to be superior to methotrexate alone not only for reducing signs and symptoms of disease, but also for retarding the progression of structural joint damage. Predicting which patients will ultimately show radiologic joint damage is imprecise at best, although some factors such as an elevated serum level of acute-phase reactants, high burden of joint inflammation, and the presence of erosive disease are associated with increased likelihood of developing structural injury.

In 2012 a joint task force of the ACR and EULAR updated the treatment guidelines for RA. They do make a distinction between patients with early RA (<6 months of disease duration) and patients with established RA. These guidelines highlight the need to switch or add DMARD therapy after 3 months of worsening or persistent moderate/high disease activity. If disease still persists after 3 months of intense DMARD therapy, addition of a biologic agent is warranted. Treatment with a biologic agent or aggressive combination DMARD therapy was also recommended as initial therapy in certain patients with high disease activity and poor prognosis. However, it has not been clearly established that this more intensive initial approach is superior to starting

with methotrexate alone and, in the absence of an inadequate therapeutic response, moving rapidly to combination therapy. Some patients may not respond to an anti-TNF drug or may be intolerant of its side effects. Initial responders to an anti-TNF agent that later worsen may benefit from switching to another anti- TNF agent.

The 2012 guidelines recommend that with loss or lack of effectiveness of anti-TNF after 3 months, one should switch to another anti-TNF or non-TNF biologic agent. In patients with high disease activity and a serious adverse event from an anti-TNF agent, a non-TNF drug should be used. Studies have also shown that oral triple therapy (hydroxychloroquine, methotrexate, and sulfasalazine) is a reasonable first step for the treatment of early RA, including its use as a step-up strategy where treatment is initiated with methotrexate alone and then combined at 6 months with hydroxychloroquine and sulfasalazine if the disease is not adequately controlled.

3. PHYSICAL THERAPY AND ASSISTIVE DEVICES

All patients should receive a prescription for exercise and physical activity. Dynamic strength training, community-based comprehensive physical therapy, and physical-activity coaching (emphasizing 30 min of

moderately intensive activity most days a week) have all been shown to improve muscle strength and perceived health status. Foot orthotics for painful valgus deformity decrease foot pain and resulting disability and functional limitations. Judicious use of wrist splints can also decrease pain; however, their benefits may be offset by decreased dexterity and a variable effect on grip strength.

4. SURGERY

Surgical procedures may improve pain and disability in RA—most notably the hands, wrists, and feet, typically after the failure of medical therapy with varying degrees of reported long-term success. For large joints, such as the knee, hip, shoulder, or elbow, total joint arthroplasty is an option for advanced joint disease. A few surgical Soptions exist for dealing with the smaller hand joints. Silicone implants are the most common prosthetic for MCP arthroplasty and are generally implanted in patients with severe decreased arc of motion, marked flexion contractures, MCP joint pain with radiographic abnormalities, and severe ulnar drift. Arthrodesis and total wrist arthroplasty are reserved for patients with severe disease who have substantial pain and functional impairment. These two procedures appear to have equal efficacy in terms

of pain control and patient satisfaction. Numerous surgical options exist for correction of hallux valgus in the forefoot, including arthrodesis and arthroplasty, as well as primarily arthrodesis for refractory hind foot pain.

PREGNANCY & RA

Pregnancy Up to 75% of female RA patients will note overall improvement in symptoms during pregnancy, but often will flare after delivery. Flares during pregnancy are generally treated with low doses of prednisone; hydroxychloroquine and sulfasalazine are probably the safest DMARDs to use during pregnancy. Methotrexate and leflunomide therapy are contraindicated during pregnancy due to their teratogenicity in animals and humans. The experience with biologic agents has been insufficient to make specific recommendations for their use during pregnancy. Most rheumatologists avoid their use in this setting; however, exceptions are considered depending on the circumstances.

ELDERLY PATIENTS WITH RA

Elderly Patients RA presents in up to one-third of patients after the age of 60; however, older individuals may receive less aggressive treatment due to concerns about increased risks of drug toxicity. Studies suggest that conventional DMARDs and biologic agents are equally

effective and safe in younger and older patients. Due to comorbidities, many elderly patients have an increased risk of infection. Aging also leads to a gradual decline in renal function that may raise the risk for side effects from NSAIDs and some DMARDS, such as methotrexate. Renal function must be taken into consideration before prescribing methotrexate, which is mostly cleared by the kidneys. To reduce the risks of side effects, methotrexate doses may need to be adjusted downward for the drop in renal function that usually comes with the seventh and eighth decades of life. Methotrexate is usually not prescribed for patients with a serum creatinine greater than 2 mg/dL.

MATERIALS AND METHODS

STUDY POPULATION

This study is to be conducted in 100 patients (Control 50 & 50 cases of rheumatoid arthritis patients) attending Rheumatology & general medicine Outpatient department at Govt Rajaji hospital, Madurai.

Inclusion criteria

1. All (Male/Female) Rheumatoid arthritis patients (Irrespective of disease duration and treatment duration) according to ACR-EULAR criteria.

2. Age 30-50 Years

Exclusion criteria

1. Patients with Rheumatoid arthritis on biological agents (TOFACITINIB/TOCILIZUMAB)

2. Known Diabetic/CAD/CKD/Hereditary Dyslipidemia

3. Metabolic syndrome

2. Obesity

3. Hypothyroidism

ANTICIPATED OUTCOME

Increased prevalence of dyslipidemia (low HDL) in Rheumatoid arthritis patients with high CRP level.

DATA COLLECTION

The following information collected from patients who attended the Rheumatology/general medicine clinic in the form of Age, Sex, Duration of symptoms, Anthropometry measurements, Biochemical parameters [Rheumatoid factor, lipid profile ESR, CRP], Complication of Rheumatoid arthritis.

I excluded the patient with Patients with Rheumatoid arthritis patient on biological agents (TOFACITINIB/TOCILIZUMAB), those on drugs impairing lipid metabolism, conditions associated with impairing lipid metabolism.

LABORATORY INVESTIGATIONS

- FASTING PLASMA GLUCOSE
- TWO-HOURS PLASMA GLUCOSE
- FASTING LIPID PROFILE
- ERYTHROCYTE SEDIMENTATION RATE
- C- REACTIVE PROTEIN
- RHEUMATOID FACTOR

DESIGN OF STUDY

Observational study.

PERIOD OF STUDY

6 MONTHS (MARCH 2016 TO AUGUST 2016)

COLLABORATING DEPARTMENTS:

Department of Pathology

Department of Biochemistry

Department of Microbiology

ETHICAL CLEARANCE: obtained

CONSENT: Individual written and informed consent.

STATISTICAL ANALYSIS: For continuous variables, Independent sample t-test was performed to find the differences between cases and controls and for categorical variables Pearson's chi-square test was performed.

CONFLICT OF INTEREST: NIL

FINANCIAL SUPPORT: NIL

PARTICIPANTS

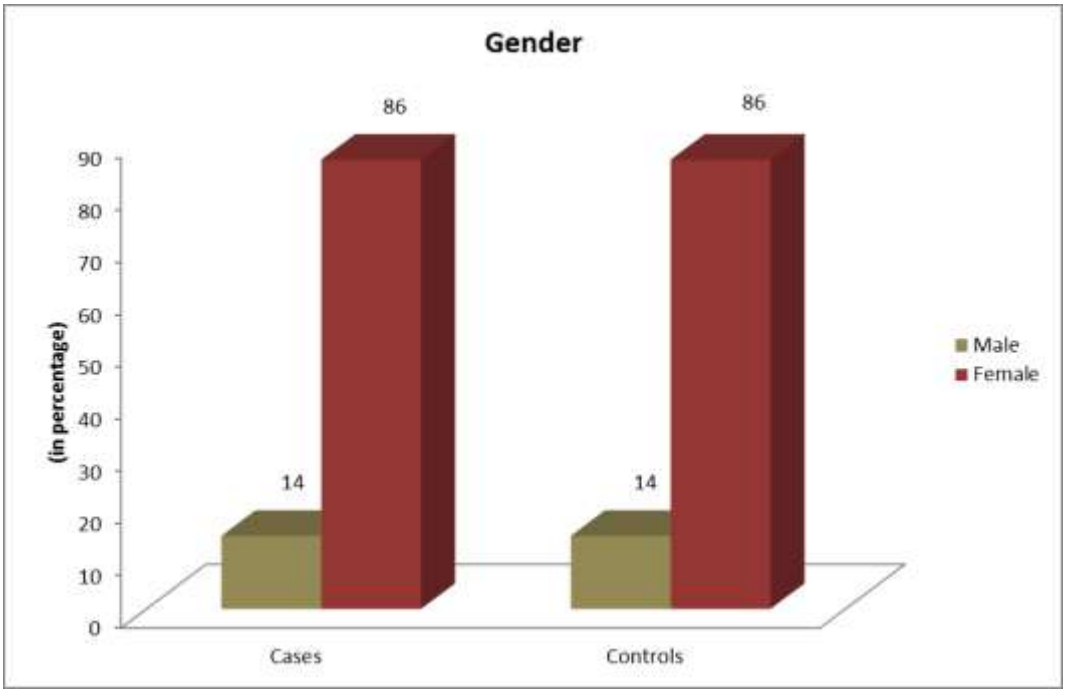
This study is to be conducted in 100 patients (Control 50 & 50 cases of rheumatoid arthritis) attending Rheumatology & General medicine Outpatient department at Govt Rajaji hospital, Madurai.

STATISTICAL METHODS

All data were entered in Excel 2007 and statistical analysis was performed using the statistical software SPSS 16.0. Data were expressed as frequency (with percentages), mean values (with SD) and minimum and maximum values. For continuous variables, Independent sample t-test was performed to find the differences between cases and controls and for categorical variables Pearson's chi-square test was performed. Correlation was performed to find the relationship between two continuous variables. Results were defined as statistically significant when the *P* value (2-sided) was less than 0.05.

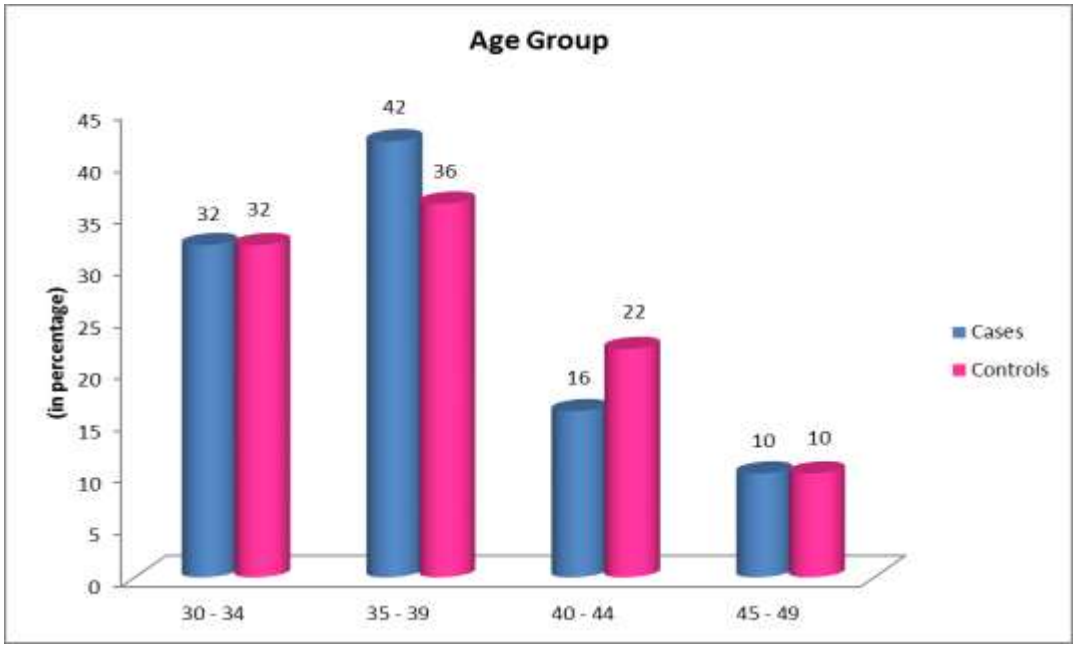
RESULTS

Gender	Group			
	Cases		Controls	
	No	%	No	%
Male	7	14.0	7	14.0
Female	43	86.0	43	86.0
Total	50	100.0	50	100.0



In our study, total cases are 100 (50 cases and 50 controls). Among that 86% are female, 14% are male in both case group and control group.

Age Group (in yrs)	Group			
	Cases		Controls	
	No	%	No	%
30 – 34	16	32.0	16	32.0
35 – 39	21	42.0	18	36.0
40 – 44	8	16.0	11	22.0
45 – 49	5	10.0	5	10.0
Total	50	100.0	50	100.0



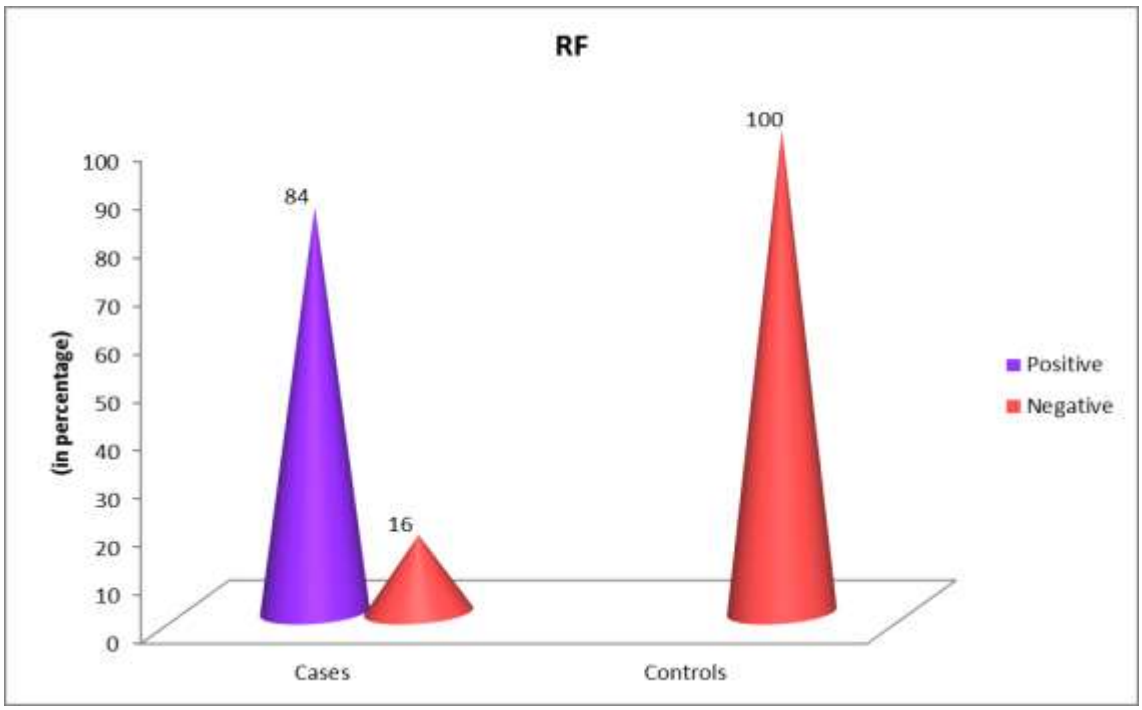
In case group, cases are in the age of 30-34 yrs (32%), 35-39yrs (42%) 40-44yrs (16%) 45-49yrs (10%), majority in the age of 30-39yrs.

In control group cases are in the age of 30-34 yrs (32%), 35-39yrs (36%) 40-44yrs (22%) 45-49yrs (10%).

	Group			
	Cases		Controls	
	N=50		N=50	
	Mean±SD	(min, max)	Mean±SD	(min, max)
Age (in yrs)	37.4±4.5	(30, 48)	37.5±4.5	(30, 47)

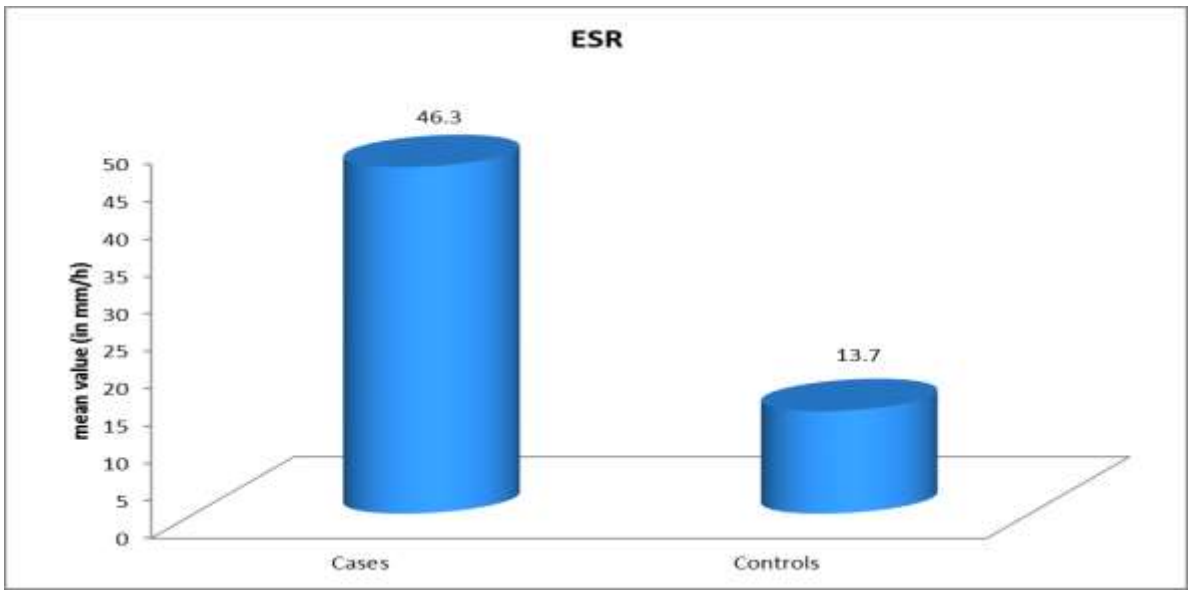
In rheumatoid arthritis case group, mean age of onset is 37.4yrs.

RF	Group			
	Cases		Controls	
	No	%	No	%
Positive	42	84.0	-	-
Negative	8	16.0	50	100.0
Total	50	100.0	50	100.0
p-value	P<0.001 (Significant)			



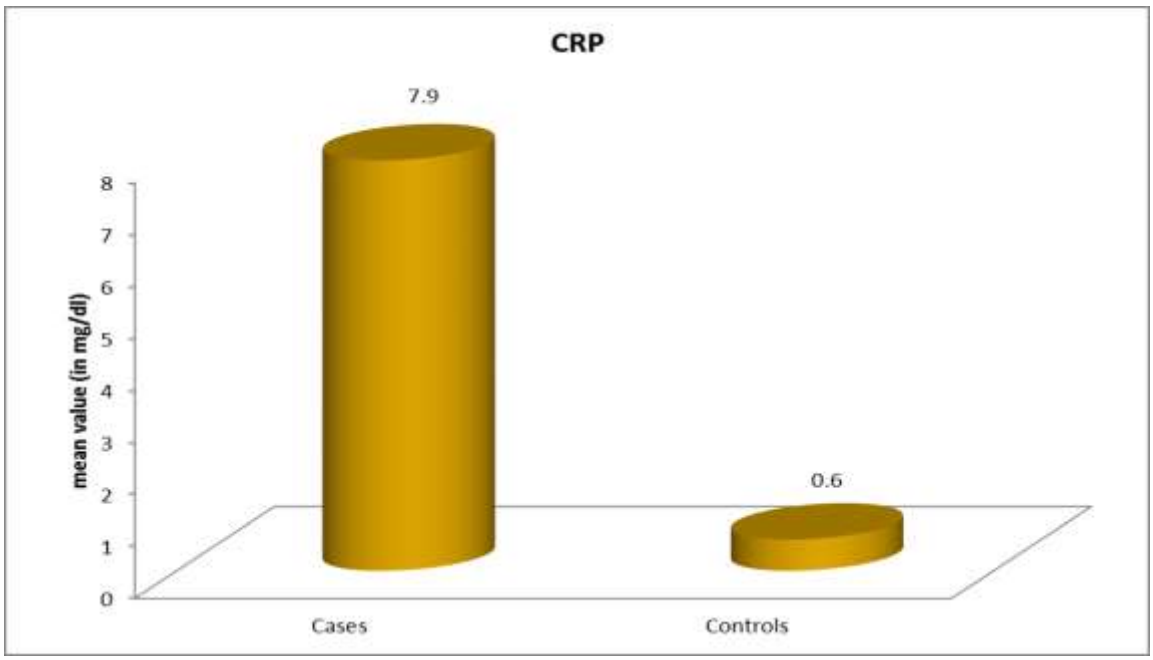
Rheumatoid factor positivity seen only in case group, not in control group. Positive cases are about 84% in case group. Comparing with case and control group rheumatoid factor positivity is significant ($p < 0.001$).

	Group			
	Cases		**Controls**	
	N=50		**N=50**	
	Mean±SD	**(min, max)**	**Mean±SD**	**(min, max)**
ESR	46.3±22.8	(13, 120)	13.7±2.7	(9, 20)
p-value	<0.001			



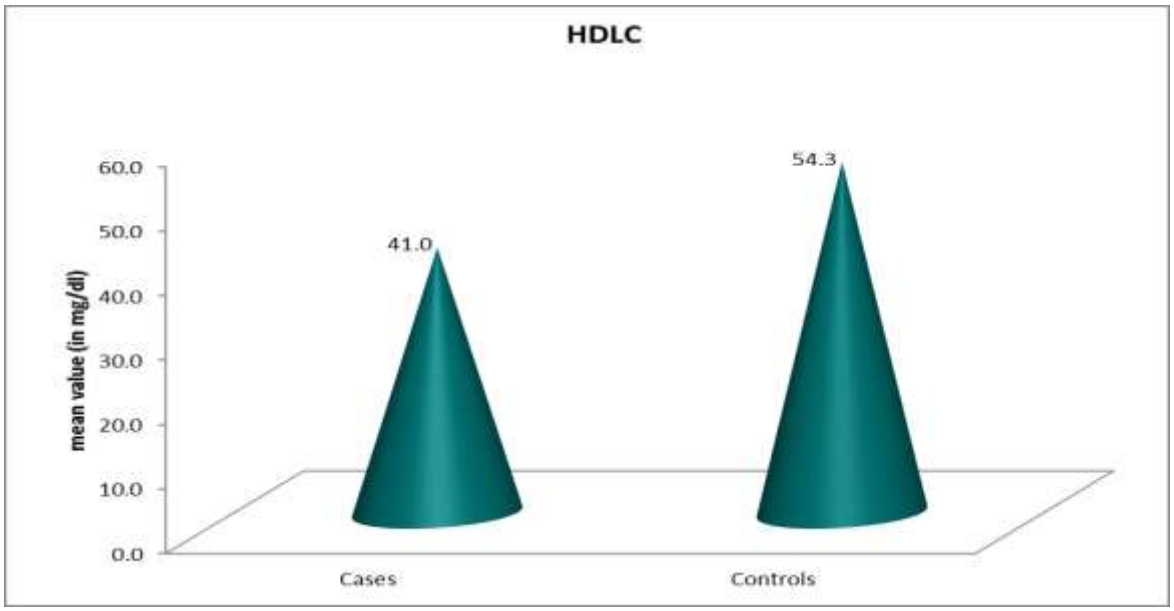
ESR values in case group minimum value 13mm/Hr, maximum value 120mm/Hr, mean value is 46.3mm/Hr. In control group ESR is within normal range. Comparing ESR level in case and control group, ESR level is statistically significant in case group (p value <0.001)

	Group			
	Cases		**Controls**	
	N=50		**N=50**	
	Mean±SD	**(min, max)**	**Mean±SD**	**(min, max)**
CRP	7.9±5.5	(0.3, 22.4)	0.6±0.2	(0.1, 1.2)
p-value	<0.001			



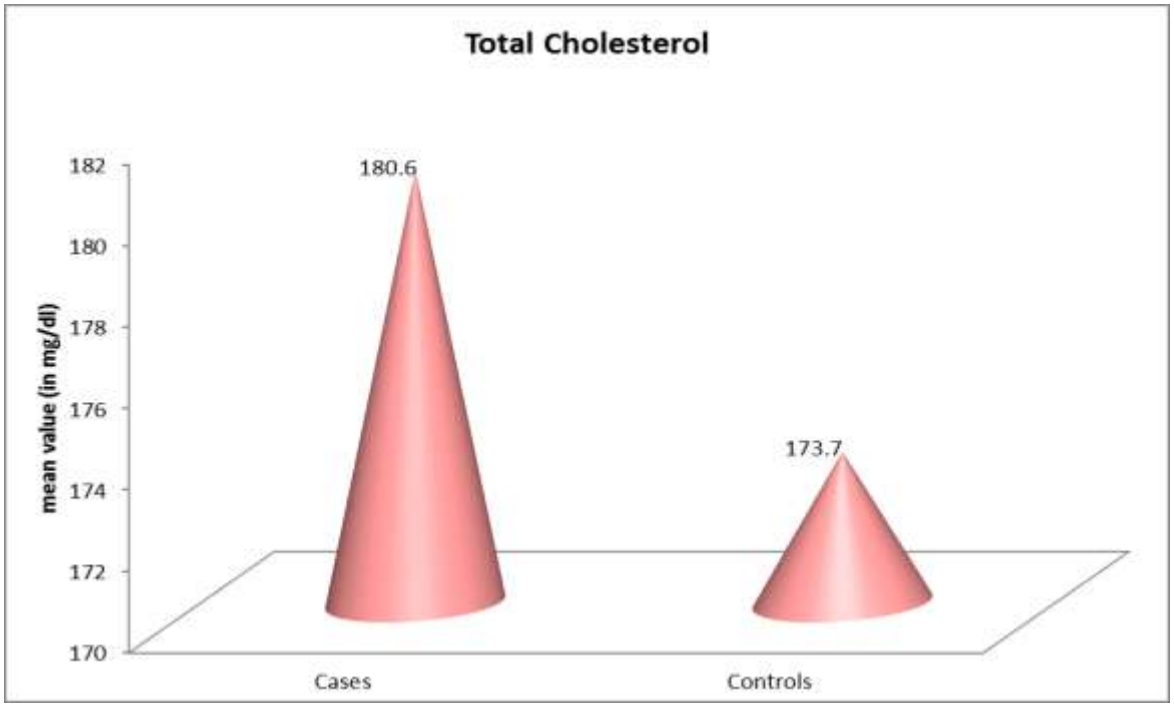
CRP level in case group minimum level is 0.3mg/dl, maximum level is 22.4mg/dl, mean value is 7.9mg/dl. In control group CRP is within normal range. Comparing CRP level in case and control group, CRP level is statistically significant in case group (p value <0.001)

	Group			
	Cases		Controls	
	N=50		N=50	
	Mean±SD	(min, max)	Mean±SD	(min, max)
HDL	41.0±7.4	(29, 59)	54.3±4.2	(46, 63)
p-value	<0.001			



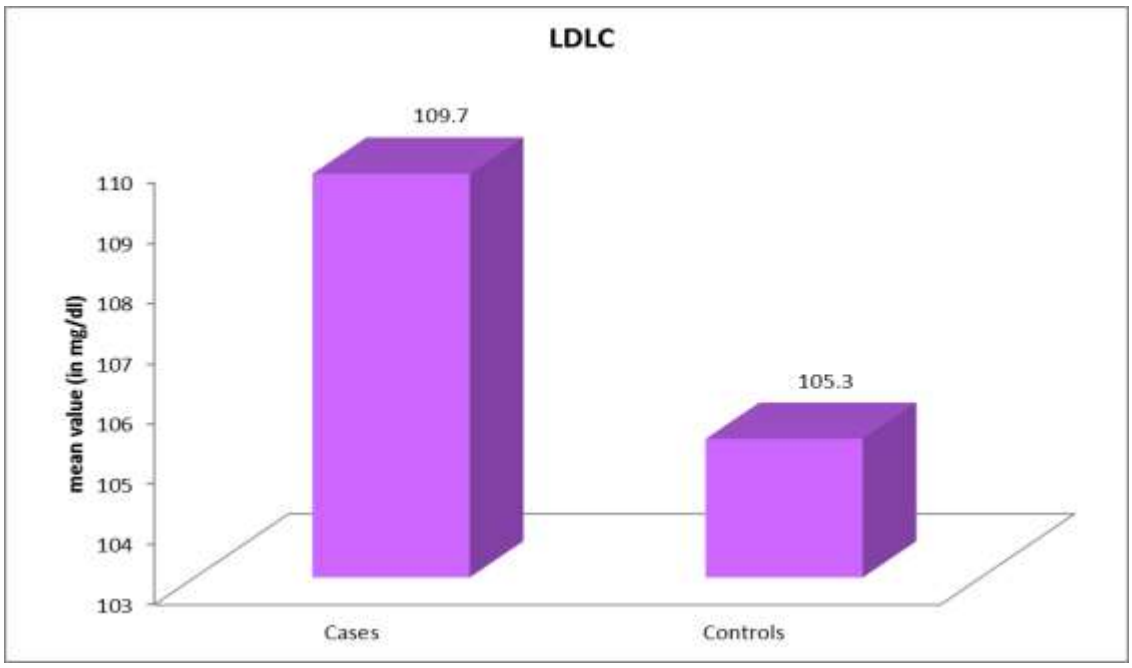
HDL is in the normal range in control group. In case group HDL is significantly low . Comparing case and control group HDL level is statistically significant p value (<0.001) in case group.

	Group			
	Cases		**Controls**	
	N=50		**N=50**	
	Mean±SD	**(min, max)**	**Mean±SD**	**(min, max)**
Total Cholesterol	180.6±20.6	(156, 256)	173.7±9.5	(156, 190)
p-value	0.033			



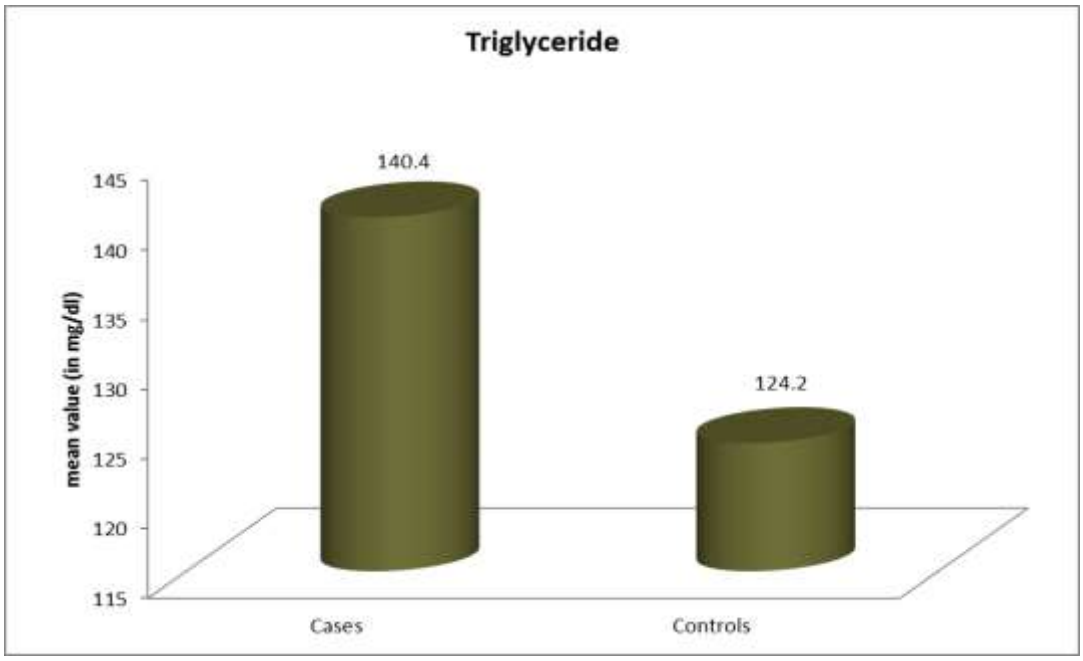
Total cholesterol is in the normal range in control group. Comparing case and control group Total cholesterol level is statistically significant p value (0.033).

	Group			
	Cases		Controls	
	N=50		N=50	
	Mean±SD	(min, max)	Mean±SD	(min, max)
LDL	109.7±15.9	(88, 156)	105.3±8.2	(88, 123)
p-value	0.082			



LDL is in the normal range in control group. Comparing case and control group LDL level is not statistically significant p value (<0.082).

	Group			
	Cases		**Controls**	
	N=50		**N=50**	
	Mean±SD	**(min, max)**	**Mean±SD**	**(min, max)**
Triglyceride	140.4±18.1	(110, 190)	124.2±11.8	(100, 145)
p-value	P<0.001			



TG is in the normal range in control group. Comparing case and control group TG level is statistically significant p value (<0.001).

Correlation between Lipid profile and ESR (mm/Hour) for Rheumatoid Arthritis patients		
Lipid profile	**Correlation co-efficient (r)**	**p-value**
TC mg/dl	0.782	<0.001
LDL mg/dl	0.642	<0.001
HDL mg/dl	-0.798	<0.001
TG mg/dl	0.831	<0.001

In case group TC,LDL,TG levels are directly proportional to ESR level (p value <0.001). HDL level is inversely proportional to ESR level (p value <0.001). Correlation co efficient for HDL is -0.798 . In control group ESR, lipid profile are in normal range. No correlation is found in control group regarding ESR and TC,HDL,LDL,TG levels. ESR and HDL level correlation in RA case group, it is statistically significant (p value <0.001).

Correlation between Lipid fractions and CRP (mg/dl) for Rheumatoid Arthritis patients		
Lipid fractions	**Correlation co-efficient (r)**	**p-value**
TC mg/dl	0.738	<0.001
LDL mg/dl	0.615	<0.001
HDL mg/dl	-0.791	<0.001
TG mg/dl	0.816	<0.001

In case TC,LDL,TG levels are directly proportional to CRP level (p value <0.001). HDL level is inversely proportional to CRP level (p value <0.001). Correlation co efficient for HDL is -0.791. In control group CRP, lipid profile is in normal range. No correlation is found in control group regarding CRP and TC, HDL,LDL,TG levels. CRP and HDL level correlation in RA case group, it is statistically significant (p value <0.001).

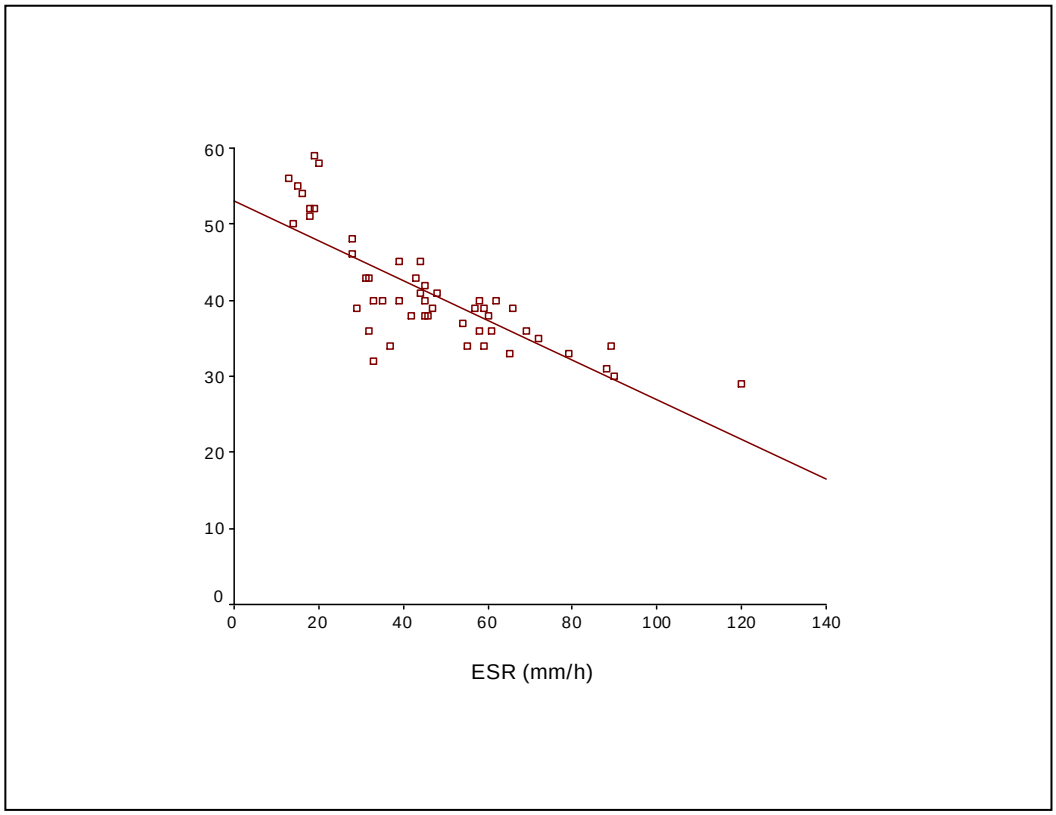


Fig (1): Correlation between high density lipoprotein-cholesterol and Erythrocyte Sedimentation Rate

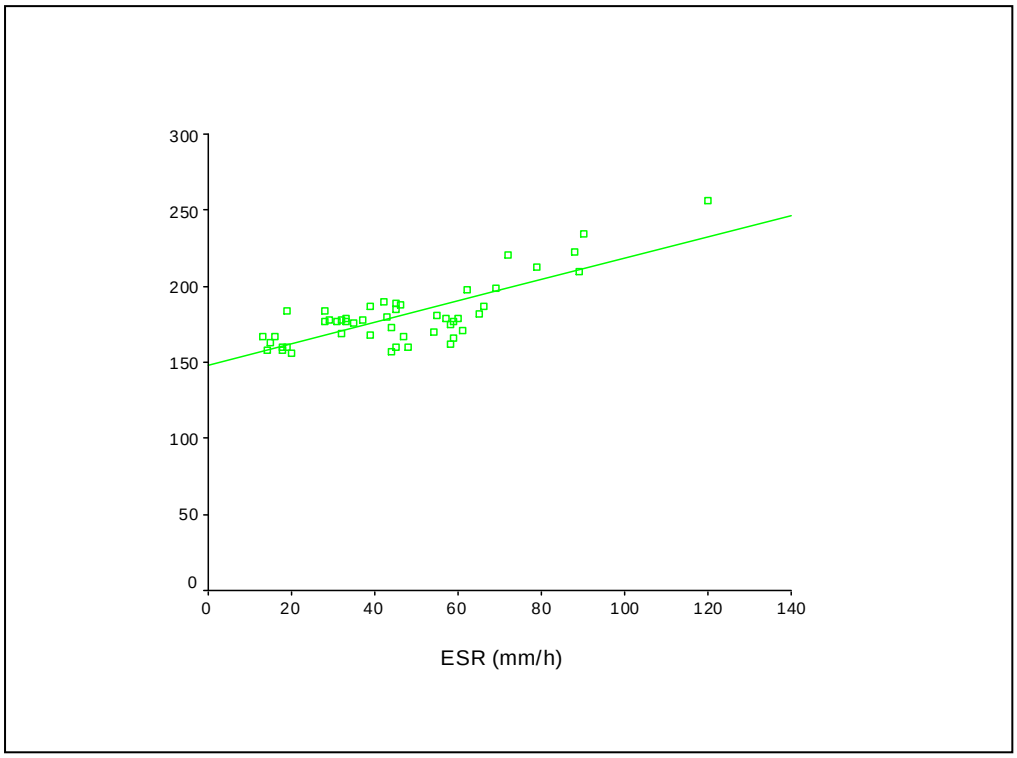


Fig (2): Correlation between Total Cholesterol and Erythrocyte Sedimentation Rate

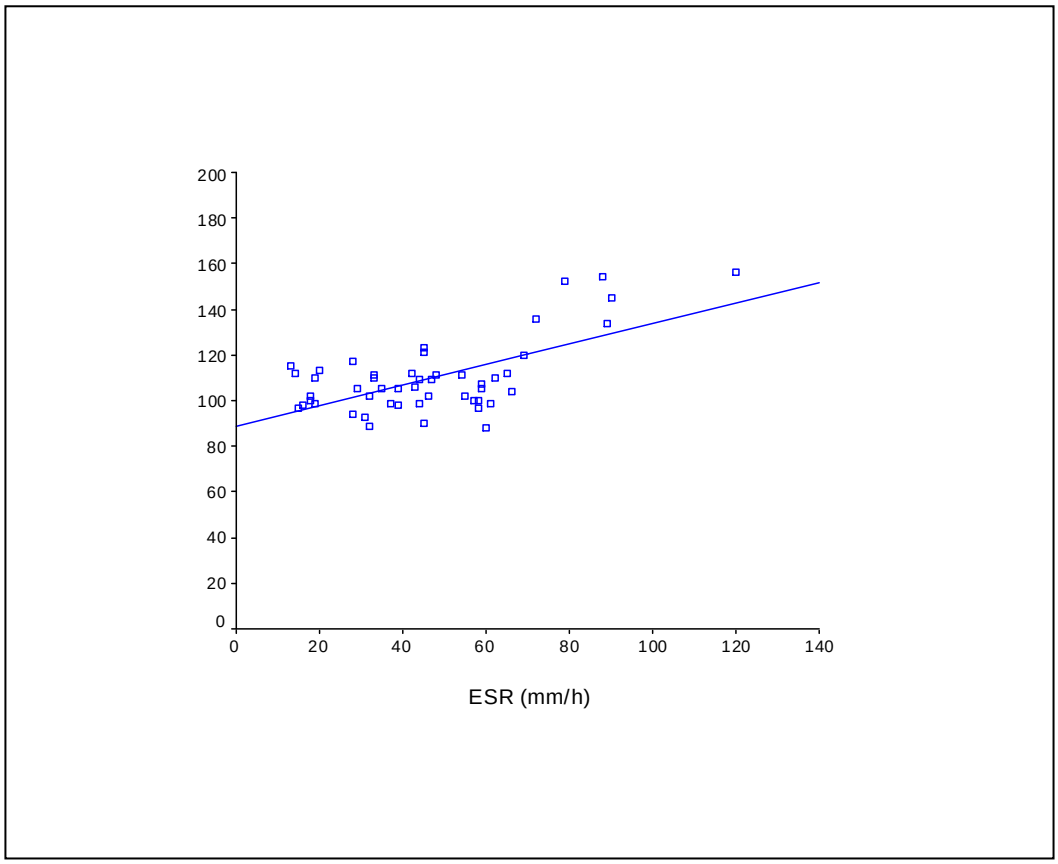


Fig (3): Correlation between low density lipoprotein-cholesterol and Erythrocyte Sedimentation Rate

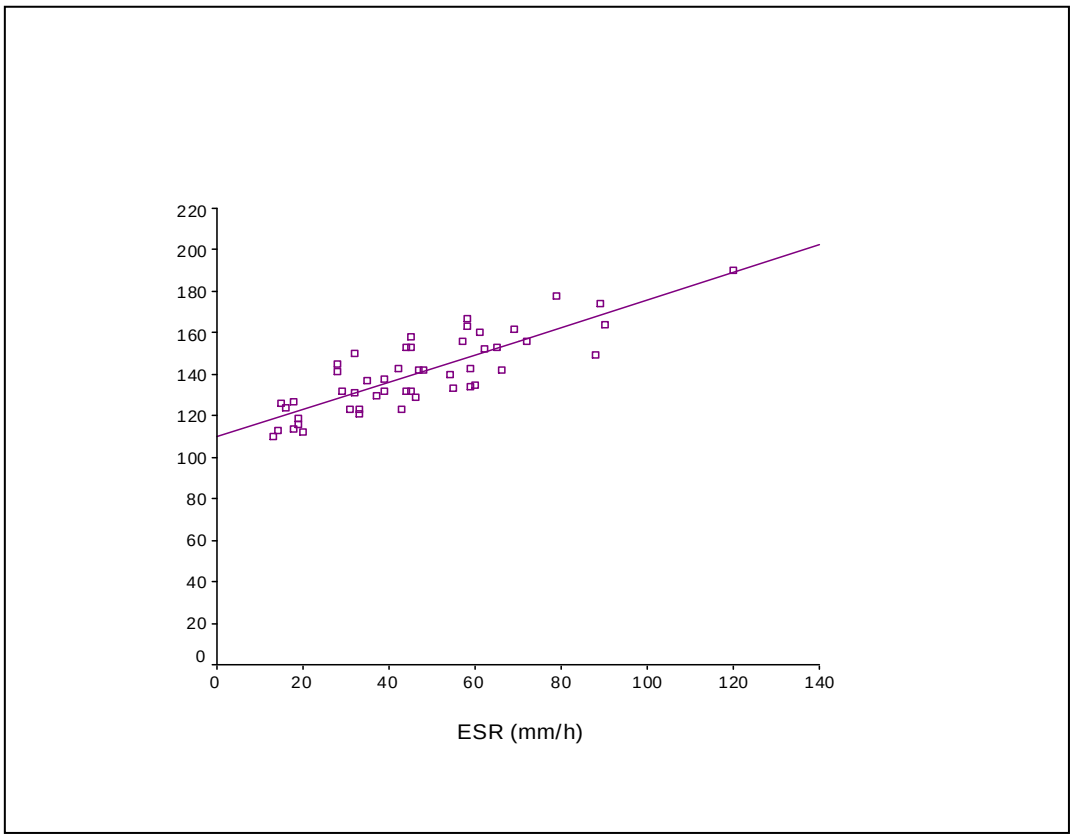


Fig (4): Correlation between Triglyceride and Erythrocyte Sedimentation

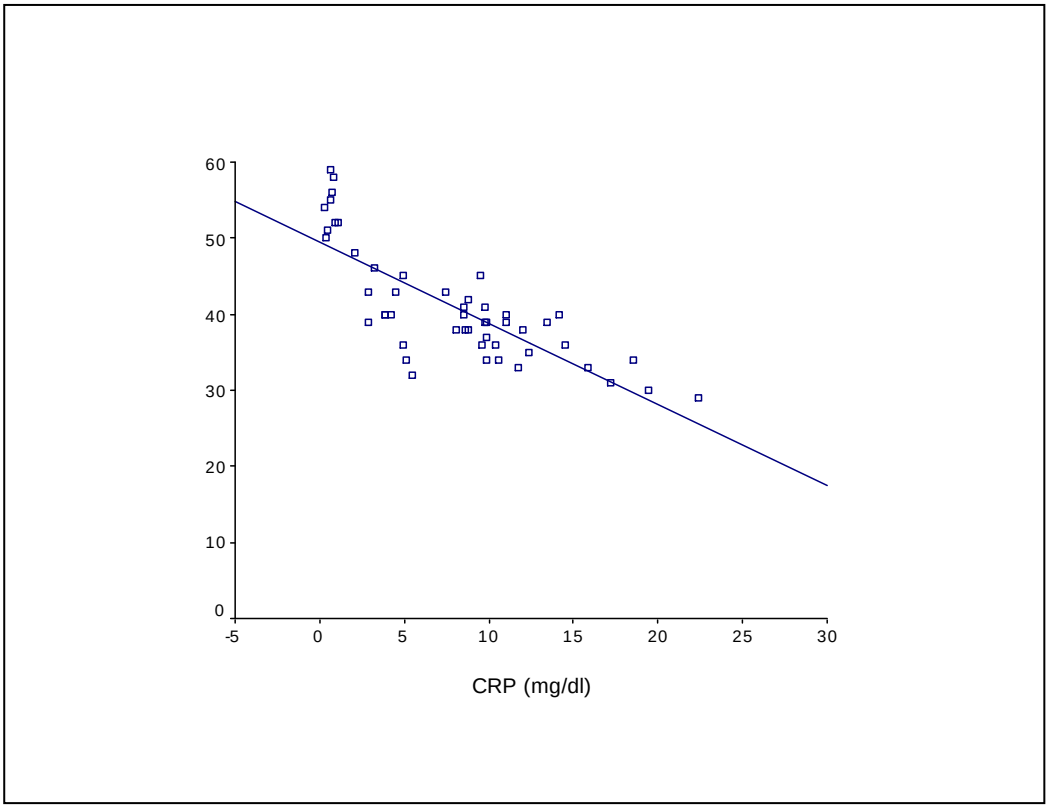


Fig (5): Correlation between high density lipoprotein-cholesterol and C-reactive protein

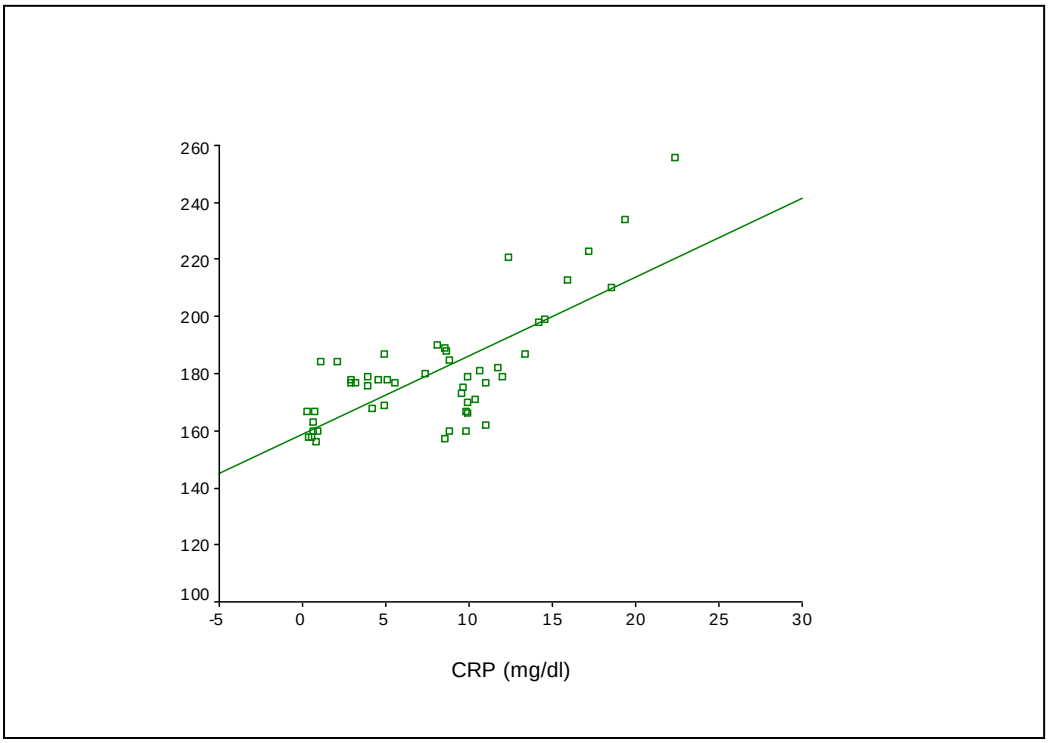


Fig (6): Correlation between Total Cholesterol and C-reactive protein

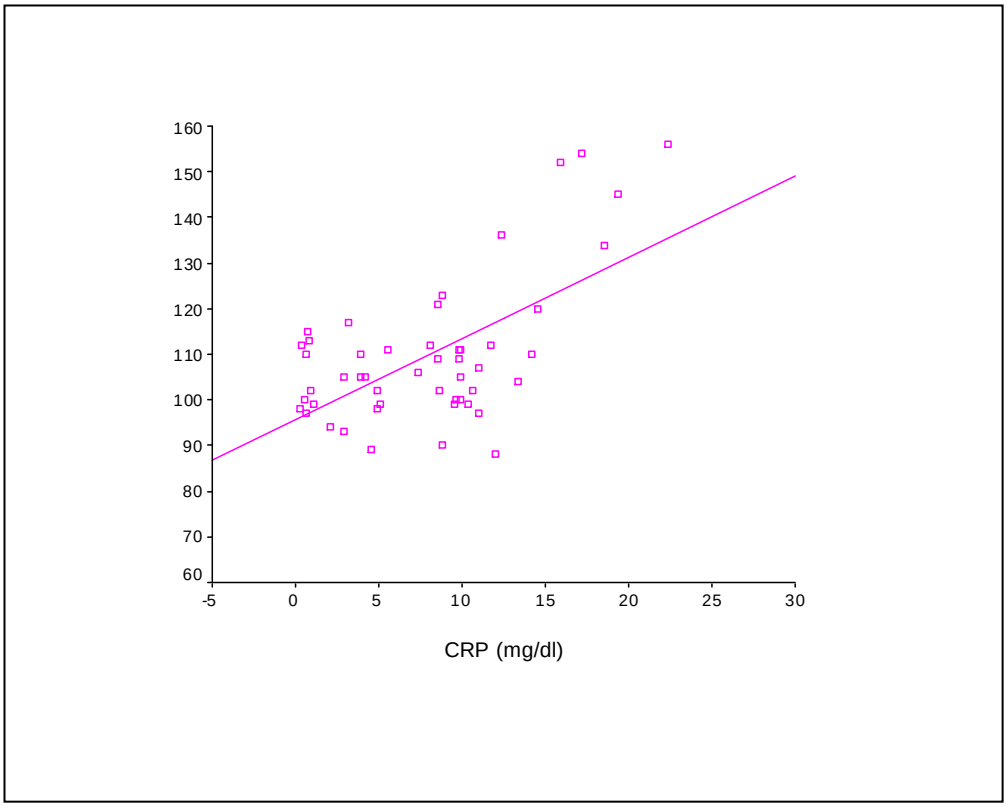


Fig (7): Correlation between low density lipoprotein-cholesterol and C-reactive protein

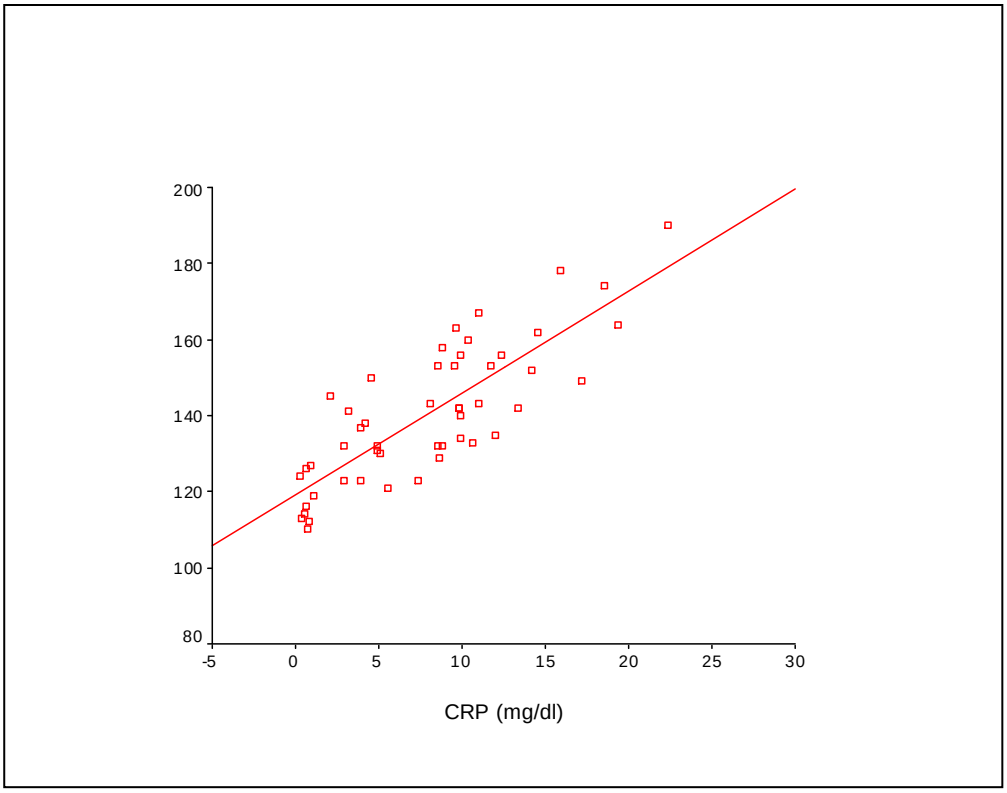


Fig (8): Correlation between Triglyceride and C-reactive protein

DISCUSSION

Rheumatoid arthritis (RA) is a proatherogenic disease associated with increased cardiovascular (CV) mortality.1 2 Besides genetic and traditional CV risk factors,3 4 chronic inflammation has emerged as a pivotal component implicated in the development of this process. A chronic inflammatory burden, determined by the mean values of C-reactive protein (CRP) was associated with subclinical atherosclerosis and increased risk of CV events.5 6 In a large retrospective cohort study, CV disease-related mortality was increased in RA patients with elevated measures of inflammation markers.7 The presence of a proinflammatory state leads to a decrease of HDL cholesterol in patients with RA.8 The anti-inflammatory effect, DMARD agents have demonstrated a reduction of the CV death rate in patients with RA.9–12 This reduction in the rate of CV events seems to be directly related to better control of the rheumatic disease. Therefore, the relationship between CV disease and lipid levels in patients with RA may be different from that observed in the general population. Chronic inflammation leads to oxidative changes that alter HDL structure and reduce apolipoprotein-A-I in patients with active RA.13 Levels of paraoxonase-1, an antioxidant enzyme associated with

HDL, are lower in patients with RA compared with healthy controls.14 Therefore, because of inflammation there is an impairment of the normal antiinflammatory, antioxidate and cardioprotective function of HDL cholesterol that turns out to be proinflammatory. A recent study that assessed a retrospective cohort using 2005–2010 data supported the association of inflammatory markers and serum lipids with the risk of CV events in RA.15 This study implied that inflammatory markers and HDL cholesterol levels are associated with increased and reduced incident CV disease, respectively. According to their results, higher CRP and erythrocyte sedimentation rate levels and lower HDL cholesterol levels were associated with higher incidence of myocardial infarction.15

HDL level is inversely proportional to ESR level (p value <0.001) in CASE GROUP. Correlation co efficient for HDL is -0.798 (p value <0.001). HDL level is inversely proportional to CRP level (p value <0.001). Correlation co efficient for HDL is -0.791 (p value <0.001) in CASE GROUP.

In control group CRP,ESR,lipid profile is in normal range.

No correlation is found in control group regarding CRP/ESR and TC, HDL,LDL,TG levels.

Semb et al16 showed that intensive treatment with statins led to a comparable decrease in lipid levels and a 20% reduction in overall risk of CV disease in patients with and without inflammatory joint disease. A significant reduction of CRP levels in patients with RA taking statins compared with placebo has also been observed.16 In a randomised controlled trial of atorvastatin in RA, McCarey et al17 demonstrated a moderate decrease in disease activity and a significant reduction in total cholesterol and LDL cholesterol in statin-treated patients with RA.

Early diagnosis and early introduction of treatment will reduce disease activity and control inflammation that will reduce risk of cardiovascular disease and improve long term survival of Rheumatoid arthritis patients.

LIMITATION

- Sample size is small.
- The study population involved patients seeking medical care in our hospital which is a tertiary care center and hence they may not represent the general population.

SUMMARY

This observational study was conducted to identify impaired lipid metabolism in Rheumatoid arthritis patients and to compare CRP level with HDL level in rheumatoid arthritis patients and to improve the long term survival of Rheumatoid arthritis patients by early detection of dyslipidemia and timely institution of treatment

With 50 RA patients & 50 CONTROL cases were selected carefully and were evaluated on clinical and laboratory aspects after institutional ethical clearance with an informed consent. The data were entered in Microsoft Excel spread sheet and analysed statistically.

Irrespective of duration of disease and treatment, disease activity is found to be important key factor in induction of impaired lipid metabolism and other cardiovascular risk factors.

So with early diagnosis and early introduction of treatment we can reduce the prevalence of dyslipidemia in Rheumatoid arthritis patient. With all these measures we can reduce the risk of cardiovascular disease and improve long term survival of Rheumatoid arthritis patients.

CONCLUSION

- Long duration of disease and disease activity is important risk of factor dyslipidemia.
- Impaired LIPID metabolism carries high risk of cardiovascular disease.
- Patients with active RA were characterized by an atherogenic lipid profile.
- The decrement in HDL-C level was inversely correlated with the increment of CRP level in most of clinical studies.
- Thus, early intervention to control disease activity may reduce the risk of the atherosclerotic process and cardiovascular events in RA patients.
- Active RA was associated with an adverse lipid profile that improved significantly upon effective treatment of RA with disease-modifying anti-rheumatic drugs (DMARD) suggesting it was the decrease in RA disease activity that reversed the altered lipid profiles.

- Early diagnosis and early introduction of treatment will reduce disease activity and control inflammation that will reduce risk of cardiovascular disease and improve long term survival of Rheumatoid arthritis patients.

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ANNEXURE

PROFORMA

Name:

Age / Sex:

Occupation:

Presenting complaints:

- H/o joint pain/swelling/deformity
- H/o early morning stiffness,
- H/o fever,
- H/o malaise,
- H/o breathing difficulty,
- H/o chest pain,
- H/o foreign body sensation in eyes,
- H/o Redness of eye
- H/o cough with expectoration
- H/o Hemoptysis
- H/o nodule over bone

- H/o weakness of limbs/sensory disturbance
- H/o abdominal pain/ distension
- H/o leg swelling
- H/o Leg ulcer
- H/o Dry eye/mouth
- H/o swelling of parotid region

Past History:

- H/o DM
- H/o HT
- H/o TUBERCULOSIS
- H/o CAD
- H/o COPD
- H/o STROKE/ PERIPHERAL VASCULAR DISEASE
- H/o CKD
- H/o ENDOCRINOPATHIES
- H/o DYSLIPIDEMIC SYNDROME
- H/o DRUG INTAKE

Clinical Examination:

General Examination:

Consciousness,

Pallor,

Jaundice,

Clubbing,

Lymphadenopathy,

Pedal edema,

Rheumatoid Nodule,

Skin ulcer

BMI:

Vitals:

PR

RR

BP

SPO2

System examination:

CVS:

RS:

ABDOMEN:

CNS:

Musculoskeletal examination:

Laboratory investigations:

- FBS,PPBS,RFT
- THYROID FUNCTION TEST
- FASTING LIPID PROFILE
- RHEUMATOID FACTOR
- ERTHROCYTE SEDIMENTATION RATE
- C-REACTIVE PROTEIN

KEY WORDS (ABBREVIATIONS)

RA	-	Rheumatoid arthritis
RF	-	Rheumatoid factor
TNF	-	Tumor necrosis factor
IL	-	Interleukin
ACR-EULAR	-	American college of Rheumatology- European league against Rheumatism
DMARDs	-	Disease modifying antirheumatic drugs
CCP	-	cyclic citrullinated peptide
CRP	-	C-REACTIVE PROTEIN
ESR	-	ERYTHROCYTE SEDIMENTATION RATE
HDL	-	HIGH DENSITY LIPOPROTEIN
LDL	-	LOW DENSITY LIPOPROTEIN
TG	-	TRIGLYCERIDE
TC	-	TOTAL CHOLESTEROL

MASTER CHART FOR CASE GROUP

S.NO	SEX	AGE	RF	ESR	CRP	OBESITY	HDL	TOTAL CHOLESTEROL	LDL	TG
1	FEMALE	39	NEGATIVE	13	0.7	NO	56	167	115	110
2	FEMALE	41	NEGATIVE	20	0.8	NO	58	156	113	112
3	FEMALE	32	NEGATIVE	14	0.4	NO	50	158	112	113
4	FEMALE	37	NEGATIVE	18	0.5	YES	51	158	100	114
5	MALE	39	NEGATIVE	19	0.6	NO	59	160	110	116
6	MALE	48	NEGATIVE	16	0.3	NO	54	167	98	124
7	MALE	37	NEGATIVE	15	0.6	NO	55	163	97	126
8	MALE	38	NEGATIVE	18	0.9	NO	52	160	102	127
9	MALE	40	POSITIVE	33	5.5	NO	32	177	111	121

10	MALE	44	POSITIVE	37	5.1	YES	34	178	99	130
11	MALE	45	POSITIVE	32	4.9	NO	36	169	102	131
12	FEMALE	36	POSITIVE	29	2.9	NO	39	178	105	132
13	FEMALE	32	POSITIVE	43	7.4	NO	43	180	106	123
14	FEMALE	39	POSITIVE	66	13.4	YES	39	187	104	142
15	FEMALE	38	POSITIVE	62	14.2	NO	40	198	110	152
16	FEMALE	39	POSITIVE	48	9.8	NO	41	160	111	142
17	FEMALE	38	POSITIVE	59	11	NO	39	177	107	143
18	FEMALE	39	POSITIVE	35	3.9	NO	40	176	105	137
19	FEMALE	31	POSITIVE	39	4.2	NO	40	168	105	138
20	FEMALE	40	POSITIVE	44	8.5	NO	41	157	109	132
21	FEMALE	38	POSITIVE	54	9.9	YES	37	170	111	140

22	FEMALE	30	POSITIVE	28	3.2	NO	46	177	117	141
23	FEMALE	31	POSITIVE	89	18.5	NO	34	210	134	174
24	FEMALE	46	POSITIVE	45	8.5	NO	40	189	121	153
25	FEMALE	33	POSITIVE	69	14.5	NO	36	199	120	162
26	FEMALE	32	POSITIVE	39	4.9	NO	45	187	98	132
27	FEMALE	41	POSITIVE	32	4.5	NO	43	178	89	150
28	FEMALE	38	POSITIVE	57	9.9	NO	39	179	100	156
29	FEMALE	38	POSITIVE	45	8.8	NO	42	160	90	132
30	FEMALE	37	POSITIVE	58	11	YES	40	162	97	167
31	FEMALE	38	POSITIVE	44	9.5	NO	45	173	99	153
32	FEMALE	46	POSITIVE	79	15.9	NO	33	213	152	178
33	FEMALE	32	POSITIVE	58	9.6	NO	36	175	100	163

34	FEMALE	34	POSITIVE	28	2.1	NO	48	184	94	145
35	FEMALE	47	POSITIVE	60	12	NO	38	179	88	135
36	FEMALE	37	POSITIVE	59	9.9	NO	34	166	105	134
37	FEMALE	38	POSITIVE	46	8.6	NO	38	188	102	129
38	FEMALE	33	POSITIVE	31	2.9	NO	43	177	93	123
39	FEMALE	40	POSITIVE	61	10.4	NO	36	171	99	160
40	FEMALE	42	POSITIVE	120	22.4	NO	29	256	156	190
41	FEMALE	39	POSITIVE	65	11.7	NO	33	182	112	153
42	FEMALE	33	POSITIVE	88	17.2	YES	31	223	154	149
43	FEMALE	36	POSITIVE	19	1.1	NO	52	184	99	119
44	FEMALE	32	POSITIVE	90	19.4	NO	30	234	145	164
45	FEMALE	39	POSITIVE	55	10.6	YES	34	181	102	133

46	FEMALE	34	POSITIVE	42	8.1	NO	38	190	112	143
47	FEMALE	33	POSITIVE	47	9.8	NO	39	167	109	142
48	FEMALE	31	POSITIVE	72	12.4	NO	35	221	136	156
49	FEMALE	33	POSITIVE	45	8.8	NO	38	185	123	158
50	FEMALE	41	POSITIVE	33	3.9	NO	40	179	110	123

MASTER CHART FOR CONTROL GROUP

S.NO	SEX	AGE	RF	ESR	CRP	OBESITY	HDL	TOTAL CHOLESTEROL	LDL	TG
1	FEMALE	33	NEGATIVE	13	0.2	NO	56	167	115	110
2	FEMALE	34	NEGATIVE	20	0.3	NO	58	156	113	112
3	FEMALE	37	NEGATIVE	14	0.4	NO	50	158	112	113
4	FEMALE	43	NEGATIVE	18	0.5	YES	51	158	100	114
5	MALE	32	NEGATIVE	19	0.6	NO	50	160	110	116
6	MALE	36	NEGATIVE	16	0.3	NO	52	167	98	124
7	MALE	37	NEGATIVE	15	0.3	NO	49	163	97	126
8	MALE	38	NEGATIVE	18	0.9	NO	48	160	102	127
9	MALE	39	NEGATIVE	14	0.8	NO	46	177	111	121

10	MALE	40	NEGATIVE	16	1	YES	49	178	99	130
11	MALE	41	NEGATIVE	16	0.1	NO	50	169	102	131
12	FEMALE	42	NEGATIVE	18	0.2	NO	51	178	105	132
13	FEMALE	43	NEGATIVE	13	0.3	NO	52	180	106	123
14	FEMALE	43	NEGATIVE	9	0.4	NO	53	187	104	118
15	FEMALE	46	NEGATIVE	11	0.5	NO	54	178	110	139
16	FEMALE	45	NEGATIVE	12	0.6	NO	55	160	111	142
17	FEMALE	38	NEGATIVE	12	0.7	NO	56	177	107	143
18	FEMALE	39	NEGATIVE	13	0.8	NO	57	176	105	137
19	FEMALE	31	NEGATIVE	9	0.9	NO	58	168	105	138
20	FEMALE	40	NEGATIVE	11	1	NO	59	157	109	132
21	FEMALE	38	NEGATIVE	10	1.1	YES	60	170	111	140

22	FEMALE	30	NEGATIVE	12	1	NO	51	177	117	141
23	FEMALE	31	NEGATIVE	13	0.9	NO	52	178	121	119
24	FEMALE	46	NEGATIVE	14	0.8	NO	54	180	123	137
25	FEMALE	33	NEGATIVE	17	0.7	NO	49	170	120	139
26	FEMALE	32	NEGATIVE	11	0.4	NO	50	167	98	132
27	FEMALE	41	NEGATIVE	12	0.4	NO	55	178	89	120
28	FEMALE	38	NEGATIVE	13	0.8	NO	52	179	100	131
29	FEMALE	38	NEGATIVE	14	0.9	NO	51	160	90	132
30	FEMALE	37	NEGATIVE	14	0.9	YES	59	162	97	145
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32	FEMALE	46	NEGATIVE	16	0.9	NO	57	189	109	132
33	FEMALE	32	NEGATIVE	12	0.8	NO	56	175	100	100

34	FEMALE	34	NEGATIVE	19	1.2	NO	59	184	94	105
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38	FEMALE	33	NEGATIVE	11	0.6	NO	52	177	93	123
39	FEMALE	40	NEGATIVE	13	0.6	NO	51	171	99	106
40	FEMALE	42	NEGATIVE	17	0.9	NO	55	180	111	109
41	FEMALE	39	NEGATIVE	15	0.7	NO	63	182	112	101
42	FEMALE	33	NEGATIVE	13	0.5	YES	62	169	99	129
43	FEMALE	36	NEGATIVE	15	0.4	NO	61	184	98	119
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ETHICS COMMITTEE CERTIFICATE

Name of the Candidate	:	Dr.S.Karthikeyan
Course	:	PG in MD., General Medicine
Period of Study	:	2014-2017
College	:	MADURAI MEDICAL COLLEGE
Research Topic	:	An observational study to compare CRP level with HDL level in rheumatoid arthritis patients
Ethical Committee as on	:	27.07.2016

The Ethics Committee, Madurai Medical College has decided to inform that your Research proposal is accepted.

Member Secretary Chairman Dean / Convenor

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