"A STUDY ON CORRELATION OF CAROTID ARTERY INTIMA-MEDIA THICKNESS (AS A MARKER OF ATHEROSCLEROSIS) WITH ACTIVITY AND DURATION OF RHEUMATOID ARTHRITIS"

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BONAFIDE CERTIFICATE

This is to certify that the dissertation entitled **"A STUDY ON CORRELATION OF CAROTID ARTERY INTIMA-MEDIA THICKNESS (AS A MARKER OF ATHEROSCLEROSIS) WITH ACTIVITY AND DURATION OF RHEUMATOID ARTHRITIS"** submitted by **DR.PRABHUSWAMY K. M.** to the Tamil Nadu Dr. M.G.R Medical University, Chennai, in partial fulfilment of the requirement for the award of M.D DEGREE (Branch–I) GENERAL MEDICINE is a bonafide research work carried out by him under direct supervision & guidance.

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DECLARATION

I, **Dr.PRABHUSWAMY K. M.** solemnly declare that the dissertation titled '**A STUDY ON CORRELATION OF CAROTID ARTERY INTIMA-MEDIA THICKNESS (AS A MARKER OF ATHEROSCLEROSIS) WITH ACTIVITY AND DURATION OF RHEUMATOID ARTHRITIS'** is a bonafide work done by me.

I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree and diploma to any university, board either in India or abroad.

The dissertation is submitted to The Tamil Nadu Dr.M.G.R. Medical University, towards partial fulfilment of requirement for the award of M.D. Degree in GENERAL MEDICINE (BRANCH –I)

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TABLE OF CONTENTS

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic chronic inflammatory disease in which etiology is unknown. It is the commonest inflammatory arthritis affecting 0.5 to 1 percent of general population all over the world. It is characterized by symmetric polyarthritis involving peripheral joints, resulting in joint destruction and disability. Although it is a disease of joints, abnormal immunological responses can lead to a variety of extra-articular manifestations including the involvement of blood vessels and heart.[1] As compared to general population, people with rheumatoid arthritis experience disability, increased mortality and shortened life expectancy.[2]

Cardiovascular involvement is the leading cause of mortality in patients with Rheumatoid arthritis.[3] This increased mortality due to cardiovascular involvement has been attributed to accelerated atherosclerosis which has been found to be independent of traditional risk factors for atherosclerosis.[4] Accelerated atherosclerosis in Rheumatoid arthritis has been attributed to inflammation[5], increased homocysteine levels[5], imbalance in homeostasis[7,8], immobility[9], decreased antioxidants level[10], side effects due to medications[11,12], and abnormal lipid levels[13-16]. Among the above mentioned causes, inflammation has the

strongest association for accelerated atherosclerosis in Rheumatoid arthritis patients.

In RA patients, indirect evidence of accelerated atherosclerosis comes from studies involving measurement of Carotid artery intima media thickness (CIMT) as a marker of atherosclerotic burden and cardiovascular risk[19,20]. Measurement of CIMT is an economical and noninvasive test which is quite reliable and sensitive for assessment of atherosclerosis[21]. Increased atherosclerosis in carotid arteries is indicative of atherosclerosis in multiple vascular beds including coronary arteries. So, measurement of CIMT is an important surrogate marker of increased cardiovascular risk including acute coronary syndrome[22]. Early diagnosis of atherosclerosis by measuring CIMT might trigger the preventive steps against atherosclerosis in RA patients thereby decreasing cardiovascular mortality.

In this background, a cross sectional study of CIMT in 40 cases of Rheumatoid arthritis patients of various age groups and duration of symptoms was conducted in south Indian patients, in southern districts of Tamilnadu, who were attending Government Rajaji Hospital, Madurai. The study was undertaken in the department of medicine, Government Rajaji Hospital, Madurai.

I hope this study may help to decrease cardiovascular mortality in Rheumatoid arthritis patients by early detection of accelerated atherosclerosis, there by instituting preventive treatment against atherosclerosis.

REVIEW OF LITERATURE

Rheumatoid arthritis (RA) is a symmetric chronic inflammatory polyarthritis that mainly affects the small joints of the hands and feet.

HISTORICAL ASPECTS

First detailed case report of Rheumatoid arthritis was given by 'Augustine Jacob Landre-Beauvais', a French medical student in 1850, who described acute onset of polyarthritis in a 35 year old female, which gradually ceased leaving behind deformities of hands and wrists, only to recur.

Garrod coined the term Rheumatoid arthritis in 1859. However the term came into use in 1941, prior to that it was known by many different terms such as proliferative arthritis, atrophic arthritis etc..

Soranus, an Epherian, who lived in second century AD, wrote a treatise describing a polyarthritis associated with morning stiffness in which "joints become twisted sideways or bent over backwards, or resting immovable upon their neighbours".

Two thousand years ago, Charaka in India described a chronic disease with joint swellings and subcutaneous nodules. The problem with accepting this or other

earlier descriptions as first case reports is that, each of them had clear references to what might have been tophaceous gout.

In the translation from Latin by Short, of Syndenhams(1676), description of a polyarticular disease characterized by remissions and exacerbations, and his observation that "the joints of his fingers had been as it were inverted and bulging out with the knots showing in their inner rather than the outer aspects of the fingers" the first description of swan neck deformity was made.

EPIDEMIOLOGY

Approximately 0.5 to 1 percent of adult population is affected by Rheumatoid arthritis worldwide. Prevalence of RA in India is 0.5 to 0.75 percent. It is more common in females than in males, the ratio being 2-3:1. There are evidences to suggest that the prevalence of RA has remained the same, but overall incidence is decreasing. This is because the individuals with RA are living longer.

Throughout the world there are some ethnic groups with high incidence of RA. The Native American Yakima, Pima, and Chippewa tribes of North America are examples of ethnic groups which have reported prevalence of nearly 7% in some studies. In contrast to this 0.2-0.4% is the reported prevalence rate in many population studies from Africa and Asia.

ETIOLOGY

Etiology of Rheumatoid arthritis (RA) is unknown. Combined influence of genetic and environmental factors has been proposed to be responsible for manifestation of the disease. Either genetic or environmental factors are insufficient alone for the full expression of the disease.

Most compelling evidence for genetic component is the concordance rate of 12-15 percent for RA in monozygotic twins when one twin is affected, as compared to 1 percent for general population. There is also increased risk (about 2-5 percent) in fraternal twin of a patient with RA. The risk in first degree relative is 2-10 times greater than in general population.

Role of HLA-DR:

Class II MHC haplotype is one of the best studied genetic risk factors for RA. About 40 percent of genetic influence in RA is accounted for the structure of class II MHC molecules in antigen presenting cells. A genetic link of RA with HLA-DR was described in 1970s. The observation made was that in 70 percent of RA patients, genetic association with HLA-DR4 was present as in contrast to controls where only 30% association was there. It indicates that the relative risk of getting RA in individuals with HLA-DR4 is approximately 4 to 5.

Rheumatoid arthritis susceptibility is associated with the third hyper variable region of DRβ-chains from amino acids 70 through 74. The epitope is glutamine-leucine-alanine-alanine (QKRAA), which is a sequence seen in DR4 and DR14, in addition to some DR1β-chains.

HLA-DR alleles observed to have association with Rheumatoid arthritis are[40]

- HLA-DR1,
- HLA-DR4Dw4,
- HLA-DR4Dw14
- HLA-DRw14Dw16

There are many other additional genetic influences in RA as follows

1. Many healthy individuals carry QKRAA motif and they do not develop RA. So, some other genes must also be involved for manifestation of RA.
2. The converse hypothesis could also be possible, that is, appropriate T-cell mediated response may be prevented because of limited binding of QKRAA to an arthrotropic agent.

3. The association between the shared epitope and RA might have little to do with antigen recognition and might function by shaping the T cell repertoire in the thymus (or autoantibody production, as noted with anticitrullinated peptide antibodies).

4. Specific DR sequences might alter intracellular MHC trafficking and antigen loading, indirectly affecting antigen presentation in a nonspecific fashion.

5. There is some evidence that certain DR4 epitopes are protective, such as DERAA in the same region of the molecule. Various hypotheses have attempted to explain this observation, including the possibility that the protective epitope contributes to regulatory T cell function. Although more controversial, class II associations related to the DQ region of the class II MHC locus also have been described for RA.

Non–Class II Major Histocompatibility Complex Associations in Rheumatoid Arthritis

Gene	Region of Gene Studied	Associated with Rheumatoid Arthritis[*]
PTPN22	Coding	+
PADI4	Coding	+
STAT4	Intron	+
TRAF1-C5	Intron	+
TNF-α	Promoter	+
IL-1	Coding region; association with IL-1β strongest	+/-
IL-1Ra	Coding region	+
IL-3	Promoter	+
IL-4	IntronPromoter	+-
IL-6	Promoter	-
IL-10	Promoter	-
IL-12	3′ untranslated region	-
IFN-γ	Intron microsatellite	+/-
CCR5	CCRδ32 allele	+
RANTES	Promoter	+
MIF	Promoter	+
RAGE	Ligand-binding domain	+
CTLA4	3′ untranslated region	+
TGF-β	Coding region	+
FcRγIII	Coding region	+

CCR5, chemokine receptor 5; c-5, complement 5; FcRγIII, Fc receptor γIII; IFN-γ, interferon-γ; IL, interleukin; IL-1Ra, interleukin-1 receptor antagonist; MIF, macrophage inhibitory factor; RAGE, receptor for advanced glycosylation end products; RANTES, regulated on activation, normally T cell expressed and secreted; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; TRAF1, TNF-receptor associated factor 1.

Gender:

Rheumatoid arthritis is predominant in women. Female to male ratio is 2:1 to 3:1 which is significant. This is attributed to the role of estrogens which are predominant sex hormones in females. The auto antibody producing B-cells exposed to estrogens are more resistant to apoptosis and hence the auto reactive B cell clones might escape tolerance. The effect of estrogens on T-lymophocytes is controversial, as estrogens tend to promote T-cell differentiation towards T-helper cells which produce anti –inflammatory cytokines like IL-4 and IL-13, which are present in only limited amounts in RA synovium. Estrogen receptors are expressed on fibroblast-like synoviocytes (FLS) and, when stimulated, increase production of metalloproteinases in the synovium. In macrophage cell lines, estrogen can enhance production of TNF-α. Taken together, these data suggest that the hormone milieu can have significant effects on the cells that are known to participate in RA. The effects are complex, however, and the specific mechanisms responsible for increased susceptibility of women to RA are uncertain.

Other endocrinal influences, including corticotropin releasing hormone or estrogen synthase, have been linked with Rheumatoid arthritis. Nulliparity also has been described as a risk factor, but not all studies confirm this.

During pregnancy, there can often be remission of the disease in the last trimester. In the first or second trimester, more than three quarters of pregnant patients with RA will improve, but 90 percent of these experience a flare of disease associated with an increase in RF titers in the weeks or months after child birth. The mechanism of protection is not defined, but might be due to the expression during pregnancy of suppressive cytokines such as IL-10, production of alpha fetoprotein, or alterations in cell mediated immunity.

Tobacco:

Numerous environmental factors certainly contribute to RA susceptibility, although no specific exposure has been identified as a pivotal agent. Smoking is the best defined environmental risk factor for seropositive RA in certain populations. The reason for its influence on the development of synovitis is not fully defined, but could involve the activation of innate immunity and PADI in the airway. Citrullinated peptides have been detected in bronchoalveolar lavage samples of smokers, and this could provide a stimulus for generation of anticitrullinated peptide antibodies in susceptible individuals. Repeated activation of innate immunity, especially in an individual with underlying genetically determined autoreactivity, potentially could contribute to autoreactivity and the initiation of RA.

Although genetic factors predispose an individual to developing RA, the environment clearly also contributes. Many pathogens have been associated with RA, including viruses, retroviruses, and *Mycoplasma,* although a precise etiologic link has not been established.

Possible Infectious Causes of RA:

Infectious Agent	**Potential Pathogenic Mechanisms**
1. *Mycoplasma*	Direct synovial infection; superantigens
2. Parvovirus B19	Direct synovial infection
3. Retroviruses	Direct synovial infection
4. Enteric bacteria	Molecular mimicry (QKRAA)
5. *Mycobacterium*	Molecular mimicry (proteoglycans, QKRAA), immunostimulatory DNA
6. Epstein-Barr virus	Molecular mimicry (QKRAA)
7. Bacterial cell walls	Macrophage activation

Data suggest that a specific RA pathogen is unlikely. Repeated inflammatory insults, especially through specialized receptors that recognize common molecules produced by pathogens, in a genetically susceptible individual might contribute to breakdown of tolerance and subsequent autoimmunity.

Evidence of autoimmunity can be present in RA many years before the onset of clinical arthritis. Autoantibodies, such as RFs and anticitrullinated protein antibodies, are commonly associated with RA. Autoantibodies occur in RA that recognize either joint antigens, such as type II collagen, or systemic antigens, such as glucose phosphate isomerase. The autoantibodies potentially can contribute to synovial inflammation through several mechanisms, including local activation of complement.

Autoantibody titers usually do not correlate well with disease activity. Improvement can be associated with modest decreases in levels of RFs or anticitrullinated peptide antibodies, although the changes tend to be relatively modest and are not consistent. These observations suggest that autoantibodies, although they contribute to the pathogenesis of RA, are not the primary driving factor.

Potential Auto-antigens in Rheumatoid Arthritis

1. Cartilage antigens
2. Type II collagen
3. gp39
4. Cartilage link protein
5. Proteoglycans
6. Aggrecan
7. Citrullinated peptides
8. Glucose-6-phosphoisomerase
9. HLA-DR (QKRAA)
10. Heat-shock proteins
11. Heavy-chain binding protein (BiP)
12. hnRNP-A2
13. Immunoglobulins (IgG)

CLINICAL FEATURES

The incidence of Rheumatoid arthritis increases in 25 to 55 years of age, after that it plateaus till the age of 75 and then decreases.

Patterns of onset

A) Insidious onset:

- RA has an insidious, slow onset over weeks to months in 55% to 65% of cases. The initial symptoms may be systemic or articular.
- In some individuals, fatigue, malaise, swollen hands, and diffuse musculoskeletal pain may be the first nonspecific complaints, with joints becoming involved later.
- Patient often can identify one joint that was involved first, quickly followed by others. Asymmetric initial presentations (often with more symmetry developing later in the course of disease) are common.
- Morning stiffness is a cardinal sign of inflammatory arthritis that can appear even before pain and may be related to the accumulation of edema fluid within inflamed tissues during sleep. To be specific for joint inflammation, morning stiffness (e.g., “difficulty moving around”) should persist for at least 30 to 45 minutes before disappearing.

- A low-grade fever without chills is rarely present.
- A small but significant weight loss is common and reflects the catabolic effects of cytokines and an associated anorexia.

B) Acute or intermediate onset:

- 8% to 15% have an acute onset of symptoms that peak within a few days.
- Fever, suggesting an infectious process, can be a prominent sign.
- An intermediate type of onset, in which symptoms develop over days or weeks, occurs in 15% to 20% of patients.

<u>Joint involvement</u>

- Initial joint involvement can be single joint (monoarticular), less than or equal 4 joints (oligoarticular) or polyarticular (>5 joints).
- The joints most commonly involved first in RA are the metacarpophalangeal (MCP) joints, proximal interphalangeal (PIP) joints, metatarsophalangeal joints, and wrists.
- Larger joints generally become symptomatic after small joints.

- Synovitis in large joints is likely to remain asymptomatic for a longer time than in smaller ones, and a biopsy specimen of an asymptomatic knee often shows histologic evidence of synovitis.

Unusual patterns or variants of disease

a) Palindromic pattern of onset:

    - Palindromic rheumatism was described by Hench and Rosenberg in 1942.[41]
    - Pain usually begins in one joint or in periarticular tissues; symptoms worsen for several hours to a few days and are associated with swelling and erythema.
    - Then, in reverse sequence, symptoms resolve, leaving no residua.
    - An intercritical period, similar to that of gout, is asymptomatic.
    - Half of patients with palindromic rheumatism go on to develop RA, particularly patients with HLA-DR4.

b) Effect of Age on Onset:

- Older individuals (≥65 years old) developing RA often present with stiffness, limb girdle pain, and diffuse boggy swelling of the hands, wrists, and forearms.
- Individuals with onset at age 60 years or older are less likely to have subcutaneous nodules or RF at the onset of disease, despite the high prevalence of RF in the general population in this age group.
- Generally, elderly individuals who develop RA tend to have a more benign course than younger patients; there is a lower frequency of positive tests for RF, but there is a strong association with HLA-DR4. The onset is slow, but the stiffness is often incapacitating.

c) Rheumatoid Arthritis and Paralysis: Asymmetric Disease

- Joints are typically spared on the paralyzed side, and the degree of protection shows a rough correlation with the extent of paralysis.
- The protective effect on the affected side is less if a neurologic deficit develops in a patient who already has RA.

d) Arthritis Robustus:

- Most patients are men; their disease is characterized by proliferative synovitis, often with deformity, that seems to cause little pain and even less disability.
- Periarticular osteopenia is unusual, whereas new bone proliferation at joint margins near significant erosions of bone and cartilage are common.
- Bulky subcutaneous nodules develop. Subchondral cysts also develop, presumably from the excessive pressure developed from synovial fluid within a thick joint capsule during muscular effort.

e) Rheumatoid Nodulosis:

- Whether rheumatoid nodulosis is a variant subset of RA or a different entity has not been clarified.
- The clinical picture is of a palindromic set of recurrent pain and swelling in different joints, radiologic subchondral bone cysts, and subcutaneous rheumatoid nodules.
- Second-line drugs helped articular disease, but not other components of the process.[42]

Course and complications of established Rheumatoid arthritis

The spectrum of the clinical course of RA can range from patients who have mild pauciarticular synovitis, negative serum RF, with few radiographic changes, to patients who have unrelenting pain, synovitis, joint damage, and extra-articular manifestations.

Involvement of specific joints:

a) Hand and Wrist:

- Swelling of the proximal, but not the distal interphalangeal joints results in ‘spindling’ of fingers.
- Hyperextension of the proximal interphalangeal joints and flexion of the distal interphalangeal joints result in “swan neck deformity”.
- Flexion of the proximal interphalangeal joints and extension of the distal interphalangeal joints result in “boutonniere or button hole deformity”.
- Hyperextension of the first interphalangeal joint and flexion of the first metacarpophalangeal joint with a consequent loss of thumb mobility can occur.

- Extensor tendon rheumatoid granulomata and tendon rupture results in "dropped finger".
- Radial deviation of wrist and ulnar deviation of the digits often with palmar subluxation of proximal phalanges result in "Z-deformity".
- Wrist synovitis with median nerve entrapment can result in "carpal tunnel syndrome".

b) Shoulder:

- RA of the shoulder not only affects synovium within the glenohumeral joint, but also involves the distal third of the clavicle, various bursae and the rotator cuff, and multiple muscles around the neck and chest wall. Presentations due to shoulder involvement are
  - Severe shoulder pain.
  - Superior subluxation of head of humerus due to rotator cuff weakness.
  - Rotator cuff tears or insufficiency.
  - Marked soft tissue swelling of the anterolateral aspect of the shoulders due to chronic subacromial bursitis.

- Rarely, the shoulder joint may rupture, with symptoms resembling those of obstruction of venous return from the arm.

c) Elbow:

- The frequency of elbow involvement varies from 20% to 65%, depending on the severity of disease in the patient populations studied.
- One of the earliest findings, often unnoticed by the patient, is a loss of full extension.
- RA rarely manifests with severe pain in the elbow, perhaps because the elbow is a stable hinge joint.

d) Ankle and Foot:

- Swelling of the metatarsophalangeal joints results in ‘broadening’ of forefoot.
- Lateral deviation and dorsal subluxation of the toes.
- Plantar subluxation of metatarsal heads.
- Eversion at the hindfoot (subtalar joint).
- Hallus valgus deformity.

e) Hip and knee:

- The hip is less frequently involved early in RA than in juvenile RA.
- Symptoms of hip synovitis are pain in the lower buttock or groin.
- About half of patients with well-established RA have radiographic evidence of hip disease.
- Early in knee disease, often within 1 week after the onset of symptoms, quadriceps atrophy is noticeable and leads to the application of more force than usual through the patella to the femoral surface.
- Another early manifestation of knee disease in RA is a loss of full extension, a functional loss that can become a fixed flexion contracture unless corrective measures are undertaken.
- Flexion of the knee that has a moderate to large effusion markedly increases the intra-articular pressure. This increased intra-articular pressure may cause an outpouching of posterior components of the joint, producing a “popliteal or Baker's cyst”.

f) Cervical Spine:

- The diskovertebral joints in the cervical spine often manifest osteochondral destruction in RA and on lateral radiographs may be found to be narrowed.
- There is significant pain, but passive range of motion in the absence of muscle spasm may be normal.
- The atlantoaxial joint is prone to subluxation in several directions.
- The earliest and most common symptom of cervical subluxation is pain radiating up into the occiput. Two other serious, but less common, clinical patterns are as follows:

  1. Slowly progressive spastic quadriparesis, frequently with painless sensory loss in the hands

  2. Transient episodes of medullary dysfunction associated with vertical penetration of the dens and probable vertebral artery compression; paresthesias in the shoulders or arms may occur during movement of the head

g) Thoracic, Lumbar, and Sacral Spine:

- The thoracic, lumbar, and sacral portions of the spine are usually spared in RA.
- The exceptions are the apophyseal joints; rarely, synovial cysts at the apophyseal joint can impinge as an epidural mass on the spinal cord, causing pain, neurologic deficits, or both.

h) Temporomandibular Joint:

- The temporomandibular joint is commonly involved in RA. Histories reveal that 55% of patients have jaw symptoms at some time during the course of their disease.
- Physical examination of the rheumatoid patient should include palpation of the temporomandibular joint for tenderness and auscultation for crepitus.
- Occasionally, patients have acute pain and an inability to close the mouth, necessitating intra-articular glucocorticoid therapy to suppress the acute process.
- Temporomandibular joint abnormalities are common in nonrheumatoid populations. The only specific findings for RA in the

temporomandibular joint are erosions and cysts of the mandibular condyle detected by CT or MRI.

- There is no correlation between clinical and CT findings of the temporomandibular joint in RA.[43]

i) Cricoarytenoid Joints:

- Careful histories may reveal hoarseness in 30% of rheumatoid patients due to involvement of Cricoarytenoid Joints.
- Asymptomatic cricoarytenoid synovitis occasionally may lead to aspiration of pharyngeal contents, particularly at night.

j) Ossicles of the Ear:

- Many rheumatoid patients experience a decrease in hearing as a result of conductive hearing loss.
- This is due to erosions and shortening of the ossicles produced by the erosive synovitis in RA patients, not due to ankylosis.

k) Sternoclavicular and Manubriosternal Joints:

- Sternoclavicular and manubriosternal joints, both possessing synovium and a large cartilaginous disk, are often involved in RA.

- Because of their relative immobility, there are few symptoms.
- Patients occasionally complain of experiencing pain in sternoclavicular joints, while lying on their sides in bed.
- Manubriosternal involvement is almost never clinically important, although by tomographic criteria it is common in RA.

Extra-articular Complications of Rheumatoid Arthritis

Generally, the number and severity of extra-articular features vary with the duration and severity of the disease. Several of these features may be related to extra-articular foci of an immune response,[44] based on evidence of independent and qualitatively different production of RF in the pleural space, pericardium, muscle, and even meninges.

These patients with systemic immune responses have true rheumatoid disease, not just RA.

Extra-articular manifestations of RA are associated with excess mortality.[45]

Following are the extra-articular manifestations of Rheumatoid arthritis.

A) Skeleton:

- RA can be associated with generalized osteopenia and osteoporosis owing to the
  - Effects of drugs (especially corticosteroids)
  - Cytokine-induced and RANKL-induced activation of osteoclasts.
  - And the fact that certain groups of patients with the disease, especially postmenopausal women, have other risk factors that enhance the potential for bone loss.
- Bone densitometry should be performed routinely in patients with RA, and treatment with bisphosphonates should be considered as an adjunct to therapy.

B) Muscles:

- More recent studies have pointed to at least five different types of muscle disease in RA, although clinically relevant active myositis is uncommon:

    1. Diminution of muscle bulk with atrophy of type II fibers
    2. Peripheral neuromyopathy, usually due to a mononeuritis multiplex
    3. Steroid myopathy
    4. Active myositis and muscle necrosis with foci of endomysial mononuclear cell infiltration
    5. Chronic myopathy resembling a dystrophic process, probably the end stage of inflammatory myositis

- In some patients, the lymphocytes in muscle synthesize IgM RF, emphasizing the systemic nature of RA.
- The patchy “nodules of myositis” contain plasma cells and lymphocytes.

C) Skin:

- The most frequently recognized skin lesion in RA is **the rheumatoid nodule**, but there are several other manifestations as well.
    - The mature rheumatoid nodule has a central area of necrosis rimmed by a corona of palisading fibroblasts that is surrounded in turn by a collagenous capsule with perivascular collections of chronic inflammatory cells.
    - Occurring in 15% to 20% of patients with definite or classic RA, nodules are found most often on extensor surfaces or pressure points, such as the olecranon process and the proximal ulna.
    - Rheumatoid nodules can be formed in sacral region, occipital region, vocal cords, heart, lung, vertebral bodies, sclera, and in CNS involving leptomeninges more than parenchyma leading to complications in respective regions.
- "Senile" purpura resulting from skin atrophy and capillary fragility is especially common in patients treated with glucocorticoids.
- Palmar erythema is common.

- Manifestations of vasculitis range from occasional nail fold infarcts to a deep, erosive, scarring pyoderma gangrenosum.
- Palpable purpura in rheumatoid patients is often related to a reaction to a drug that the patient is taking, but can be primary and a direct function of the severity of articular disease.
- Livedo reticularis, the lacy, dusky purple, asymptomatic discoloration seen on the extremities, is believed to signify a deep dermal vasculopathy.
- Cutaneous sinuses near joints develop rarely in seropositive patients with long-standing disease and positive tests for RF.

D) Eye:

- Keratoconjunctivitis sicca as a component of sicca complex (Keratoconjunctivitis sicca, xerostomia and salivary gland enlargement) of Sjögren's syndrome.
- Scleritis, episcleritis and scleromalacia perforans.
- Glaucoma.

E) Infection:

- The incidence of infections as a complication of RA has paralleled the use of glucocorticoids, biologics, and immunosuppressive agents.
- Pulmonary infections, skin sepsis, and pyarthrosis are the most common infection in RA. [46] [47]

F) Cancer:

- There is an increased risk for malignancy in RA patients particularly
  - Lymphoma.
  - Lung carcinoma- commonly bronchoalveolar variety.
  - Two to three times higher risk of Hodgkin's disease, non-Hodgkin's lymphoma, and leukemia than the normal population; this is independent of immunosuppressive therapy.

G) Hematological abnormalities:

- A mild normocytic normochromic anemia that correlates with ESR elevation and the activity of the disease.
- Thrombocytosis.
- Eosinophilia and mild leukocytosis.

H) Vasculitis:

- Rheumatoid vasculitis affects a subset of patients with established, often severe, RA with a prevalence of less than 5% of all cases.
- Variables associated with the development of rheumatoid vasculitis include the following:
  - ✓ Male gender
  - ✓ High titers of RF in serum
  - ✓ Hypocomplementemia
  - ✓ Joint erosions
  - ✓ Subcutaneous nodules and other extra-articular features
  - ✓ Long-standing disease
  - ✓ Circulating cryoglobulins
- Clinical vasculitis usually takes one of the following forms:
  - ➢ Distal arteritis (including from splinter hemorrhage, nail fold infarcts, and gangrene)
  - ➢ Cutaneous ulceration (including pyoderma gangrenosum)

- Peripheral neuropathy (mononeuritis multiplex)
- Arteritis of viscera, including heart, lungs, bowel, kidney, liver, spleen, pancreas, lymph nodes, and testis
- Palpable purpura

I) Renal disease:

- The kidney is rarely involved directly in RA, but often is compromised indirectly by therapy.
- Amyloidosis: AA amyloidosis, along with vasculitis and sepsis, is one of the most important life-threatening complications of RA.
- Renal papillary necrosis: related to Phenacetin abuse.
- NSAID related renal failure.
- Membranous nephropathy: related to therapy with gold salts and penicillamine in treatment of RA.
- Rarely, a focal necrotizing glomerulitis is seen in patients dying with RA and disseminated vasculitis.

J) Pulmonary disease:

There are at least six forms of lung disease in RA, as follows:

1) Pleural disease:

Characteristics of exudative rheumatoid effusions are as follows:

- ✓ Glucose, 10 to 50 mg/dL
- ✓ Protein, greater than 4 g/dL
- ✓ Cells (mononuclear), 100 to 3500/mm^3
- ✓ Lactate dehydrogenase, elevated
- ✓ CH_{50}, depressed

The low glucose concentrations are of interest. An impaired transport of glucose into the pleural space seems to be the cause of this.

2) Interstitial fibrosis

3) Nodular lung disease

4) Bronchiolitis obliterans with organizing pneumonia

5) Arteritis, with pulmonary hypertension

6) Small airways disease

K) Cardiac complications:

In patients with RA, Cardiovascular disease is the most common cause of mortality, primarily due to myocardial infarction and congestive heart failure.

Following are the cardiac complications:

- Atherosclerosis

There are multiple risk factors for coronary artery disease in RA patients in addition to the risk factors that are relevant in the general population.

- ✓ Patients with prolonged RA have more atherosclerosis than patients of the same age with more recent disease onset.[48]
- ✓ **Even after controlling the traditional risk factors of atherosclerosis (like diabetes, hypertension, hypercholesterolemia, obesity, and cigarette smoking), the incidence of carotid atherosclerosis and coronary artery disease is higher in patients with RA.[49]** Presence of increased inflammatory mediators in serum in this patients appears to be responsible for this.

- ✓ It also is apparent that, all else being equal, tobacco smoking is an important factor in augmenting early atherosclerosis in RA patients.[50]

- Other cardiac complications of RA are
  - ➢ Pericarditis
  - ➢ Myocarditis
  - ➢ Endocardial inflammation
  - ➢ Conduction defects
  - ➢ Coronary arteritis
  - ➢ Granulomatous Aortitis or valvular disease.

DIAGNOSIS

Criteria to establish the diagnosis of RA are based on an effective clinical history and physical examination, laboratory tests, and exclusion of other diagnoses.

2010 AMERICAN COLLEGE OF RHEUMATOLOGY/EUROPEAN LEAGUE AGAINST RHEUMATISM (ACR-EULAR) CLASSIFICATION CRITERIA FOR RHEUMATOID ARTHRITIS*

Criteria	**Score**
Joint Involvement	
1 large joint**	0
2-10 large joints	1
1-3 small joints*** (with or without involvement of large joints)	2
4-10 small joints (with or without involvement of large joints)	3
10 joints (at least 1 small joint)	5
Serology (at least 1 test result needed for classification)	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
Acute-Phase Reactants (at least 1 test result needed for classification)	
Normal CRP and normal ESR	0
Abnormal CRP and abnormal ESR	1
Duration of Symptoms	
Less than 6 weeks	0
6 or more weeks	1
*Target population: patients who have at least 1 joint with definite clinical synovitis in whom the synovitis is not better explained by another disease. ** Large joints include shoulders, elbows, hips, knees, and ankles. *** Small joints refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists. RF = rheumatoid factor; ACPA = anticitrullinated protein antibody; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.	

Application of ACR-EULAR criteria gives a score of 0-10. A score of ≥6 fulfills the requirement for definite RA.

Initial laboratory tests often show the results in the following list (essential tests are indicated with an asterisk (*). The other tests listed are largely of academic interest and should not be ordered routinely.

- Normal white blood cell count and differential*
- Thrombocytosis*
- Mild anemia (hemoglobin 10 g/dL), normochromic and either normocytic or microcytic*
- Normal urinalysis*
- ESR 30 mm/hr or greater and C-reactive protein level greater than 0.7 pg/mL*
- Normal renal, hepatic, and metabolic tests*
- Normal serum uric acid level

- Positive RF test (about 70% to 80% of patients; present in many normal individuals, patients with other rheumatic diseases, and individuals with chronic infections)*

- Anticitrullinated protein antibody (about 80% to 90% of patients; can be seen in other diseases, including active tuberculosis) (especially useful in early synovitis)*

Some investigators are convinced that anticitrullinated protein antibody will replace RF in the future as the autoantibody most useful in diagnosis. At this time, until it is cost-effective, it can be used to supplement RF in the presence of a strong clinical suspicion.

- Other autoantibodies (commonly found but with limited differential diagnosis utility, including antinuclear antibody, SS-A, SS-B)

- Polyclonal gammopathy as determined by serum protein electrophoresis

- Normal or elevated serum complement level

- Negative antineutrophil cytoplasmic antibody and anti–double-stranded DNA antibody tests

- "Typical" arthrocentesis, when obvious fluid is present, in RA reveals the following:

    - ✓ Joint fluid is straw-colored, is slightly cloudy, and contains many flecks of fibrin
    - ✓ 5000 to 25,000 white blood cells/mm3, and at least 50% of these are polymorphonuclear leukocytes
    - ✓ No crystals
    - ✓ Complement C4 and C2 levels are depressed, but C3 level can be normal
    - ✓ Normal synovial fluid glucose level
    - ✓ Cultures are negative.

COURSE OF THE DISEASE

Epidemiologic studies suggest that the disease is not changing, but that earlier, more effective treatment has diminished morbidity.

There are now well-tested criteria for clinical remission.

One composite system using the Disease Activity Score is a mathematical method that includes swollen and tender joints, ESR, and patient assessments of global health (DAS28 scoring). Notably, this criterion does not mean that the patient truly has complete remission without any evidence of synovitis.

The American College of Rheumatology criteria require absence of joint tenderness, fatigue, joint pain, joint swelling, and morning stiffness, along with a normal ESR for the patient to be called under remission.

Although the initial radiographic score is, as expected, a powerful predictor of subsequent radiographic damage, a high titer of RF and anticitrullinated protein antibodies continue to be powerful predictors of deteriorating radiographic damage in subjects receiving conventional therapy.[51]

It has been shown in several studies that the Health Assessment Questionnaire is an excellent predictor of work disability and mortality [52] and can be discrepant from damage measured by radiographs.

Mortality:

- In well-established RA, the median life expectancy is less than in control populations. [53] [54]
- Infection, renal disease, and respiratory failure traditionally have been the primary factors contributing to excess mortality in RA patients, **although it has been belatedly recognized that congestive heart failure, ischemic heart disease, and peripheral atherosclerosis deserve the appellation as the prime killers of rheumatoid arthritis patients.**
- **This increased incidence of cardiovascular events in RA patients is independent of traditional risk factors, such as age, sex, smoking status, diabetes mellitus, hypercholesterolemia, systolic blood pressure, and body mass index.[55]**
- The generally accepted explanation is that inflammatory cytokines that are produced in excess in RA (e.g., TNF-α, platelet-derived growth factor) have the capacity to activate endothelial and subendothelial myofibroblasts, and numerous inflammatory cells are found in atheromatous plaques.

- **Ultrasonography has shown that RA patients have greater thickness of the common carotid and femoral arteries than do healthy controls, a finding that was independent of glucocorticoid therapy, but related to the duration and severity of RA.[56]**

- The following factors and pathobiologic mechanisms could contribute to atherosclerosis in RA:

    - ✓ Immune complex–mediated endothelial damage.
    - ✓ Acute-phase reactants (C-reactive protein and serum amyloid A, both of which have pro-inflammatory activity).
    - ✓ Inflammatory cytokines.
    - ✓ High expression of endothelial cell leukocyte adhesion molecules.
    - ✓ Medications (e.g., steroids).
    - ✓ Prothrombotic factors (e.g., increased platelets, fibrinogen, and thromboxane).
    - ✓ Endothelial cell dysfunction induced by inflammation.

- **Considerations of therapy in rheumatoid patients must factor in the effects on atherogenesis.** These considerations might include, in patients with an unfavorable vascular profile,

    - ✓ Supplementation with omega-3 fatty acids in the diet.
    - ✓ Early use of HMG-CoA Reductase inhibitors (statins that, in addition to lipid-lowering effects, reduce C-reactive protein).
    - ✓ Attempts to reduce elevated levels of homocysteine induced by methotrexate.
    - ✓ Avoidance of cyclosporine.
    - ✓ Aggressive weight-loss disciplines and
    - ✓ Smoking cessation.

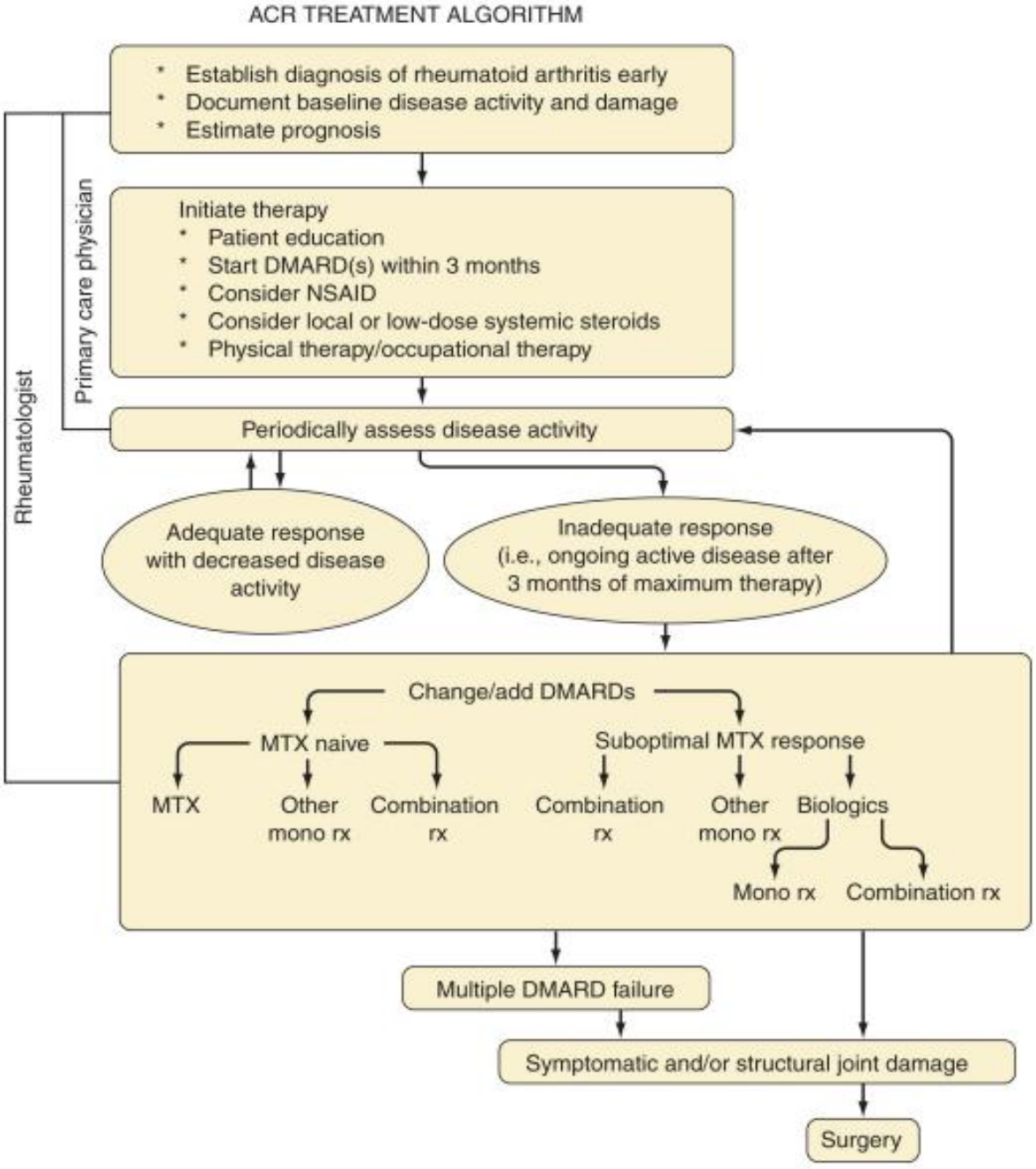
- In addition to cardiovascular causes of death associated with RA are causes of death due to the complications (articular and extra-articular) of RA and to side effects of therapy.

    - ➢ Potentially morbid articular complications include the various forms of atlantoaxial subluxation, cricoarytenoid synovitis, and sepsis of involved joints.

- Extra-articular complications directly causing a higher mortality include Felty's syndrome, Sjögren's syndrome, pulmonary complications, and diffuse vasculitis.

Factors that correlate with a poorer prognosis and greater likelihood of joint destruction in RA:

- Positive RF in serum.[57]
- Positive anticitrullinated protein in serum.
- Rheumatoid nodules.[58]
- Elevated Health Assessment Questionnaire level of disability.[59]
- Depression.[60]
- Persistent ESR elevation (serving as a surrogate for disease control).
- Presence of the shared epitope (QKRAA) on class II major histocompatibility genes.


ACR TREATMENT ALGORITHM
* Establish diagnosis of rheumatoid arthritis early
* Document baseline disease activity and damage
* Estimate prognosis
Initiate therapy
* Patient education
* Start DMARD(s) within 3 months
* Consider NSAID
* Consider local or low-dose systemic steroids
* Physical therapy/occupational therapy
Primary care physician
Rheumatologist
Periodically assess disease activity
Adequate response with decreased disease activity
Inadequate response (i.e., ongoing active disease after 3 months of maximum therapy)
Change/add DMARDs
MTX naive
Suboptimal MTX response
MTX
Other mono rx
Combination rx
Combination rx
Other mono rx
Biologics
Mono rx
Combination rx
Multiple DMARD failure
Symptomatic and/or structural joint damage
Surgery

TREATMENT:

The American College of Rheumatology (ACR) treatment guidelines call for a comprehensive approach to the patient with involvement of the primary care provider and the rheumatologist, and provide a general guideline for starting, changing, or adding DMARDs to the treatment of a patient with active disease

A) Disease modification therapy:

- DMARD therapy generally begins with the initiation of therapy with the traditional small molecules, such as
  - ✓ **methotrexate (MTX),**
  - ✓ **hydroxychloroquine (HCQ), or**
  - ✓ **sulfasalazine (SSZ)**
- Although other small molecule treatments exist (e.g., **azathioprine**, **gold salts**, **penicillamine**, **cyclosporine**), these agents are used infrequently and usually reserved for patients refractory to other therapy or with idiosyncratic side effects with the other agents.

- Newer generation DMARDs:

  - ✓ **Leflunomide**
  - ✓ TNF-α inhibitors **adalimumab**, **etanercept**, and **infliximab**
  - ✓ Interleukin (IL)-1 receptor antagonist **Anakinra**.
  - ✓ Selective costimulation modulator **Abatacept**.
  - ✓ The B cell–targeted approach using **Rituximab (RTX).**
  - ✓ The IL-6 receptor antibody **Tocilizumab**

These agents have been well studied in clinical trials showing efficacy alone or in combination with traditional therapies.

B) <u>Adjunctive drug therapy:</u>

- **Glucocorticoid therapy**

  - ✓ Long term low dose (5-10mg/day of prednisolone or its equivalent) therapy as adjunct to DMARDs.
  - ✓ In low to moderate doses before the effect of DMARD therapy starts, which often take few weeks to months.

- ✓ 1 to 2 weeks of high dose glucocorticoids to treat the acute disease flares.
- ✓ Intraarticular injection of intermediate acting glucocorticoids (like triamcinolone acetonide) to treat few actively inflamed joints.

- **Non-steroidal anti-inflammatory drugs (NSAIDs)**

  NSAIDs are the most often used and are a very effective adjunctive therapy in RA, providing analgesic and anti-inflammatory benefits. The anti-inflammatory effect is due to nonselective inhibition of COX-1 and COX-2.

  Long term use should be minimized to prevent adverse effects like gastritis, peptic ulcer disease and renal failure.

- **Analgesics**
  - ✓ Acetaminophen.
  - ✓ Codeine or other narcotic derivatives.

METHODS OF ASSESSING DISEASE ACTIVITY OF RHEUMATOID ARTHRITIS AND RESPONSE TO THERAPY:

Many quantitative approaches exist for this purpose.

1) ACR response criteria.
2) DAS/DAS28.
3) HAQ (Health Assessment questionnaire).
4) Simplified Disease Activity Index (SDAI).
5) Clinical Disease Activity Index (CDAI).

DAS28 (DISEASE ACTIVITY SCORE 28):

This scoring system integrates the measures of physical examination, acute phase response, and general health status as assessed by patient on visual analogue scale.

DAS28 is calculated by using the formula

DAS 28 = 0.56√TJC + 0.28√SJC + 0.70 (log ESR) + 0.014 GH

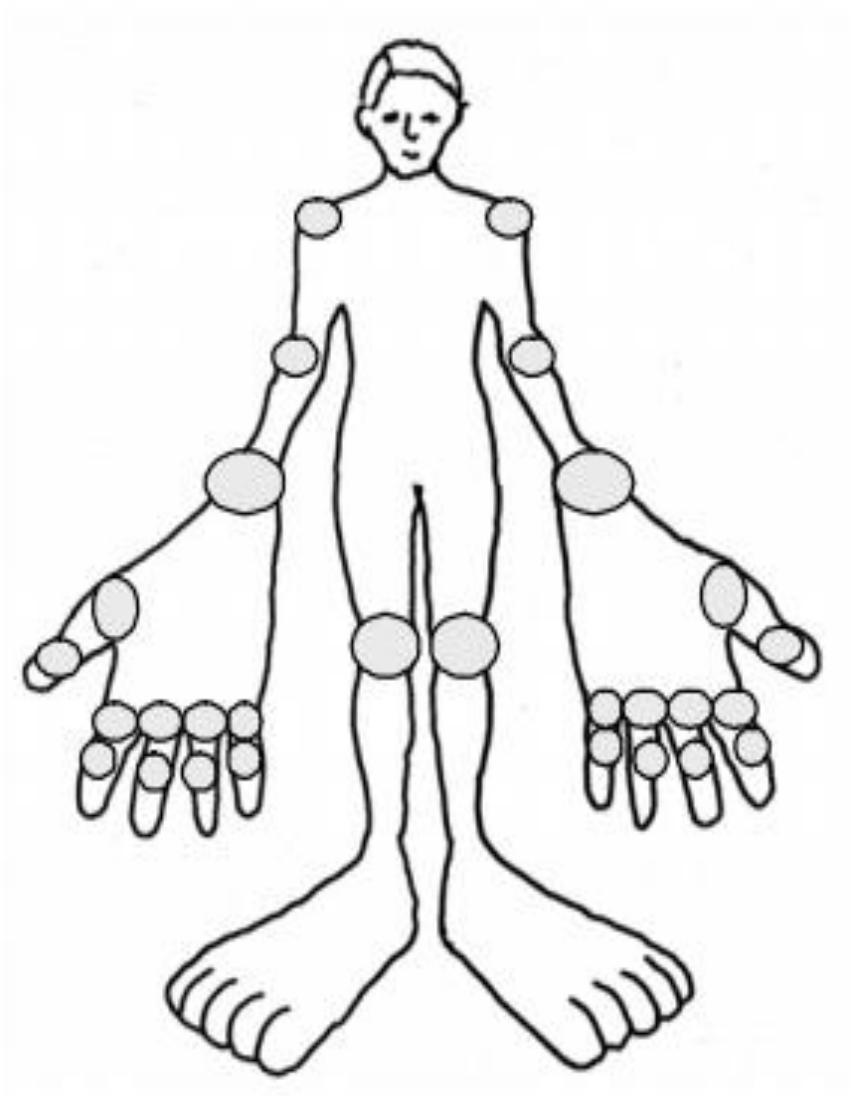
Where,

- TJC is tender joint count
- SJC is swollen joint count
- GH is general health status as assessed by patient on visual analogue scale (VAS).

General health status is assessed by patient on Visual Analogue Scale (VAS) marked from 0 to 100, where '0' indicating very good health status and '100' corresponding to very poor health status. As the number increases from '0' towards '100', it indicates decreasing health status.

Joints assessed in DAS28:

- Total 28 joints will be assessed for tenderness and swelling.
- Proximal interphalangeal joints of hands (5+5), distal interphalangeal joints of hands (5+5), wrist joint (1+1), Elbow joint (1+1), shoulder joint (1+1) and knee joint (1+1).



This scoring system provides absolute indication of RA disease activity on a scale of 0.49 to 9.07.

DAS28	**DISEASE ACTIVITY**
>5.1	High
3.2-5.1	Moderate
2.6-3.1	Low
<2.6	Remission

Disease response to therapy can be assessed by using DAS28 in RA patients by applying EULAR Response Criteria as follows,

DAS28 at endpoint	**Improvement in DAS28 from baseline**		
	>1.2	**>0.6 and <1.2**	**<0.6**
<3.2	Good	Moderate	none
3.2-5.1	Moderate	Moderate	None
>5.1	Moderate	Moderate	None

AIMS AND OBJECTIVES OF THE STUDY

A) To determine whether carotid artery intima media thickness (CIMT) is advanced in patients with Rheumatoid arthritis (RA), as compared to healthy controls.

B) To study the correlation if any between Carotid Intima Media Thickness (CIMT) and duration of Rheumatoid arthritis.

C) To study the correlation if any between Carotid Intima Media Thickness (CIMT) and activity of Rheumatoid arthritis.

MATERIALS AND METHODS

SETTING:

Rheumatology outpatient clinic, Government Rajaji Hospital (GRH), Madurai, Tamilnadu.

DESIGN OF THE STUDY:

Matched cross sectional study.

PERIOD OF STUDY:

April2012 – October 2012.

DETAILS OF STUDY MATERIALS AND METHODS:

The study was performed in 40 Rheumatoid arthritis (RA) patients and 40 healthy control subjects.

The RA patients were selected from consecutive patients attending Rheumatology outpatient clinic at Govt. Rajaji Hospital (GRH), Madurai, who were diagnosed according to 2010 American College of Rheumatology-European League against Rheumatism (ACR-EULAR) criteria.

40 healthy controls were selected from among the people who were attending local health-check program at GRH Madurai.

Written informed consent was taken from all cases and controls.

The following **exclusion criteria** were used to avoid confounding by other known risk factors for atherosclerosis:

a) Hypertension (BP > 140/90 mmHg) or use of antihypertensive medications.

b) Hypercholesterolemia (Total cholesterol>240mg/dl, LDL >160 mg/dl, triglycerides >200 mg/dl) or use of lipid lowering medication.

c) Diabetes Mellitus (diagnosed according to WHO criteria) or use of anti-diabetic medication.

d) History of coronary artery disease.

e) History of cerebrovascular accidents (CVA).

All the subjects included in our study (both cases and controls) were not known cases of IHD (ischemic heart disease), Diabetes Mellitus, or Hypertension and did not suffer any cerebrovascular events in the past. And also did not have any evidence of hepatic or renal impairment.

The RA patients included in the study as subjects were divided in to three groups based on the duration of disease. These were:

- Group-1: Those subjects who had RA for less than 2 years.
- Group-2: Those subjects who had RA between two to five years.
- Group-3: those subjects who had Ra for more than 5 years.

Another 40 healthy (age and sex matched) subjects were taken into group-4 as controls.

All the RA patients included in the study were evaluated for their disease activity using the disease activity score "DAS28". This score is calculated by using the formula

$$DAS\ 28 = 0.56\sqrt{TJC} + 0.28\sqrt{SJC} + 0.70\ (\log ESR) + 0.014\ GH$$

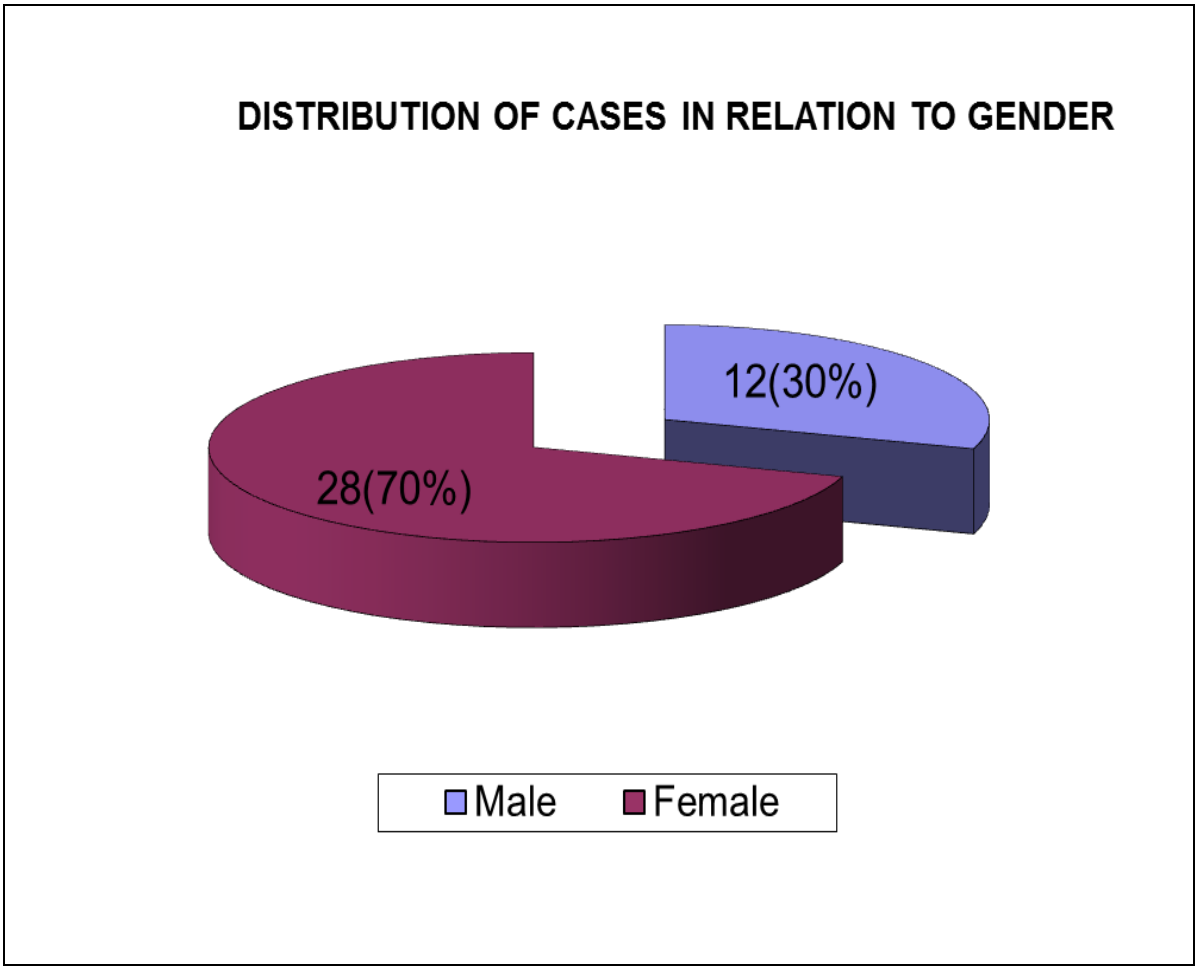
Where,

- TJC: Tender joint count.
- SJC: Swollen joint count.
- GH: General health status as assessed by patient on visual analogue scale (VAS).

All the subjects including the controls were evaluated for carotid intima media thickness by using carotid ultrasonography. Carotid ultrasonography was carried out by skilled radiologist by using gray scale ultrasonography and then followed by colour flow imaging.

Carotid intima media thickness (CIMT) was measured in common carotid artery bilaterally by examining throughout common carotid artery up to 2cm proximal to bifurcation. CIMT measurement was taken at the site of greatest thickness, and three readings were taken from each side at different points within the region of interest. All measurements were taken in diastole, measured in phase when the lumen diameter is at its smallest and IMT at its largest. The mean value of 6 readings (3 from each side) was taken as the final CIMT for evaluation.

The results obtained were subjected to one way ANOVA test for statistical analysis.


DISTRIBUTION OF CASES IN RELATION TO GENDER
12(30%)
28(70%)
Male
Female

OBSERVATIONS AND RESULTS

A. Characteristics of the cases and controls included in the study:

Table – 1

Distribution of cases in relation to gender

Sex	No. of cases	Percentage
Male	12	30
Female	28	70
Total	40	100

Total of 40 cases were enrolled for the study. Among them 12 cases (30%) were males and 28 cases (70%) were females. So, females form the major number in our study.

Control subjects were also in similar distribution as that of cases in relation to total number and gender distribution.

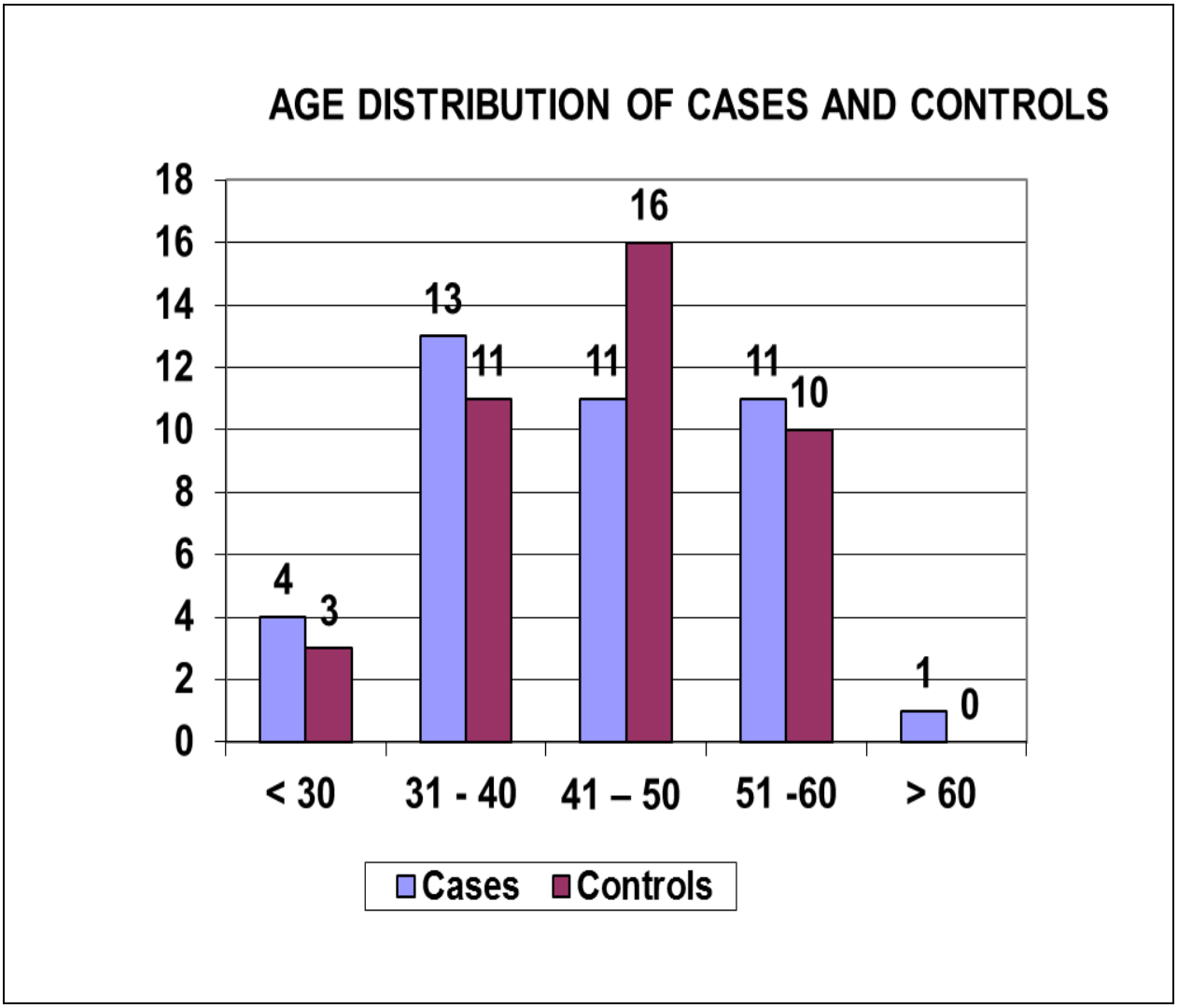

AGE DISTRIBUTION OF CASES AND CONTROLS
18
16
14
12
10
8
6
4
2
0
4
3
13
11
11
16
11
10
1
0
< 30
31 - 40
41 – 50
51 -60
> 60
Cases
Controls

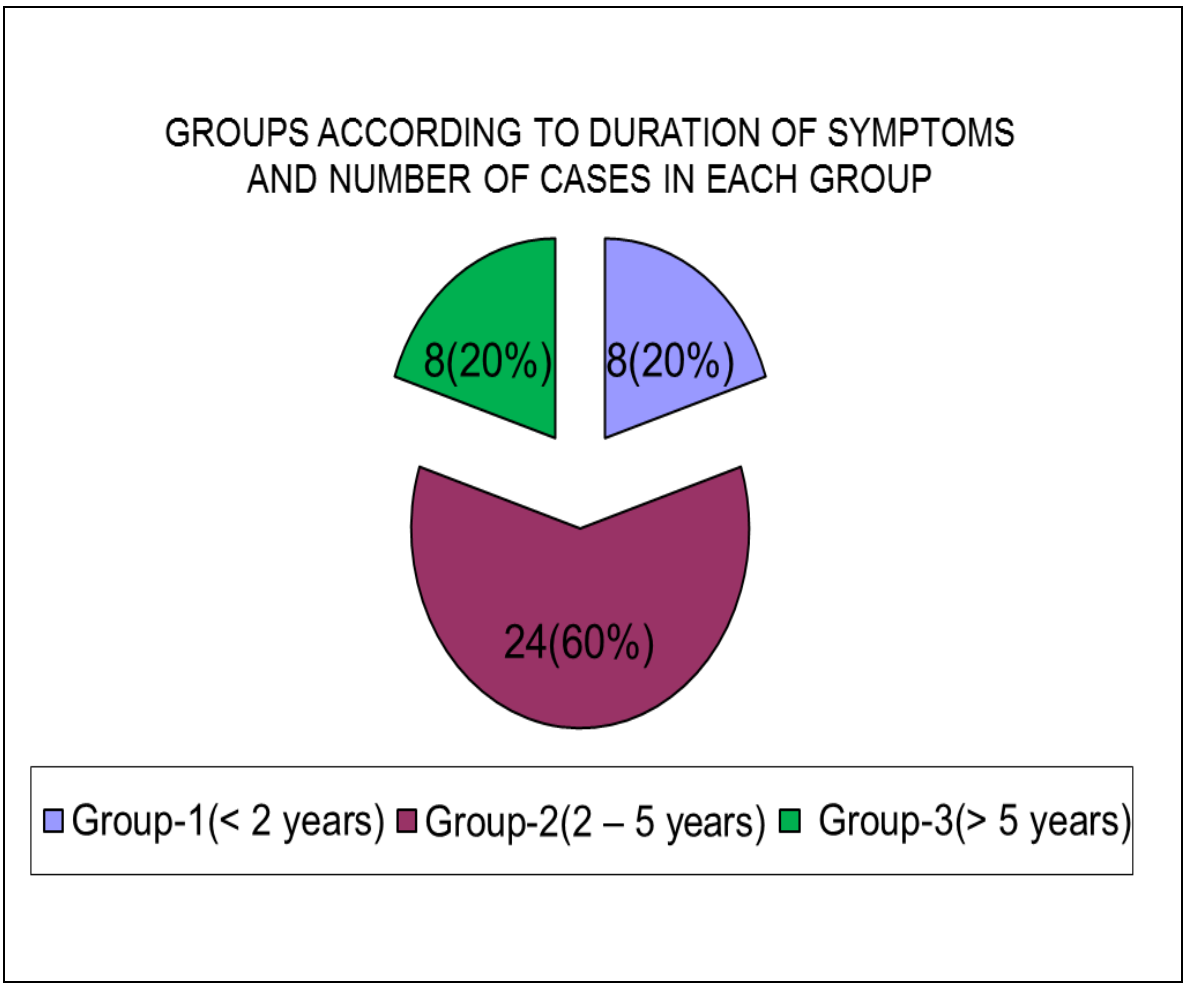
Table – 2

Distribution of cases and controls in relation to age

Age in years	No. of Cases	No. of Controls
< 30	4	3
31 - 40	13	11
41 – 50	11	16
51 -60	11	10
> 60	1	0
Total	40	40
Mean age **S.D**	43.9yrs 10.52	44.37yrs 9.41

Among the 40 cases, majority of are between 3rd and 5th decade and the controls share the same character. Mean age for cases is 43.9 years and mean age for controls is 44.375years.

GROUPS ACCORDING TO DURATION OF SYMPTOMS
AND NUMBER OF CASES IN EACH GROUP



B. The study comprised of three groups among the cases based on the duration of the disease and the healthy control subjects were taken as group-4. The following were the observations:

Table – 3

Three groups according to Duration of disease

Duration of symptoms	No. of cases	Percentage
GROUP-1 (< 2 years)	8	20
GROUP-2 (2 – 5 years)	24	60
GROUP-3 (> 5 years)	8	20
Total	40	100

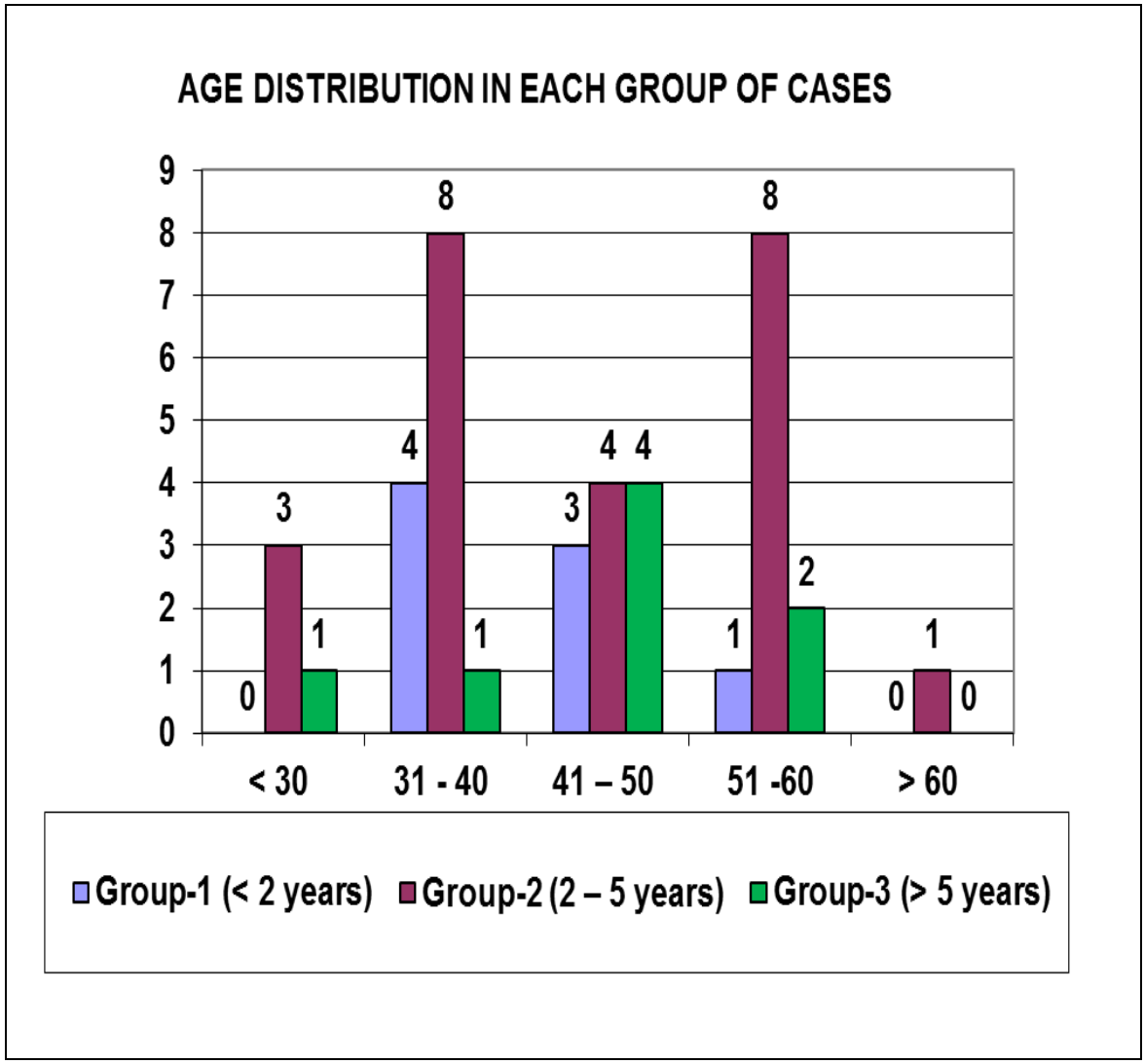

AGE DISTRIBUTION IN EACH GROUP OF CASES
9
8
7
6
5
4
3
2
1
0
0
3
1
4
8
1
3
4
4
1
8
2
0
1
0
< 30
31 - 40
41 – 50
51 -60
> 60
Group-1 (< 2 years)
Group-2 (2 – 5 years)
Group-3 (> 5 years)

Table – 4

Age Distribution in each Group of cases

Age in years	Group-1	Group-2	Group-3
< 30	0	3	1
31 - 40	4	8	1
41 – 50	3	4	4
51 -60	1	8	2
> 60	0	1	0
Total	8	24	8

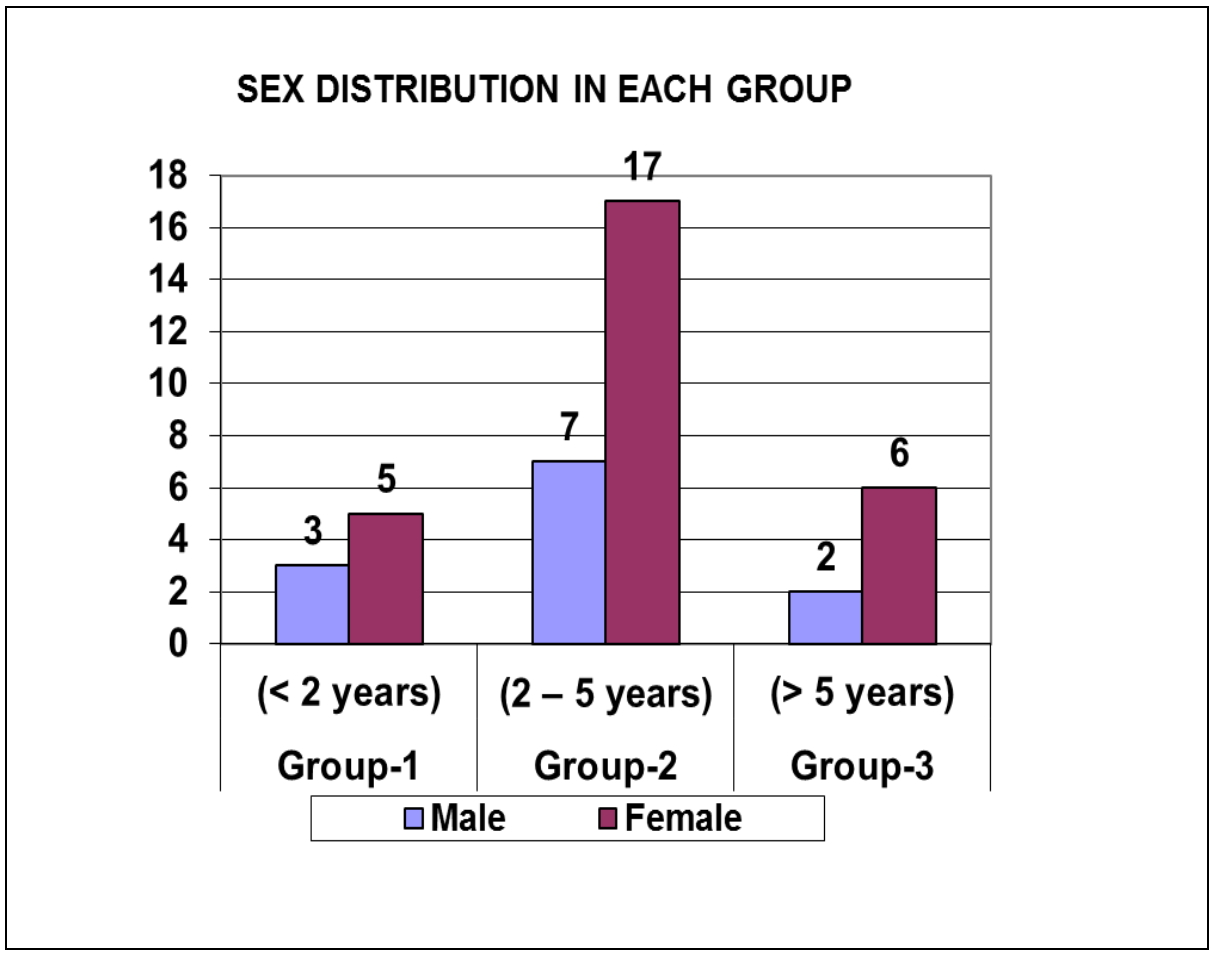

SEX DISTRIBUTION IN EACH GROUP
18
16
14
12
10
8
6
4
2
0
3
5
7
17
2
6
(< 2 years)
Group-1
(2 – 5 years)
Group-2
(> 5 years)
Group-3
Male
Female

Table – 5

Sex distribution in each group

Sex	Group-1	Group-2	Group-3
Male	3	7	2
Female	5	17	6
Total	8	24	8

Out of 40 RA cases, 8 cases (20%) were present in group-1, 24 cases (60%) were present in group-2, and 8 cases (20%) were present in group-3 (Table-3). And the majority of patients were females in all the three groups.

Table -6

Mean age distribution in each group

GROUPS	Age in years	
	Range	mean
GROUP-1	33-52	42.5±7.05
GROUP-2	27-65	46.39±11.73
GROUP-3	19-55	43.5±11.08
GROUP-4 (controls)	20-60	44±9.41

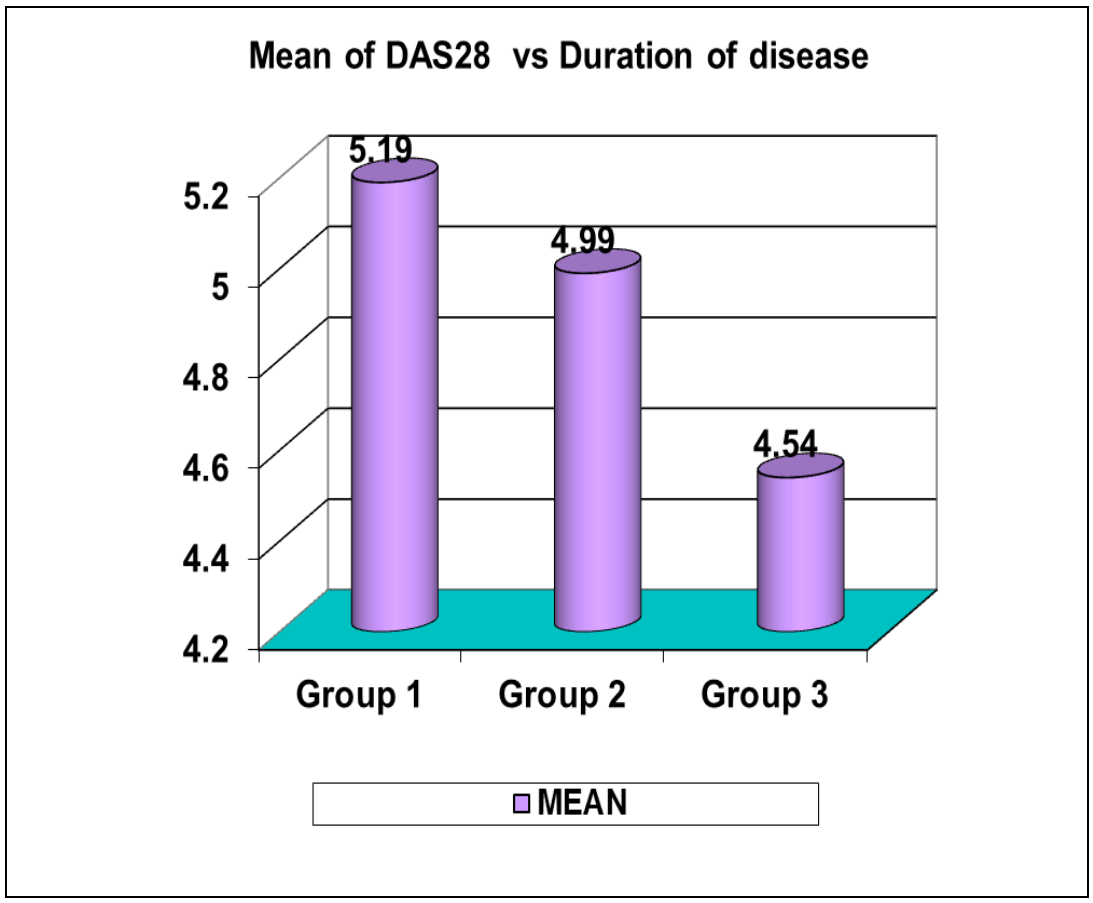
The mean age of all the three groups among cases was comparable. Also the mean age of cases and controls were comparable.

C. The groups were compared for various biochemical parameters.

Table – 7: Biochemical parameters in each group

BIOCHEMICAL PARAMETERS	Group I < 2 years		Group 2 2 – 5 years		Group 3 > 5 years		Control	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Blood sugar	84.0	14.57	101.9	19.99	87.1	23.18	89.2	22.17
Blood Urea	25.0	7.65	25.96	7.01	29.25	8.56	27.77	9.07
Creatinine	0.875	0.116	0.846	0.118	0.887	0.181	0.893	0.135
Cholesterol	159.3	21.82	167.8	22.76	169.0	20.2	168.5	16.99
TGL	145.8	11.81	150..2	15.25	156.1	21.3	153.4	11.9
LDL	88.1	13.54	92.46	15.38	82.62	13.8	92.6	13.2
VLDL	33.4	3.62	36.00	5.23	37.3	3.28	35.0	3.59
HDL	39.3	2.82	39.7	3.00	39.4	2.13	39.3	2.59

All the groups were comparable – including the mean values of sugar and lipid profile (atherogenic biochemical risk indices).


Mean of DAS28 vs Duration of disease
5.19
4.99
4.54
5.2
5
4.8
4.6
4.4
4.2
Group 1
Group 2
Group 3
MEAN

D. Disease duration and activity of disease are compared in RA patients

TABLE – 8

DAS28 vs Duration of disease.

Groups according to Duration of disease	**DAS28**	
	Mean	**SD**
Group-1 (< 2 years)	5.19	0.78
Group-2 (2 – 5 years)	4.99	1.28
Group-3 (> 5 years)	4.54	0.87

The disease activity as per DAS28 was comparable in all three groups with a p value of >0.05

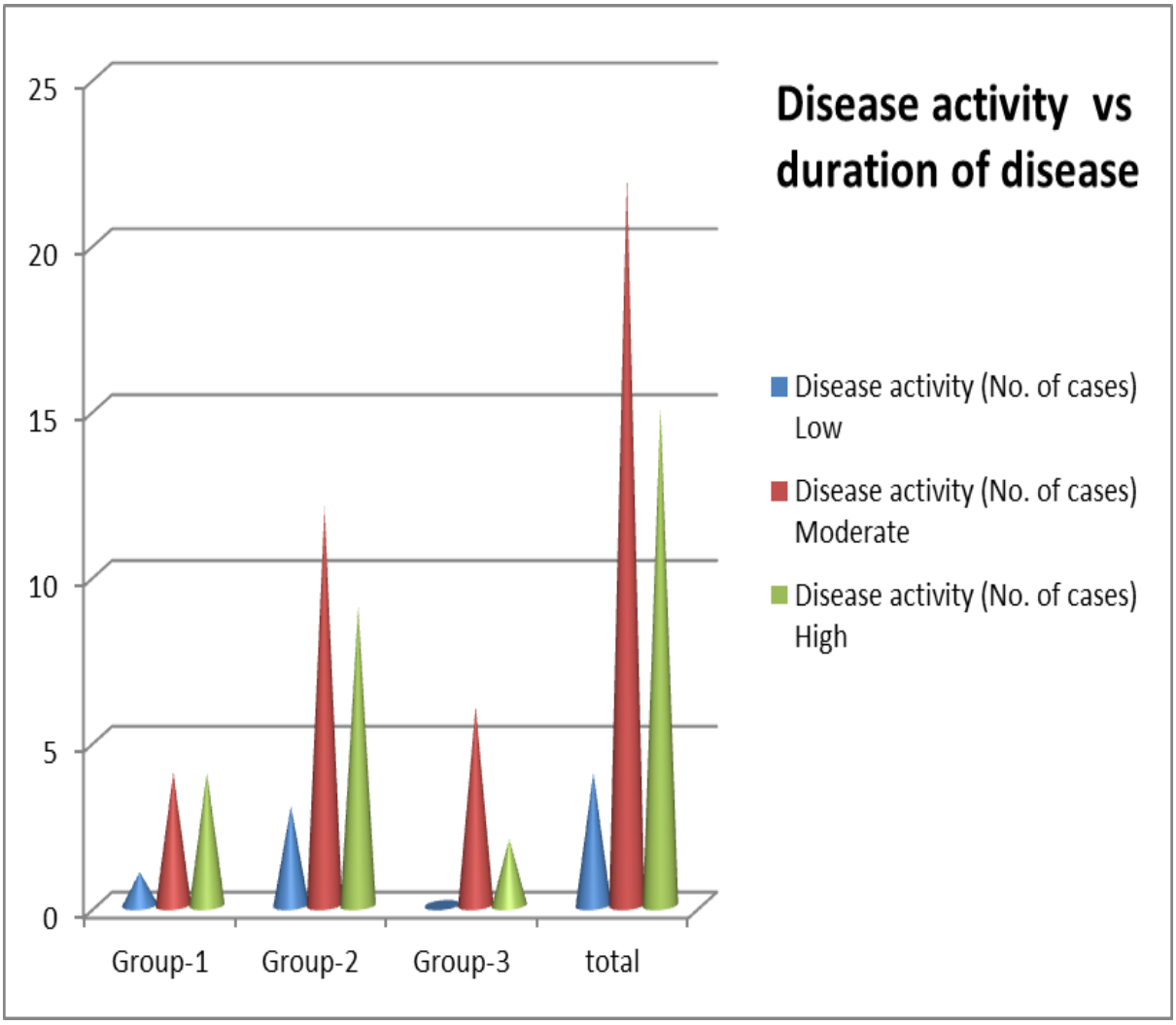
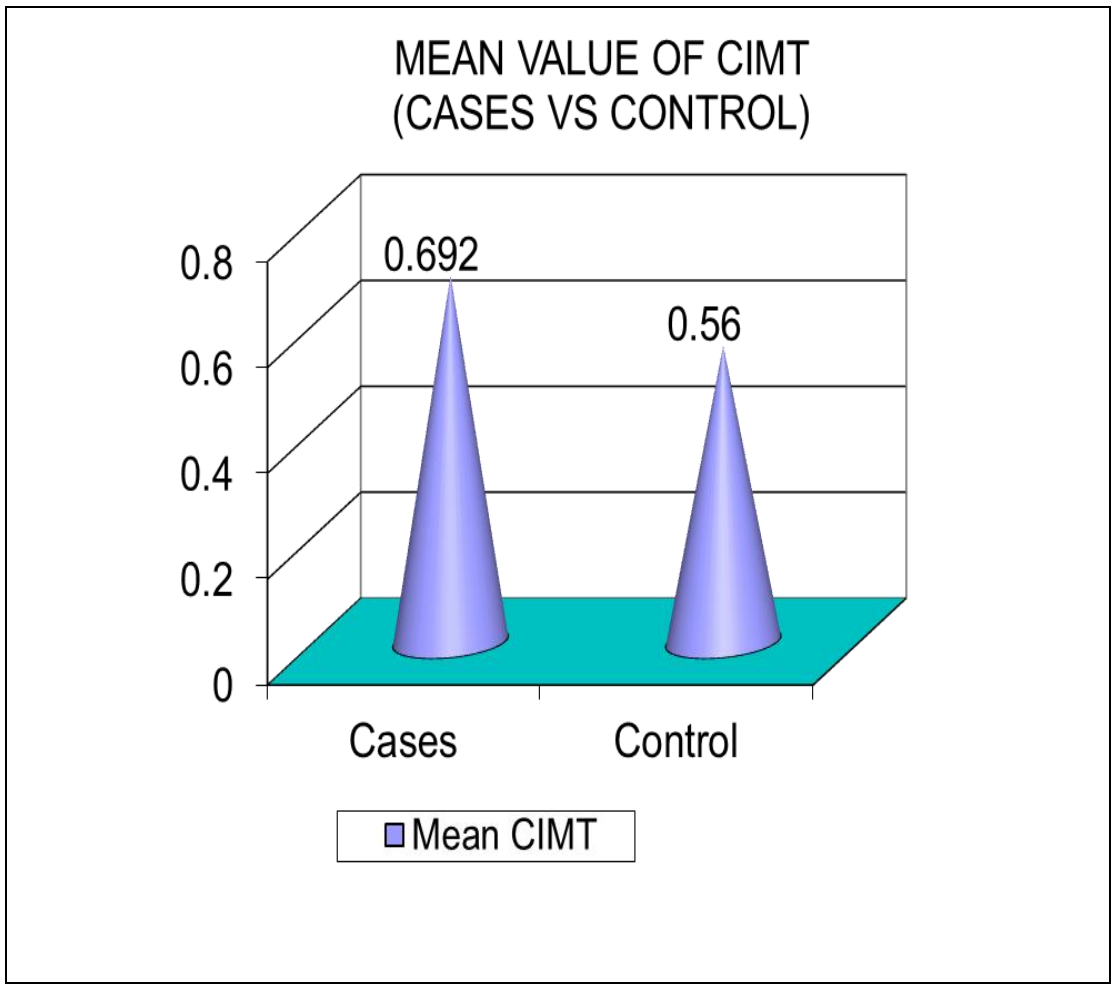

Disease activity vs duration of disease
25
20
15
10
5
0
Group-1
Group-2
Group-3
total
Disease activity (No. of cases) Low
Disease activity (No. of cases) Moderate
Disease activity (No. of cases) High

Table -9

Disease activity and duration of disease compared

Duration of disease	Disease activity (No. of cases)		
	Low	**Moderate**	**High**
Group-1 (<2years)	1	4	4
Group-2 (2-5years)	3	12	9
Group-3 (>5years)	0	6	2
Total	4	22	15

Overall, majority of cases in our study were in moderate disease activity. In group-1, patients with moderate and high disease activity were equal in number. In both group-2 and group-3, majority were in moderate disease activity.


MEAN VALUE OF CIMT
(CASES VS CONTROL)
0.8
0.6
0.4
0.2
0
0.692
0.56
Cases
Control
Mean CIMT

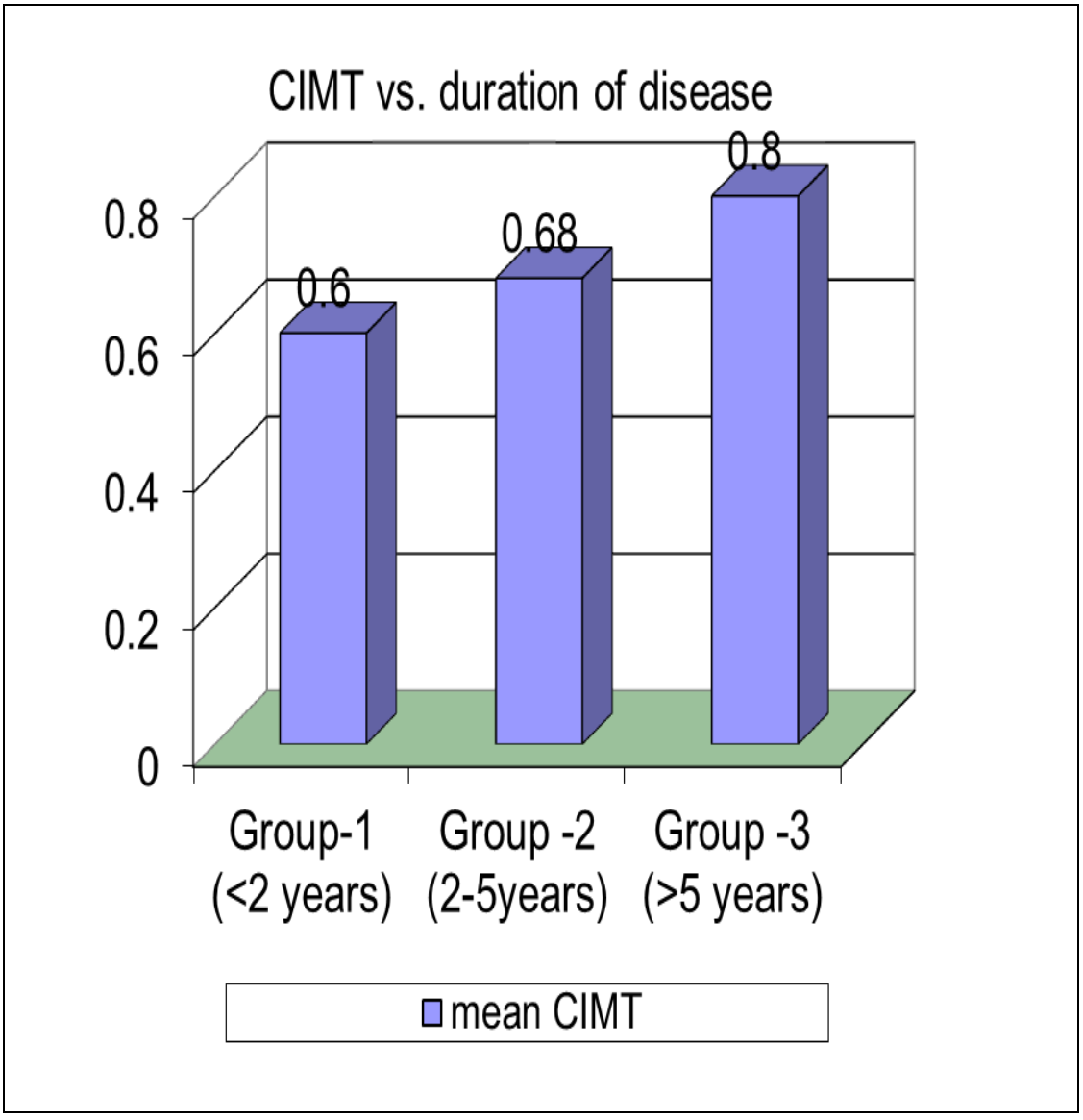
E. Carotid intima media thickness (CIMT): case vs. control

TABLE – 10

CIMT-case vs. control

STUDY GROUPS	**CIMT(mm)**	
	Mean	**SD**
Cases	0.692	0.136
Controls	o.56	0.046
p value	< 0.001 (**Statistically significant**)	

Mean value of CIMT was significantly higher in cases compared to control group with a significant p-value of <0.001.

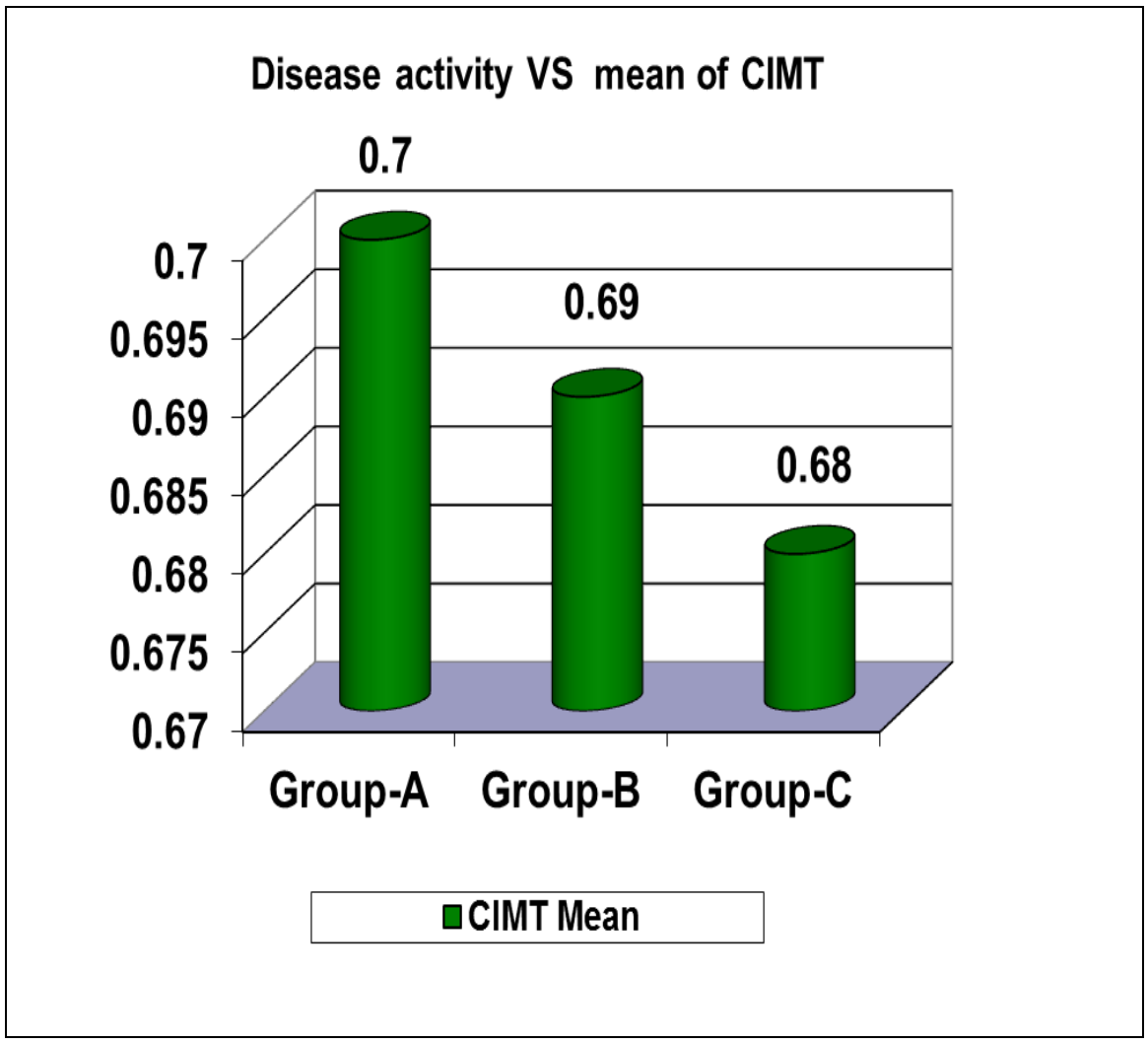

CIMT vs. duration of disease
0.8
0.6
0.4
0.2
0
0.6
0.68
0.8
Group-1 (<2 years)
Group -2 (2-5years)
Group -3 (>5 years)
mean CIMT

F. Carotid intima media thickness (CIMT) compared with duration of disease

Table-11: CIMT vs. Duration of disease

Duration of disease	**CIMT(mm)**	
	Mean	**SD**
Group-1 (< 2 years)	0.60	0.10
Group-2 (2 – 5 years)	0.68	0.12
Group-3 (> 5 years)	0.80	0.14
p value	0.012 **(Statistically significant)**	

The CIMT mean value was 0.60±0.10 mm for group-1, 0.68±0.12 mm for group-2 and 0.80±0.14mm for group-3. The increase in CIMT with duration of disease was significant (with a p value of 0.012, which is statistically significant).


Disease activity VS mean of CIMT
0.7
0.69
0.68
0.7
0.695
0.69
0.685
0.68
0.675
0.67
Group-A
Group-B
Group-C
CIMT Mean

G. **CIMT compared with Activity of the disease**.

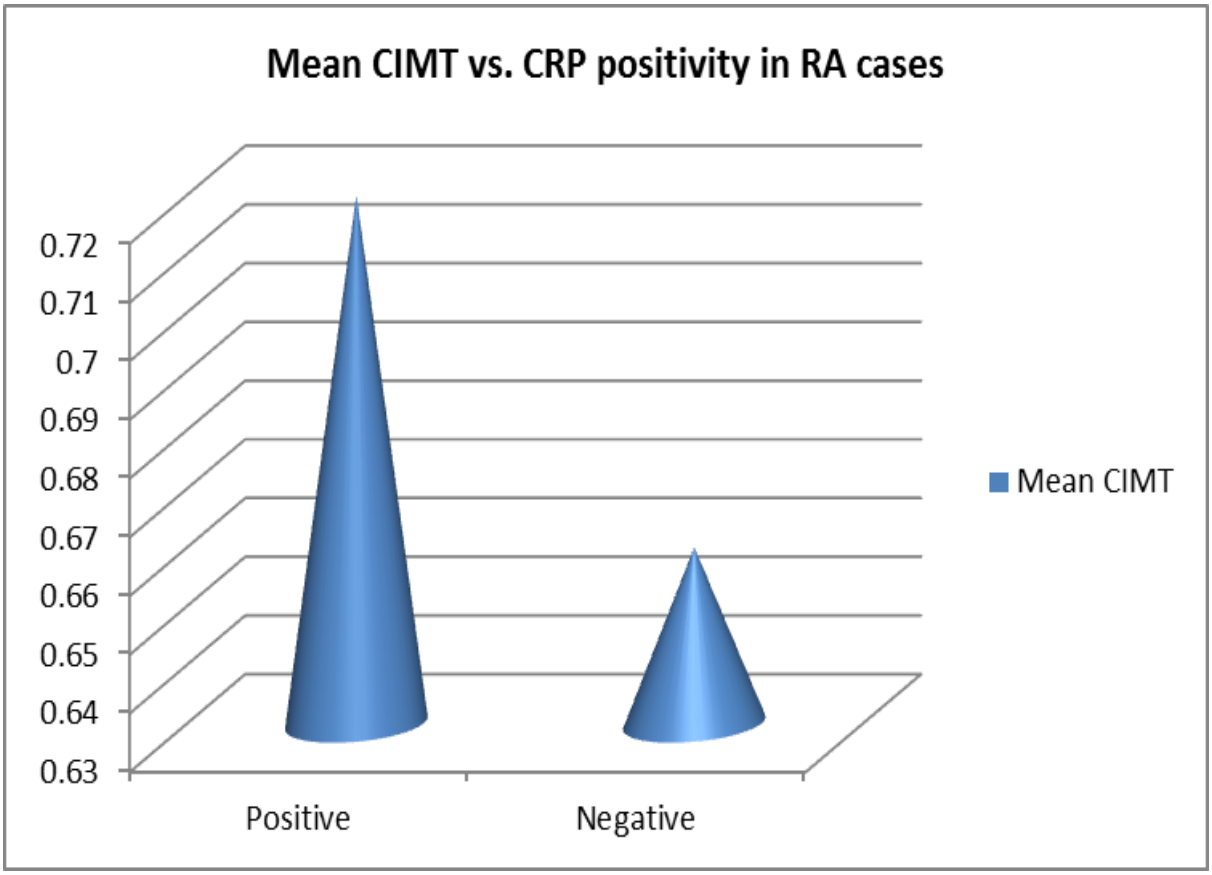
Table – 12: Activity of RA vs. CIMT

Disease activity	**CIMT(mm)**	
	Mean	**SD**
Group-A(Low)	0.70	0.08
Group-B(Moderate)	0.69	0.12
Group-C(High)	0.68	0.15
P value	0.978 **(statistically not significant)**	

Based on DAS28 score, the cases were again grouped as 3 groups.

- Group-A: with low disease activity with DAS28 of 2.6-3.1
- Group-B: with moderate disease activity with DAS28 of 3.2-5.1.
- Group-C: with high disease activity with DAS28 of >5.1.

In these groups, the relationship between CIMT and disease activity was studied (table-12). The comparison between various sub-groups A, B and C, in relation to CIMT was found to be statistically not-significant with p value >0.05.


Mean CIMT vs. CRP positivity in RA cases
0.72
0.71
0.7
0.69
0.68
0.67
0.66
0.65
0.64
0.63
Positive
Negative
Mean CIMT

H. **Correlation of CIMT with CRP positivity in RA patients**.

Table-13: CRP in cases

CRP	Number of cases	Percentage
positive	17	42.5%
negative	23	57.5%
total	40	100%

Table-14: Mean CIMT vs. CRP positivity status.

CRP	CIMT	
	Mean	**SD**
Positive	0.72	0.14
Negative	0.66	0.12
P value	0.176 (statistically not significant)	

Another observation made in our study is out of 40 cases of RA, 17 cases (42.5%) were reported to be CRP-positive. On comparing the mean of CIMT of CRP-positive cases with CRP-negative cases, CRP positive cases had a relatively high mean CIMT value than CRP-negative patients but with p value of 0.176 which is statistically not significant.

DISCUSSION

Atherosclerosis is a disease of the arterial system of our body, in which the blood vessel wall will become thickened and hardened by "plaques". The composition of atherosclerotic plaque is cholesterol and other lipids, inflammatory cells, and calcium deposits.

Atherosclerosis is an inflammatory disease. There are striking similarities between the inflammatory and immunological mechanisms operating in atherosclerotic plaque and in rheumatoid synovitis. The common pathophysiological features in the affected tissues include an abundance of activated macrophages which release or induce release of inflammatory mediators, including cytokines (e.g., IL-1 and TNF), adhesion molecules with matrix metalloproteinases, growth factors and T-cell infiltrates.

Both atherosclerosis and Rheumatoid arthritis are associated with elevated levels of acute phase reactants – C-reactive protein (CRP), serum amyloid A, ESR, fibrinogen, and secondary phospholipase 2[25].

It has been reported in many studies that the accelerated atherosclerosis associated with Rheumatoid arthritis to be independent of traditional risk factors of atherosclerosis.

In the present study, hypertension, diabetes mellitus and hyperlipidemia were exclusion criteria. The atherogenic biochemical parameters (like blood sugar, cholesterol, triglycerides, LDL, and VLDL) that were estimated in our study subjects were within normal range (Table-7). So, our study was free of these traditional risk factors for accelerated atherosclerosis.

CIMT is a reliable marker for coronary atherosclerosis and peripheral vascular disease[30]. The following table shows normal carotid artery intima media thickness (CIMT) based on multiple studies, according to age and gender.

AGE (years)	Right CIMT (mm)		Left CIMT (mm)	
	Men	women	Men	Women
<30	0.39-0.48	0.39-0.43	0.42-0.49	0.30-0.47
31-40	0.42-0.50	0.42-0.49	0.44-0.57	0.44-0.51
41-50	0.46-0.57	0.44-0.53	0.50-0.61	0.46-0.57
>50	0.46-0.62	0.50-0.59	0.53-0.70	0.52-0.64

According to Homa *et al*, the intima media thickness of common carotid artery (measured at areas devoid of plaque) increases linearly with age from 0.48 mm at 40 years of age to 1.02 mm at 100 years of age **(following a formula 0.009** x **age + 0.116 mm)**[24].

The mean age of the present study (including control group) was 44.13years. So, expected CIMT is approximately 0.513 mm. In the present study, Carotid intima media thickness (CIMT) in the control group was 0.56 ± 0.046 mm (almost nearing the homa equation, i.e., 0.513 mm) whereas the Carotid intima media thickness in RA patients (cases) was higher, i.e., 0.692 ± 0.136 mm (Table-10) with p value < 0.001. A similar observation has also been shown by Gonzalez *et al*[31] and Alkabbi *et al*[32] in their respective studies. In a recent Indian study, Mahajan *et al* have similar observations[20]. All the studies (including the present study) show a significantly higher value of CIMT in RA subjects than the normal population.

The mean CIMT was significantly higher in group-3 (disease >5 years) when compared to group-1 and 2 with p value of 0.012 which is statistically significant (Table-11). This clearly suggests that CIMT increases with increase in duration of Rheumatoid arthritis. Gonzales *et al* in their study had found disease duration as

one of the best predictor for the development of severe morphologic expression of atherosclerotic disease[31]. DelRincon *et al*[33] and Mahajan *et al*[20] also had similar observations. This may be due to more years of exposure to increased inflammation[5,10,13-16], and other factors like increased arterial stiffness[33] and prothrombotic markers in RA patients[35]. Role of inflammation as a basic pathogenic mechanism in atherosclerosis is well known[33].

The mean values of CIMT for low, moderate and high disease activity sub-groups were 0.70 ± 0.08mm; 0.69 ± 0.12mm and 0.68 ± 0.15 mm respectively. These values when compared with each other were found to be statistically not-significant (p value > 0.05) (Table-12), suggesting no correlation between disease activity at a particular time and carotid intima media thickness. Similar observations were presented by Jonsson[27] and Roman *et al*[28].

On correlating the CIMT with CRP (an important marker of inflammation) in RA cases, the mean CIMT was comparatively higher in CRP positive cases than in CRP negative patients, but with a p value >0.05 which is statistically not significant.

So, rheumatoid arthritis which is a chronic inflammatory disease mainly involving joints has been found to have accelerated atherosclerosis when compared to age and sex-matched controls.

The study also shows a significant, i.e., directly proportional relation between carotid intima media thickness to longer duration of disease.

But this study did not show significant relationship between activity of disease and carotid intima media thickness.

However, in view of the relation to duration of disease, the physicians should regularly screen the established RA patients so as to identify the evidence of atherosclerosis and manage it earlier.

Prevention of cardiovascular disease in RA requires a combined approach incorporating cardiovascular risk factors screening and management, effective and sustained control of RA disease activity, a high index of suspicion and prompt investigation of suspected cardiac disease.

CONCLUSION

In this cross sectional study on Rheumatoid arthritis,

- Carotid intima media thickness in RA cases was found to be significantly increased when compared to age and sex matched healthy controls indicating that Rheumatoid arthritis is an independent risk factor for accelerated atherosclerosis
- Increase in carotid intima media thickness was found to be directly related to the duration of the disease.
- Our study did not show significant relationship between disease activity and carotid intima media thickness.

So, early diagnosis of evidence of unfavorable vascular profile in RA patients and instituting appropriate preventive therapies can decrease the cardiovascular mortality due to Rheumatoid arthritis.

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PROFORMA

Name: Age: Sex: O.P. No. :

I.P.No.

Address:

- **History:** Symptoms: Morning stiffness

  Joint pain

  Joint swelling

  Joints involved

  Duration of symptoms:

Past history of: DM

HTN

CAD

CVA

Personal history: Smoking

Alcohol intake

Treatment History:

- **Examination**

Pallor	Clubbing
Icterus	Lymphadenopathy
Cyanosis	Pedal edema

Vitals:

Pulse:	BP:
RR:	Temperature:

Rheumatological:

- Rheumatoid Nodules
- Joints involved
- Tender joints count
- Swollen joints count
- Deformity

Systemic Examination:

- CVS :
- RS :
- PA :
- CNS :

Investigations:

- Hematological

  Hb% : TC :

  DC : ESR :

- **Biochemical**

  Blood sugar :

  Urea :

  Creatinine :

  S.Uricacid :

Lipid profile: Total cholesterol

TGL

LDL

VLDL

HDL

- Chest X-ray:
- ECG :
- Echocardiogram:
- RF titre:
- CRP:
- Anti-CCPantibody:
- Carotid Intima Media thickness:

DAS28 score:

MASTER CHART

MASTER CHART-CASES

S.NO	AGE	SEX	Dur.of symptoms	DM	HT	CAD	CVA	SMOKING	ALCOHOL	EMS	TJC	SJC	Deformity	Bl.Sugar(mg/dl)	Bl.Urea(mg/dl)	S.Creatinine(mg/dl)	T.CHL(mg/dl)	TGL(mg/dl)	LDL(mg/dl)	VLDL(mg/dl)	HDL	ESR(mm/hr)	CRP	VAS	DAS28	DISEASE ACTIVITY	RF	CIMT(mm)
1	55	F	7 years	N	N	N	N	N	N	P	4	0	N	122	38	0.8	196	168	76	34	38	40	Positive	10	3.84	Moderate	Positive	8.5
2	33	M	2years	N	N	N	N	N	N	P	8	2	N	98	42	1	184	144	94	36	44	30	Negative	15	4.57	Moderate	Positive	7.5
3	50	M	4months	N	N	N	N	P	N	P	18	12	N	68	27	0.8	188	132	72	25	35	48	Positive	25	6.41	High	Positive	8
4	33	F	1year	N	N	N	N	N	N	P	2	0	N	104	16	0.8	176	146	98	33	38	90	Negative	10	4.08	Moderate	Positive	6
5	19	F	6years	N	N	N	N	N	N	P	7	4	N	60	16	0.7	172	138	82	38	40	28	Positive	20	4.65	Moderate	Positive	5.5
6	47	F	4years	N	N	N	N	N	N	P	10	0	N	69	23	0.8	180	138	68	42	36	38	Negative	15	4.53	Moderate	Positive	9
7	65	M	4years	N	N	N	N	N	N	P	26	8	N	85	17	0.7	190	155	112	40	34	75	Positive	30	7.09	High	Positive	9.5
8	28	F	2years	N	N	N	N	N	N	P	3	0	N	100	22	0.8	120	150	55	30	35	15	Negative	10	3.01	Low	Positive	6
9	44	M	1.5years	N	N	N	N	N	N	P	6	3	N	70	24	1	125	166	71	36	33	32	Negative	15	4.49	Moderate	Negative	5.5
10	40	M	7years	N	N	N	N	N	P	P	7	1	P	85	28	0.9	197	155	74	37	40	10	Negative	15	3.58	Moderate	Positive	6
11	28	F	4years	N	N	N	N	N	N	P	26	20	N	108	29	0.7	185	128	87	28	43	40	Positive	35	7.18	High	Positive	6
12	48	F	1year	N	N	N	N	N	N	P	14	6	N	74	42	1	152	140	102	34	35	38	Negative	15	5.54	High	Positive	5.5
13	37	M	1month	N	N	N	N	N	N	P	24	8	N	83	20	0.7	149	160	99	36	42	20	Positive	30	6.05	High	Positive	5
14	48	F	15years	N	N	N	N	N	N	P	14	2	N	92	38	1.1	162	180	110	43	37	30	Negative	20	5.15	High	Positive	9
15	57	F	4years	N	N	N	N	N	N	P	4	0	N	87	20	0.8	180	144	98	41	40	15	Negative	10	3.16	Low	Negative	7.5
16	27	F	4.5years	N	N	N	N	N	N	P	26	8	N	120	28	1	168	154	88	29	44	30	Positive	30	6.45	High	Positive	7
17	35	M	2years	N	N	N	N	N	N	P	14	1	N	74	23	0.8	171	143	92	38	41	65	Negative	15	5.51	High	Negative	4.5
18	51	F	3years	N	N	N	N	N	N	P	26	9	N	103	35	0.9	155	160	113	40	38	30	Positive	35	6.57	High	Negative	6
19	45	F	10years	N	N	N	N	N	N	P	22	6	P	67	26	0.9	140	188	62	40	36	38	Negative	30	6.28	High	Positive	8.5
20	35	F	2.5years	N	N	N	N	N	N	P	12	0	N	77	19	0.7	116	146	92	22	42	10	Negative	10	3.69	Moderate	Positive	6.5
21	53	F	7years	N	N	N	N	N	N	P	10	0	N	120	40	1.2	151	128	86	33	41	20	Negative	10	4.01	Moderate	Positive	8.5
22	55	F	5years	N	N	N	N	N	N	P	26	2	N	81	17	0.8	140	155	99	38	40	40	Positive	30	6.25	High	Positive	6
23	45	F	4years	N	N	N	N	N	N	P	16	0	N	124	19	0.7	162	144	78	40	37	30	Negative	15	4.83	Moderate	Negative	7
24	45	F	10years	N	N	N	N	N	N	P	4	2	N	79	23	0.8	174	138	83	35	41	35	Positive	10	4.14	Moderate	Positive	9
25	52	F	1year	N	N	N	N	N	N	P	6	2	N	75	24	0.9	182	145	102	34	38	50	Positive	15	4.78	Moderate	Positive	7.5
26	35	F	3years	N	N	N	N	N	N	P	2	0	N	138	30	0.7	200	175	79	35	45	20	Positive	10	3.03	Low	Positive	7.5
27	46	F	2years	N	N	N	N	N	N	P	12	0	N	124	20	0.8	160	122	80	33	41	30	Negative	15	4.53	Moderate	Positive	6.5
28	40	F	1year	N	N	N	N	N	N	P	10	2	N	100	25	1	140	134	78	36	38	40	Positive	20	5.03	Moderate	Positive	5.5
29	55	M	2years	N	N	N	N	P	N	P	10	0	N	78	23	0.9	188	144	94	42	40	36	Negative	15	4.49	Moderate	Positive	6
30	60	F	2.5years	N	N	N	N	N	N	P	22	6	N	81	27	0.9	192	183	130	37	41	48	Negative	35	6.51	High	Positive	6
31	58	F	4.5years	N	N	N	N	N	N	P	16	0	N	96	18	0.8	196	176	102	31	40	28	Negative	15	4.78	Moderate	Positive	8.5
32	60	F	3.5years	N	N	N	N	N	N	P	18	6	N	132	33	1	188	172	99	41	38	30	Positive	20	5.72	High	Negative	8
33	36	F	2years	N	N	N	N	N	N	P	10	2	N	120	25	0.9	144	150	78	34	43	36	Negative	15	4.89	Moderate	Positive	6.5
34	36	F	1.5years	N	N	N	N	N	N	P	12	4	N	98	22	0.8	162	144	83	33	39	32	Negative	20	5.21	High	Positive	5.5
35	40	M	3years	N	N	N	N	P	N	P	6	0	N	100	26	1	159	160	88	37	40	28	Negative	10	3.84	Moderate	Negative	6.5
36	43	M	4.5years	N	N	N	N	P	N	P	14	4	N	112	33	0.7	166	154	101	41	38	22	Positive	15	5.03	Moderate	Positive	7
37	36	F	2.5years	N	N	N	N	N	N	P	8	0	N	118	34	0.9	148	130	92	32	40	30	Negative	10	4.1	Moderate	Negative	6
38	43	M	5.5years	N	N	N	N	P	P	P	10	2	N	72	25	0.7	160	154	88	38	42	28	Positive	15	4.71	Moderate	Positive	9
39	55	M	4years	N	N	N	N	N	N	P	18	4	P	123	38	1.1	180	138	101	36	38	72	Positive	30	6.35	High	Positive	8.5
40	38	F	2.5years	N	N	N	N	N	N	P	8	0	N	98	22	0.9	156	140	99	41	35	20	Negative	10	3.82	Moderate	Negative	5

MASTER CHART - CONTROLS

SL.NO	AGE	SEX	DM	HT	CAD	CVA	SMOKING	ALCOHOL	Bl.Sugar(mg/dl)	Bl.Urea(mg/dl)	S.Creatinine(mg/dl)	T.CHL(mg/dl)	TGL(mg/dl)	LDL(mg/dl)	VLDL(mg/dl)	HDL(mg/dl)	CIMT(mm)
1	52	M	N	N	N	N	N	N	133	44	1.1	182	154	82	37	38	6
2	35	M	N	N	N	N	N	N	92	28	0.9	158	162	98	40	41	5.2
3	60	M	N	N	N	N	N	N	78	32	0.8	180	176	106	36	36	5.5
4	49	M	N	N	N	N	N	N	82	28	0.7	166	150	93	33	39	5.5
5	43	M	N	N	N	N	N	N	74	22	0.8	157	171	88	35	41	4.5
6	38	M	N	N	N	N	N	N	100	29	0.9	149	160	78	37	42	5
7	35	M	N	N	N	N	N	N	68	18	1	170	154	99	31	40	4.9
8	50	M	N	N	N	N	N	N	80	21	1	188	161	123	42	37	6.3
9	43	M	N	N	N	N	N	N	136	33	0.9	155	146	112	37	40	5.5
10	45	M	N	N	N	N	N	N	62	27	1.1	140	139	99	32	38	5.8
11	53	M	N	N	N	N	N	N	94	18	0.9	188	175	78	33	40	6
12	40	M	N	N	N	N	N	N	66	24	0.8	144	138	82	34	42	5.4
13	39	F	N	N	N	N	N	N	78	18	0.9	154	162	98	38	39	5.3
14	46	F	N	N	N	N	N	N	123	33	1	128	138	76	33	40	5
15	37	F	N	N	N	N	N	N	132	44	0.9	160	155	77	35	42	5.8
16	54	F	N	N	N	N	N	N	94	24	0.7	182	160	98	34	38	5.6
17	35	F	N	N	N	N	N	N	75	41	1	166	142	120	38	34	4.8
18	36	F	N	N	N	N	N	N	68	22	0.7	180	153	88	32	41	5.5
19	60	F	N	N	N	N	N	N	70	24	0.9	192	168	112	41	34	6.5
20	57	F	N	N	N	N	N	N	88	38	1.1	168	152	78	38	40	6.4
21	58	F	N	N	N	N	N	N	86	32	0.8	166	158	99	37	36	6
22	41	F	N	N	N	N	N	N	93	28	1	158	146	96	33	41	5.6
23	45	F	N	N	N	N	N	N	84	18	0.9	165	152	88	34	38	5.8
24	36	F	N	N	N	N	N	N	122	24	0.7	182	128	110	40	36	5.3
25	50	F	N	N	N	N	N	N	68	42	0.9	200	176	98	32	40	6
26	45	F	N	N	N	N	N	N	84	22	0.7	166	155	77	38	37	5.9
27	46	F	N	N	N	N	N	N	120	20	1.1	177	160	108	28	42	5.5
28	55	F	N	N	N	N	N	N	132	25	1	158	146	99	29	38	5.7
29	52	F	N	N	N	N	N	N	90	17	0.8	169	149	82	33	43	6.1
30	35	F	N	N	N	N	N	N	76	16	0.9	188	165	90	36	38	5.5
31	45	F	N	N	N	N	N	N	66	43	0.7	202	166	102	40	37	5.8
32	50	F	N	N	N	N	N	N	64	19	1	187	165	86	37	40	5.9
33	28	F	N	N	N	N	N	N	76	22	0.7	154	144	78	35	39	5
34	57	F	N	N	N	N	N	N	75	41	1.1	186	152	113	41	33	6.2
35	48	F	N	N	N	N	N	N	96	32	1	168	149	82	36	40	5.6
36	49	F	N	N	N	N	N	N	78	49	0.9	154	139	77	32	41	6.1
37	29	F	N	N	N	N	N	N	62	18	0.7	144	138	92	27	44	5.3
38	47	F	N	N	N	N	N	N	84	33	1	187	160	77	32	41	5.6
39	20	F	N	N	N	N	N	N	91	22	0.7	166	142	88	31	42	5
40	32	F	N	N	N	N	N	N	128	20	1	156	133	79	34	43	5.9

KEY TO MASTER CHART

- **DM** - Diabetes mellitus.
- **HT** - Hypertension.
- **CAD** - Coronary artery disease
- **CVA** - Cerebrovascular accident
- **EMS** - Early morning stiffness.
- **TJC** - Tender joint count.
- **SJC** - Swollen joint count.
- **T.CHL** - Total cholesterol.
- **TGL** - Triglycerides.
- **LDL** - Low density lipoprotein.
- **HDL** - High density lipoprotein.
- **ESR** - Erythrocyte sedimentation rate

- **CRP** - C-reactive protein
- **GH** - General health on visual analogue scale.
- **DAS28** - Disease activity score28
- **RF** - Rheumatoid factor
- **CIMT** - Carotid intima media thickness
- **P** - Present
- **N** - Not present

ETHICAL COMMITY APPROVAL FORM

Ref. No. 5336 /E4/3/2012

Govt. Rajaji Hospital,
Madurai.20. Dated: .08.2012

Institutional Review Board / Independent Ethics Committee.
Dr. N. Mohan, M.S., F.I.C.S., F.A.I.S.,
Dean, Madurai Medical College & 2521021 (Secy)
Govt Rajaji Hospital, Madurai 625020.
Convenor
grhethicssecy @gmail.com.

Sub: Establishment-Govt. Rajaji Hospital, aMadurai-20-
Ethics committee-Meeting Agenda-communicated-regarding.

The Ethics Committee meeting of the Govt. Rajaji Hospital, Madurai was held at 11.00 Am to 1.00Pm on 28.06.2012 at the Dean Chamber, Govt. Rajaji Hospital, Madurai. The following members of the committee have been attended the meeting.

1. Dr.N.Vijayasankaran,M.ch(Uro.) 094-430-58793 0452-2584397	Sr.Consultant Urologist Madurai Kidney Centre, Sivagangai Road,Madurai	Chairman
2. Dr.P.K. Muthu Kumarasamy, M.D., 9843050911	Professor & H.O.D of Medical, Oncology(Retired)	Member Secretary
3. Dr.T.Meena,MD 094-437-74875	Professor of Physiology, Madurai Medical College	Member
4. Dr. S. Thamilarasi, M.D (Pharmacol)	Professor of pharmacology	
5.Dr.Moses K.Daniel MD(Gen.Medicine) 098-421-56066	Professor of Medicine Madurai Medical College	Member
6.Dr.M.Gobinath,MS(Gen.Surgery)	Professor of Surgery Madurai Medical College	Member
7.Dr.S. Dilshadh, MD(O&G) 9894053516	Professor of OP&Gyn Madurai Medical College	Member
8.Dr.S.Vadivel Murugan., M.D, 097-871-50040	Professor of Medicine Madurai Medical College	Member
9.Shri.M.Sridher,B.sc.B.L. 099-949-07400	Advocate, 2, Deputy collectors colony 4th street KK Nagar, Madurai-20.	Member
10.Shri.O.B.D.Bharat,B.sc., 094-437-14162	Businessman Plot No.588, K.K.Nagar,Madurai.20.	Member
11.Shri. S.sivakumar,M.A(Social) Mphil 093-444-84990	Sociologist, Plot No.51 F.F, K.K Nagar, Madurai.	Member

Following Projects were approved by the committee

Sl. No	Name of P.G.	Course	Name of the Project	Remarks
1.	Dr.Prabhuswamy.K M	M.D Gen med	Carotid intima thickness in rehumatiod arthritis patients as risk factor for atherosclerosis.	Approved

Please note that the investigator should adhere the following: She/He should get a detailed informed consent from the patients/participants and maintain Confidentially.

1. She/He should carry out the work without detrimental to regular activities as well as without extra expenditure to the institution to Government.
2. She/He should inform the institution Ethical Committee in case of any change of study procedure site and investigation or guide.
3. She/He should not deviate for the area of the work for which applied for Ethical clearance.

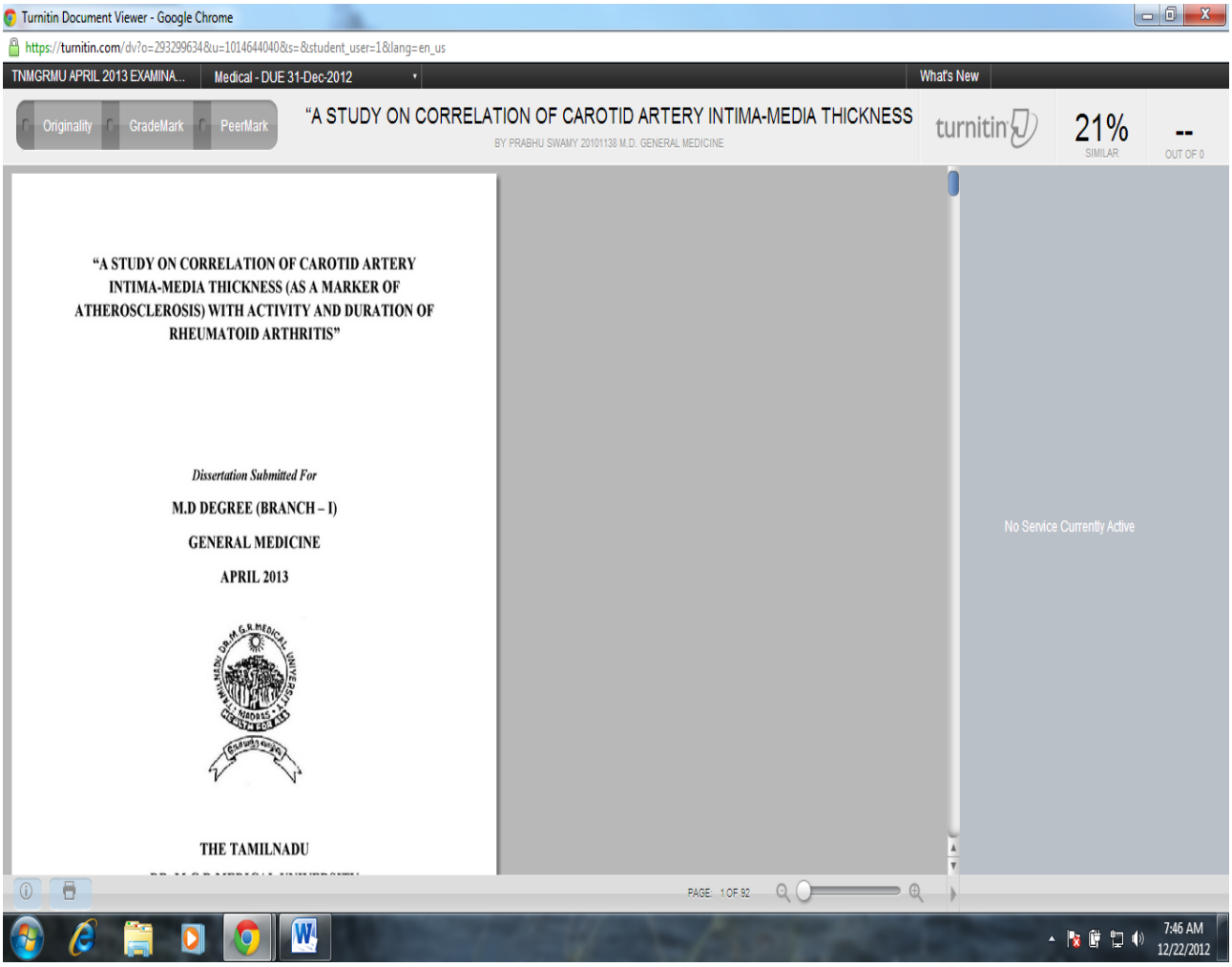
She/He should inform the IEC immediately, in case of any adverse events pr Serious adverse reactions.

4. She/he should abide to the rules and regulations of the institution.
5. She/He should complete the work within the specific period and apply for if any Extension of time is required She should apply for permission again and do the work.
6. She/He should submit the summary of the work to the Ethical Committee on Completion of the work.
7. She/He should not claim any funds from the institution while doing the word or on completion.
8. She/He should understand that the members of IEC have the right to monitor the work with prior intimation.

DEAN 17.8.12

To
All the above members and Head of the Departments concerned.
All the Applicants.

ANTIPLAGIARISM CERTIFICATE:



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Assignment title	Medical
Author	Prabhu Swamy 20101138 M.D. General Medicine
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"A STUDY ON CORRELATION OF CAROTID ARTERY INTIMA-MEDIA THICKNESS (AS A MARKER OF ATHEROSCLEROSIS) WITH ACTIVITY AND DURATION OF RHEUMATOID ARTHRITIS" Dissertation Submitted For M.D DEGREE (BRANCH – I) GENERAL MEDICINE APRIL 2013 THE TAMILNADU DR. M.G.R MEDICAL UNIVERSITY CHENNAI INTRODUCTION Rheumatoid arthritis (RA) is a systemic chronic inflammatory disease in which etiology is unknown. It is the commonest inflammatory arthritis affecting 0.5 to 1 percent of general population all over the world. It is characterized by symmetric polyarthritis involving peripheral joints, resulting in joint destruction and disability. Although it is a disease of joints, abnormal immunological responses can...