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SRI DEVARAJ URS MEDICAL COLLEGE

"STUDY ON CAROTID INTIMAL THICKNESS IN RHEUMATOID ARTHRITIS PATIENTS AS MARKER OF ATHEROSCLEROSIS IN RURAL POPULATION OF KOLAR DISTRICT "

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May 2016

DECLARATION BY THE CANDIDATE

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Dr. SRIDHAR SREENIVASAN G.G

ABSTRACT

Title : "STUDY ON CAROTID INTIMAL THICKNESS IN RHEUMATOID ARTHRITIS PATIENTS AS MARKER OF ATHEROSCLEROSIS IN RURAL POPULATION OF KOLAR DISTRICT ."

Background: Premature cardiovascular and cerebrovascular disease has been recognized as a significant cause of morbidity and mortality in rheumatoid arthritis. because of the high incidence of cardiovascular and cerebrovascular events observed in patients with RA, an important step forward might be to identify high-risk individuals who would benefit from active therapy to prevent clinical disease. carotid intima media thickness can be used as marker of atherosclerosis in these patients which determines rheumatoid arthritis patients who are at potential risk for a cardiovascular & cerebrovascular event.

Objectives: 1) To find association of carotid intimal thickness in Rheumatoid arthritis patients.

2) To study carotid intimal thickness in healthy controls
3) To compare the carotid intimal thickness in rheumatoid arthritis patients with age and sex matched healthy controls.

MATERIAL AND METHODS: A total of 138 people will be selected for the present study . Subjects for our study will be selected from patients at the Outpatient Clinic and inpatients of R.L.JALAPPA Hospital and Sri narsimharaja (SNR) Government Hospital, kolar, who are diagnosed as rheumatoid arthritis according to the RA ACR/EULAR 2010 criteria. The control group consisted of healthy non diabetic ,non hypertensive and non smokers subjects

selected from the patient bystanders attending the hospital. Carotid intima media thickness was measured in both the cases and compared with age and sex matched controls.

RESULTS:

In the study included age and gender matched cases and controls . The sample size was determined as 138(69 cases & 69 controls). Cases were positive for rheumatoid arthritis and controls did not have disease. 36.2% were in the age group > 50 yrs and 71 % cases were females 14.5% had Ischemic changes in ECG and 10.1% had CVA. Mean cholesterol in cases was 159.59 ± 15.49& in control was 156.54±14.60. Mean Triglycerides in cases was 109.94± 21.64 & in control was 103.20± 17.40 . Mean HDL levels in cases was 46.45± 6.27& in control was 48.87± 4.50. There was significant difference between cases and controls. Mean Right CIMT in cases was 0.58± 0.15& in control was 0.47± 0.04.Mean Left CIMT in cases was 0.60± 0.15& in control was 0.46± 0.04 which shows a positive correlation between rheumatoid arthritis and increase in carotid intima media thickness (CIMT). ESR,CRP and RA factor showed a positive correlation with CIMT.

CONCLUSION:

The present study revealed that subclinical atherosclerosis, detected by CIMT as surrogate marker in patients with RA . A positive co-relation was established between duration of disease, ESR,CRP,RA factor and increasing CIMT . CIMT measurement was found to be a safe, inexpensive, reproducible, and repeatable strategy for detecting subclinical atherosclerosis and helps in determining the patients at risk of CAD and enables optimized care and treatment in the prevention of CAD/CVD in rheumatoid arthritis patients.

LIST OF ABBREVATION

ACR	American College of Rheumatology
ACPA	Anti-cyclic citrullinated peptide/protein antibodies
AMI	Acute myocardial infarction
APC	Antigen presenting cell
CAD	Coronary Artery Diseses
CCA	Common carotid artery
CIMT	Carotid Intima Media Thickness
CRP	C-reactive protein
CI	Confidence interval
CVD	Cardiovascular Disease
DMARD	Disease modifying anti-rheumatic drug
ESR	Erythrocyte sedimentation rate
IL	Interleukin
HSP	heat-shock protein
HDL	High density lipoprotein
HLA	Human leukocyte antigen
ICAM-1	Intercellular adhesion molecule 1
IRR	Incidence rate ratio
IL-1Ra	IL-1 receptor antagonist

IFN-γ	interferon-γ
IL	interleukin
LDL	Low-density lipoproteins
MCP	Metacarpophalangeal
MTP	Metatarsophalangeal
NO	Nitric oxide
NOS	Nitric oxide synthase
NSAID	Non steroidal anti-inflammatory drugs
OR	Odds ratio
PIP	Proximal interphalangeal
RA	Rheumatoid arthritis
RF	Rheumatoid factor
Th1	helper T cell type 1
Th2	helper T cell type 2
TNF-α	tumor necrosis factor–α
VCAM-1	vascular cell adhesion molecule-1
↑	increase
↓	decrease

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of the joints with predominant symptoms of pain, swelling and stiffness[1]. The prevalence of rheumatoid arthritis around the world is between 0.7% to 1.5 %[2]. Malviaya et al found the prevalence in Indian rural population to be 0.75%[3]. Rheumatoid arthritis (RA) is associated with an increased risk of cardiovascular and cerebrovascular disease due to accelerated atherosclerosis,the exact mechanism for this is unknown, but RA disease-related inflammation has been postulated to affect the vasculature and contribute to endothelial dysfunction and atherosclerosis[3].

Patients with rheumatoid arthritis (RA) are more prone for accelerated atherosclerosis and Asian Indians as an ethnic group are predisposed to a high risk of premature atherosclerosis resulting in coronary artery disease (CAD)& cerebrovascular disease (CVD)[4]. Linking the two conditions have provided data positively correlating RA and atherosclerosis[4] . However, sparse data are available regarding the burden of atherosclerosis among asymptomatic adult patients with RA in south India.

Single photon emission computed tomography (SPECT) studies have confirmed that myocardial perfusion abnormalities occur earlier in patients with RA. The CAD is evident in both the genders. Vascular involvement especially in seropositive RA has been observed[4] .

The local vascular inflammation seems to induce diffuse endothelial dysfunction that initiates accelerated atherosclerosis . Atherosclerosis leading to premature cardiovascular disease and cerebrovascular disease has been recognized as a significant cause of morbidity and mortality in rheumatoid arthritis (RA)[4].

The systemic and articular inflammatory load drives the destructive progression of the disease, and the extent of inflammation in RA has been linked to an increased risk of cardiovascular mortality resulting from accelerated atherogenesis[4].

This potentiates the need to assess the cardiovascular and cerebrovascular risk status of RA patients Because of the high incidence of CAD/CVD events observed in patients with RA, an important step forward might be to identify high-risk individuals who would benefit from active therapy to prevent clinical disease. A persistent long standing immune inflammation is considered as a novel risk factor for atherosclerosis[5].

In this regard, noninvasive imaging techniques offer clinicians a unique opportunity to study the relationship of surrogate markers to the development of atherosclerosis. Among them, ultrasound techniques measuring intimal thickness is considered an efficient ways to measure subclinical atherosclerosis [5].

Apart from assessing the regular risk factors, newer means of detecting the CAD/CVD risk is to assess the carotid intimal thickness for an early detection of atherosclerosis[5].

Carotid intima-media thickness (CIMT) is a simple, reliable, inexpensive, non-invasive marker that is increasingly being used to detect subclinical atherosclerosis and has been recommended by the American Heart Association (AHA), American Society of Echocardiography (ASE) and Society for Vascular Medicine (SVM) as a screening test for heart disease in apparently healthy individuals[5]. Mortality due to coronary artery disease (CAD) has been found to be 59 per cent higher in patients with RA when compared to general population [6].

Measurement of CIMT as marker of atherosclerosis can determine the patients at risk of CAD and an early initiation of treatment in these patients can help in reduction of atherosclerosis and also reduction in the mortality of rheumatoid arthritis patients.

OBJECTIVE OF THE STUDY

1. To find association of carotid intima media thickness in rheumatoid arthritis patients.
2. To study carotid intima media thickness in healthy controls
3. To compare the carotid intima media thickness in rheumatoid arthritis patients with age and sex matched healthy controls.

REVIEW OF LITERATURE

HISTORY OF RHEUMATOID ARTHRITIS :

Arthritis and diseases of the joints have been plaguing mankind since ancient times. In 1500 BC Ebers Papyrus described a condition that is similar to rheumatoid arthritis[7]. This is probably the first reference to the disease. There is evidence of rheumatoid arthritis in the Egyptian mummies as found in several studies. G. Elliot in his studies found that rheumatoid arthritis was a prevalent disease among Egyptians[7].

Soranus, an Ephesian, who lived in the 2nd century AD, wrote a treatise describing a polyarthritis with morning stiffness in which the "joints become twisted with the toes and fingers either turned sideways or bent over backwards, or resting immovable upon their neighbours"[8].

In Charak Samhita (written in between 500 BC and AD100) the Indian literature, also described a condition that describes pain, joint swelling and loss of joint mobility and function . The great Charaka described a chronic disease with joint swellings and subcutaneous nodules. Ayurveda in ancient Indian medicine also considered arthritis as one of the Vata [9].

The first detailed case report of rheumatoid arthritis was that by a French medical student in 1800, Augustine Jacob Landre-Beauvais, who described acute onset of polyarthritis in a 35 years old female, which gradually ceased leaving behind deformity of the wrists and hands, only to recur [8].

Hippocrates described arthritis in general in 400 BC. He however did not describe the specific types of arthritis. Galen between 129 and 216 AD introduced the term rheumatismus. Paracelsus (1493-1511) suggested that substances that could not be passed in urine got stored and collected in the body especially in the joints and this caused arthritis [8].

Thomas Sydenhams (1676) description of a polyarticular disease characterized by remissions and exacerbations, and his observation that "the joints of his fingers have been as if it were inverted and bulging out with the knots showing on their inner rather than the outer aspects of the fingers"; the first description of swan neck deformity was made[8.]

Thomas Sydenham first described a disabling form of chronic arthritis that was described later by Beauvais in 1880. Brodie went on to show the progressive nature of this disease and found how rheumatoid arthritis affected the tendon sheaths and sacs of synovium in the joints. Brodie found how there was synovial inflammation or synovitis and cartilage damage associated with rheumatoid arthritis[8,9].

History of the terms Rheumatoid Arthritis, Rheumatology .

In 1858 A B Garrod named the disease rheumatoid arthritis replacing the old terms arthritis deformans and rheumatic gout, thus A B Garrod is credited to make a distinction between rheumatoid arthritis and osteoarthritis and gout [9].

In 1896 Bannatyne first described Appearance of rheumatoid arthritis affected joints [8]. However the term rheumatoid arthritis came into use in 1941, prior to that it was known by many different terms such as proliferative arthritis, atrophic arthritis etc [9].

In 1932 the International Committee on Rheumatism was formed. It later became American Rheumatism Association and then American College of Rheumatology . It was in 1940 that Camroe coined the term rheumatologist and Hollander in 1949 coined the term rheumatology [9.]

History of rheumatoid factor as serological marker:

The test was first described by Norwegian Dr Erik Waaler in 1940 and re-described by Dr HM Rose and colleagues in 1948. Re-description is said to be due to world war II and hence this test is referred as Waaler- Rose Test[10].

Therapeutic Milestones

Rheumatology has directly or indirectly contributed to the development of some of the most important therapeutic agents, such as NSAIDs, cortisone, methotrexate, sulfasalazine, hydroxychloroquine/chloroquine, mycofenolate, leflunomide, biologics & others (cyclosporine, azathioprine etc.) which have revolutionized the outcome of rheumatoid arthritis..

HISTORY OF TREATMENT OF RHEUMATOID ARTHRITIS

In the olden days treatments for rheumatoid arthritis included blood letting and leeching[11]. Practices of acupuncture, acupressure, moxibustion (use of heat), cupping were used In the Far East [11].

After several failed treatments that did not improve the condition of the patients, came the use of heavy metals in treatment of many diseases including rheumatoid arthritis. Gold, bismuth, arsenic and copper salts were used with varying rates of success [11]. Gold however has shown success over years of use and is still a part of Disease Modifying Antirheumatic drugs (DMARDs). DMARDs are widely used in treatment of Rheumatoid arthritis[11].

HISTORY OF PAIN RELIEF IN RHEUMATOID ARTHRITIS

NSAID - Pain relief was achieved using the plant extracts of Willow bark and leaves which contained salicin . Hippocrates and Galen used Willow extracts to treat pain of rheumatoid arthritis and other forms of arthritis[11]. Leroux in 1929 identified Salicylic acid as an active substance that reduces pain.

In 1853, acetyl salicylic acid (aspirin) was synthesized by Gerhardt[11]. Thereafter beginning with phenylbutazone in 1949 several other non steroidal anti-inflammatiory agents(NSAID) came into being.

CORTISONE-

1930 - Kendall isolated 6 different compounds (A-F) from adrenal gland.

1948 - Compound E was found to have anti-rheumatic properties by Kendall

1948 - Hench treated the first case of rheumatoid arthritis with compound E .

Today cortisone is an integral part of treatment of many inflammatory rheumatic and non rheumatic disorders (despite the love and hate relationship it generates)[12].

History of Disease Modifying Anti-rheumatic drugs (DMARDs)

Payne in 1895, first suggested the use of quinine to treat lupus erythematosus and rheumatoid arthritis . In 1951 Page demonstrated efficacy of quinacrine (mepacrine) in lupus erythematosus [12]. This was followed by the use of chloroquine by Baguall in 1957 and now hydroxychloroquine (HCQ). HCQ today is used extensively in many rheumatic diseases because of its multiple benefits, low toxicity, and low cost [12.]

Dating back to 2000 BC, Egyptians and Chinese used gold for medicinal purposes. In 1927 Landre had recommended its use to treat rheumatic fever.Gold salts were first used to treat rheumatoid arthritis by Forestier in 1925 on the wrong assumption of tuberculosis as its aetiological factor and back then gold was to treat tuberculosis [8].

In the 1970's and 80's gold was the most commonly used DMARD. Presently gold salts are rarely used to treat RA because of the availability of better and safer drugs[8].

Sulphasalazine was developed in 1940's as an anti-inflammatory and still forms a part of DMARDs. Philip Hench and Edward Kendall in1949 were the first who showed the successful use of cortisone in autoimmune diseases including rheumatoid arthritis [13].

Methotrexate was first synthesized in 1950's as a folate antagonist to treat leukaemia[11,13]. It was not until the 1980's that the role of methotrexate in rheumatoid arthritis was discovered. It still forms part of the DMARDs . In 1990's the role of folic acid supplementation to reduce

methotrexate toxicity was realized. Presently MTX is the anchor of treatment of RA either as monotherapy or in combination with other agents (DMARDs and biologics) [13].

HISTORY OF ANTI-TNF ANTIBODIES (BIOLOGICS):

Monocyte derived tumor necrosis (TNF) factor was first identified for its role in the pathogenesis of rheumatoid arthritis in 1975 [11,13]. In 1993 Anti-TNF antibodies were shown to be effective in the treatment of patients with rheumatoid arthritis[13].Presently there are many biologic agents that act against the components of immune response such as cells, cytokines, and signaling pathways. The major biologics being used are etanercept,adalimumab, infliximab, abatacept , While highly effective, danger of infection especially tuberculosis soon became apparent leading to the (modified) concept of diagnosis and treatment of latent tuberculosis. Cost remains an important consideration in their use. Most biologics work better in combination with methotrexate[13] .

History of CIMT:

In 1986 pignoli and colleagues for the first time reported ultrasound imaging to measure imt of carotid arteries. In 1991 salonen and collegues used cimt in vivo for evaluation of atherosclerotic changes in the carotid arteries.they demonstrated close histological relationship between carotid ,cerebral,carotid atherosclerosis[14].

Definition: Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that affects the joints, connective tissues,muscles,tendons and fibrous tissue. It tends to strike during the most productive years of adulthood,between the age of 20 and 40 years,and is a chronic disabling condition leading to considerable pain, joint destruction and disability. The prevalance varies between 0.3 and 1% and is more common in women & in developed countries[10,15].

Aetiology: Despite recent advances in knowledge regarding progression of rheumatoid arthritis,the cause remains elusive. In fact, there is probably not an exact cause. Researchers are debating whether rheumatoid arthritis is one disease or several different diseases with common features[15]. It appears to be a multi-factorial disease in which there are important genetic and environmental influences. There are no reports of clustering in space or time that support an infectious cause as a probability [15].Jobanputra et al in 1995 studied and suspected infectious agents, such as mycobacteria, Epstein-Barr virus and parvovirus as the causal agents, but without any conclusive or convincing evidence[16]. Sex hormones were implicated since there is an increased incidence in women and RA mostly improves in pregnancy, and relapses during post-partum. Nulliparous women, women in the post-partum period, and women who have an early menarche have a greater risk of developing Rheumatoid arthritis[16].

Current research is focused on elucidating the complex interactions of genetic, environmental, hormonal and auto-immune pathways [16]. While environmental stressors are likely to be involved, no definite environmental factors that precipitate disease onset have been identified . It has becomes more evident that these factors nourish the immune-pathogenesis on the initial stages of the disease and continue to fuel its maintenance and progression.

Stress theories:

One of the oldest of explanation was the stress hormone hypothesis championed by Hans Selye in 1949 -1950[16]. Roughly, his contention was that hormones released by the body, especially those released by the jacket of the adrenal glands, caused an adverse reaction to the joint tissues when they are released in excessive amounts, or in the wrong ratios under the conditions of environmental or psychological stress.

His concept was generalized and only mentioned rheumatoid arthritis as an unlikely possibility. The theory had some plausibility since arthritis can be produced by injecting deoxycorticosterone, which is a potassium excreting hormone, into a patient with Addison's disease or reproduced in similar animal studies by Selye in 1944[17].The dramatic effect that cortisone has on arthritis was demonstrated first in 1948 by Edward C. Kendall and Philip S , Hench at the Mayo Clinic in Rochester,Minnesota. Their discovery stemmed from the clinical observation that a woman with severe RA felt much better during pregnancy. They found what was responsible and It was a hormone from the outer part (the cortex) of the adrenal glands that they called 'cortisone'.On September 21, of 1948, Hench gave a synthesised version of cortisone developed by Kendall to a patient with arthritis and it became the first 'miracle drug' due to its powerful anti-inflammatory and other effects. In 1950 they shared the Nobel Prize in physiology for their discoveries relating to the hormones of the adrenal cortex[11,12]. The question of whether patients with rheumatoid arthritis might have a defective hypothalamus–pituitary–adrenal axis was first raised then. It was initially hypothesized that this was due to an impaired ability of RA patients to synthesize sufficient amounts of endogenous glucocorticoids, but intensive investigations over the next few decades failed to reveal any such significant defects in HPA axis activity in RA patients[17]. The literature review provided no compelling evidence for significant differences in either basal or stress-stimulated HPA axis activity in RA patients compared with healthy individuals. However, Jessop and Harbuz (1999) did highlight an inherent defect, which resided in the inability of RA patients to mount an appropriately enhanced glucocorticoid response to increased secretion of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6 and tumour necrosis factor (TNF) - α. They concluded that 'the HPA axis response in RA is defective precisely because it is normal[8,17].

Demir et al in 1999 showed that Following an insulin-induced hypo glycaemia, which tests the HPA axis at all levels, there were no observed differences in serum cortisol responses between patients with active RA and patients in remission . This study did not include non-RA subjects as controls, and there was no ACTH response to hypoglycaemia in either test group, suggesting a possible methodological problem. Although the HPA axis in RA is defective because its activity is not increased in response to inflammatory cytokines, as might be predicted from observations of increased corticosterone in rodent models of

inflammation[17]. The current evidence suggest that the HPA axis is not materially different in RA compared with normal healthy subjects under most experimental conditions . Stress theories did not always emphasize steroid hormones.

Histamine was suggested as possibly being involved by two University of Utah scientists, Chemist Henry Eyring and Anatomist Thomas F. Dougherty in 1955[17,18]. The theory stated that stress sets off a destructive chain reaction among the body cells with histamine acting as a destructive agent. Each cell is in a membrane envelope and, as long as the membrane is relatively impermeable, the cell functions normally. Under stress, however, the membrane starts to deteriorate.

Histamine, which is normally present inside the cell when the cell is healthy, is violently released and stimulated by the cell breakdown. It attacks the disintegrating cell, which swells and bursts, liberating still more histamine to attack neighboring cells. Over long periods of stress, the spreading destruction can lead to serious illness and may be present in every fatal illness, including cancer. Supporting evidence of histamine hyper production comes from the study in 1981 by Permin and colleagues [8,18]. They found that basophilocytes from patients with rheumatoid arthritis responded to leukocyte nuclei from normal persons with histamine

release and recorded 3.5 times as much histamine production in arthritics after the challenge than normally expected [38].

Autoimmune hypothesis

The most popular current hypothesis is the autoimmune hypothesis. When rheumatoid arthritis presents, the immune system overcompensates and acts, attacking the joints and the body in general. The same thing occurs with other autoimmune diseases; the immunological mechanisms that manifest in these diseases have been identified, but there is still no explanation as to why this occurs[19].

Immunopathogensis of RA is multifactorial. Evidence suggests that an interaction between an unknown exogenous or endogenous antigen via antigen presenting cells and CD4 T helper cells are involved in the induction of the immune response in RA[19]. Subsequent recruitment and activation of monocytes and macrophages occurs with the secretion of proinflammatory cytokines, in particular TNF-α and IL-1 into the synovial cavity. The release of these cytokines mediates tissue destruction by activation of chondrocytes and fibroblasts which release collagenases and metalloproteinases with resultant cartilage loss and bone erosion[19].

B lymphocyte deregulations, results in the production of rheumatoid factor and other auto-antibodies, as well as in the formation of immune complexes and the release of destructive mediators, which also contribute to this process. Rheumatoid factor, an autoimmune response to IgG is a key feature of RA[10,19]. High levels are relatively specific for RA but rheumatoid factor may also occur in other chronic diseases and is absent in around 30% of patients with established RA [10].

The hypothesis that rheumatoid arthritis is an allergy is in the same general category as the autoimmune hypothesis . Such a hypothesis has the advantage, not shared by the autoimmune hypothesis directly, of advancing an environmental factor, which is almost involved certainly[19].

There is evidence from several documented case reports by Buchanan et al in 1991 that occasional patients with rheumatoid arthritis may develop an aggravation of their arthritis, as a result of allergy to some ingredient in their diet. A variety of foodstuffs have been implicated including milk and milk products, corn and cereals [20].

Total fasting results in an improvement in rheumatoid arthritis, but appears to be mediated by diminution in production of chemical mediators of inflammation, rather than by elimination of a dietary allergen [20].There is conflicting evidence from studies that used various intestinal probes in patients with rheumatoid arthritis and suggested that these patients may have a 'leaky' intestinal mucosa, allowing the food allergens to be more easily absorbed [19,20].

The hypothesis pointing towards 'masked food intolerance , is an attractive theory, but one that is extremely difficult to prove practically .

Genetic theory of Rheumatoid Arthritis

Reporting of rheumatoid arthritis clusters in families resulted in Support for a genetic predisposition for rheumatoid arthritis [21]. Formal genetic studies have confirmed this familial aggregation and genetic influence is estimated at 50 to 60% as described by Ollier et al in 1999 [21].

Studies in monozygotic twins have shown a concordance rate of 15% - 30% and a relative risk of 3.5 for rheumatoid arthritis developing in monozygotic versus dizygotic twins of affected cases [21]. A high prevalence rate of 5% - 6% has been described in some Native American populations, suggesting a higher genetic burden of rheumatoid arthritis risk genes[22].

Genetic risk factors not only determine susceptibility for the disease but also correlate with the disease severity and phenotype, providing the unique opportunity to use genetic markers as prognostic tools in the management of rheumatoid arthritis. A measure used to estimate the genetic component to the disease is the coefficient of familial clustering, λs, defined as the ratio of the prevalence in affected siblings to the population prevalence [22].

Dieudé & Cornélis in 2005 described for rheumatoid arthritis, λs ranges from 2 to 12 in first-degree relatives of patients [22]. Although clearly supporting the influence of the genetic factors,this λs is rather low compared with other autoimmune diseases or common genetic diseases,leaving considerable room for any environmental events in the pathogenesis of RA .

The genetic system studied most thoroughly is the major histocompatibility complex (MHC). Stastny et al in 1978 described in their study,that rheumatoid arthritis was associated with human leukocyte antigen (HLA)-DR4 [23]. The HLA-DRB1 alleles sequence polymorphism is

characterized by a glutamine or arginine at position 70, a lysine or alanine at position 71, and an alanine at position 74. Alleles with a negatively charged amino acid at one of these positions are not associated with the disease [22,23]. MHC genes are not the only germline-encoded genes influencing susceptibility to rheumatoid arthritis.

Female sex clearly increases the risk, and female patients develop a different phenotype of the disease than do male patients [23]. However, no sex-linked genes have been identified as disease-risk genes. The recent definition of single nucleotide polymorphisms throughout the human genome has increased significantly the feasibility of this approach. Studies of T-cell receptor (TCR) and immunoglobulin genes have not been revealing; several cytokine polymorphisms, including tumour necrosis factor (TNF)-α and interferon (IFN)- γ were described to influence disease severity[15].

PATHOGENESIS OF RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA), a chronic systemic autoimmune inflammatory disorder of unknown etiology that occurs in approximately 1% of the population [14,15] . In all populations, RA is more prevalent among women than men, and usually develops in the fourth and fifth decades of life, with 80% of the total cases occurring between the ages of 35 and 50 [22,23]. The primary presenting symptoms are pain, stiffness, and swelling of the joints resulting in impaired physical function.

These symptoms are often accompanied by constitutional symptoms such as fever and malaise . Synovial inflammation underlies the cardinal manifestations of this disease, which include pain, swelling, and tenderness followed by cartilage destruction, bone erosion, and subsequent joint deformities [24].

In RA, the joint involvement is typically symmetric, a characteristic usually not found in other forms of arthritis . Despite intensive research, the precise cause of RA remains elusive[15]. Although a variety of cells play a role in RA disease progression, macrophages may be of particular importance. Once in the synovium, macrophages are capable of antigen presentation and T-cell activation. Moreover, the extent of macrophage infiltration into the synovium correlates with RA severity and progression [24].

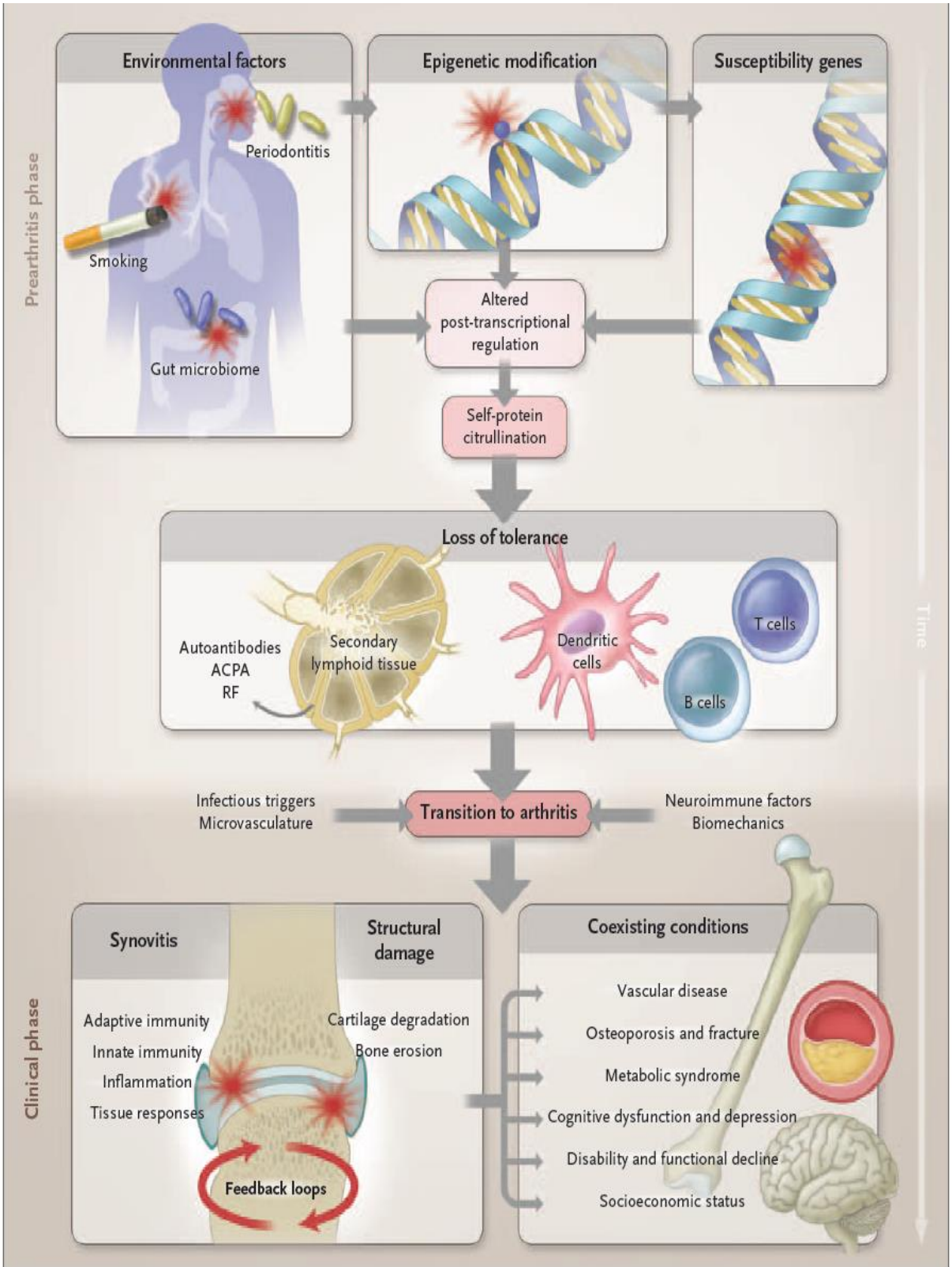


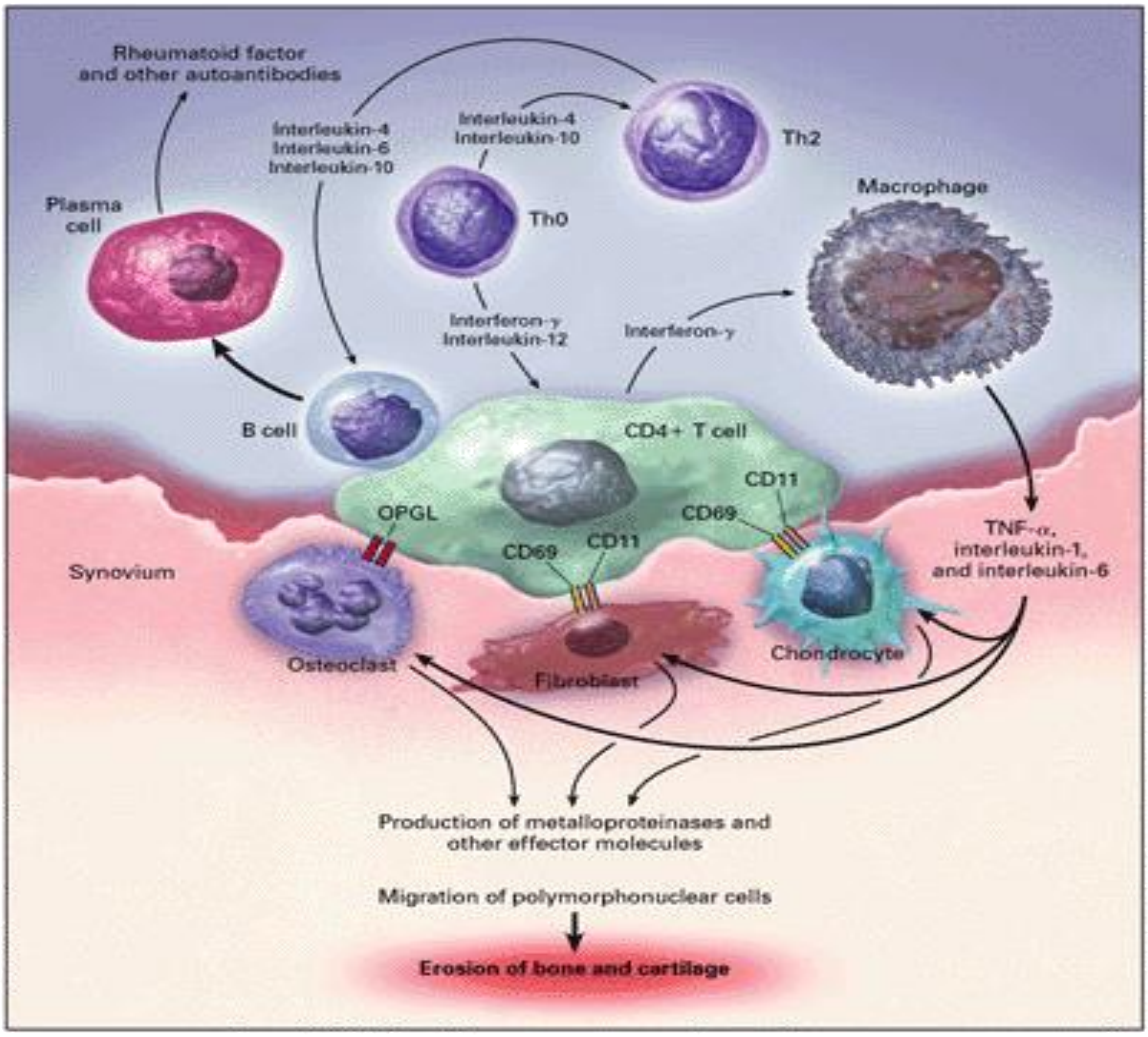
Figure 1. Multistep Progression to the Development of Rheumatoid Arthritis.

Environment–gene interactions described in the text promote loss of tolerance to self-proteins that contain a citrulline residue, which is generated by post-translational modification. This anticitrulline response can be detected in T-cell and B-cell compartments and is probably initiated in secondary lymphoid tissues or bone marrow. Thereafter, localization of the inflammatory response occurs in the joint by virtue of poorly understood mechanisms that probably involve microvascular, neurologic, biomechanical, or other tissue-specific pathways. Synovitis is initiated and perpetuated by positive feedback loops and in turn promotes systemic disorders that make up the syndrome of rheumatoid arthritis. ACPA denotes anti–citrullinated protein antibody, and RF rheumatoid factor.

Macrophage-derived cytokines, such as tumor necrosis factor alpha (TNF-a), appear to play a critically important role in the induction and perpetuation of the chronic inflammatory processes in rheumatoid joints as well as in the systemic manifestations of this disease .

TNF-a is one of the key inflammatory mediator. This cytokine is overproduced in joints of patients with RA and triggers increases in synoviocyte proliferation and a cascade of secondary mediators involved in the recruitment of inflammatory cells and in the process of joint destruction [15,25].

Figure 2: **Cytokine Signaling Pathways Involved In Rheumatoid Arthritis**



Joint erosion is known to occur early in RA, affecting about 40% of the patients during the first year and 90% during the first 2 years . Elevations in inflammatory markers are antecedents of disease progression and joint destruction in early RA [24].

The rate of cartilage and joint damage is correlated with plasma elevations in inflammatory acute phase reactants, such as C-reactive protein (CRP) and vascular endothelial growth factor, and in the synovial concentrations of matrix metalloproteinase's, matrix digesting enzymes directly responsible for joint destruction[15, 24].

PATHOGENESIS OF ATHEROSCLEROSIS IN RHEUMATOID ARTHRITIS: Atherosclerosis was formerly considered mainly a disease of lipid deposition in coronary arteries that produced plaques which grew until they obstructed the blood supply, resulting in ischemia or a cardiovascular event [14,25]. But present studies appreciate better dynamic biology of the atherosclerotic plaque and the role of inflammation and inflammatory mediators in atherogenesis and its complications [25].

Inflammatory mediators in rheumatoid arthritis and atherosclerosis: Although several factors contribute independently to the heightened cardiovascular risk observed in patients with RA, systemic inflammation likely contributes importantly to atherosclerosis [15,25] .

The cascade of events leading to atherosclerosis also participates in the pathogenesis of RA . Atherosclerosis and RA share a number of similarities, including T-cell and mast cell activation, production of pro-inflammatory cytokines such as tumor necrosis factor (TNF)–α and interleukin (IL)-6, and increased expression of leukocyte adhesion molecules [15].

Systemic inflammation characteristic of rheumatoid disease contributes to accelerated atherogenesis. Patients with RA have elevated levels of the acute-phase reactant C-reactive protein (CRP), a marker of inflammation associated with increased cardiovascular risk [25].

Patients with RA have increased carotid artery intimal-medial thickness an early measure of arterial disease and a validated biomarker of cardiovascular risk [5,25].The magnitude and chronicity of the alteration of the risk factors listed in Table 1 correlate with the degree of systemic inflammation in RA and ultimately affect cardiovascular risk. Elevated CRP or erythrocyte sedimentation rate (ESR) independently predicts radiographic progression of joint disease, increased disability, and poorer outcomes in RA [26] .

ESR also increases linearly with increased carotid artery intimal-medial thickness in both patients with RA and healthy controls [26]. Patients with RA with elevated ESR have a higher rate of cardiovascular death than do those without elevated ESR[26].

Table 1: Overview of similar inflammatory/immunologic responses in atherosclerosis and rheumatoid arthritis.

Inflammatory mediators	**Atherosclerosis**	**Rheumatoid Arthritis**
Macrophage activation		
TNF-α	↑	↑
Metalloproteinase expression	↑	↑
IL-6	↑ (UA)	↑
Mast-cell activation	↑	↑
T-cell activation		
Soluble IL-2 receptor	↑ (UA)	↑
$CD3^{+}DR^{+}$	↑ (UA)	↑
$CD4^{+}CD28^{-}$ $CD4^{+}$IFN-γ	↑ (UA)	↑
Th1/Th2 balance	↑ Th1	↑ Th1
B-cell activation		
Autoantibodies (ox-LDL, HSP)	0 or ↑	0 or ↑
Rheumatoid factor	0	↑
C-reactive protein	↑ (UA)	↑↑
Adhesion molecules (VCAM-1, ICAM-1, E-selectin, P-selectin)	↑	↑
Endothelin	↑	↑
Neoangiogenesis	↑	↑
Possible antigens	HSP, ox-LDL, Infectious agents	Collagen II, cartilage antigens, HSP, infectious agents

Appreciation has increased that inflammatory mediators and immune responses participate in the development of atherosclerosis[15,25]. The elevated levels of pro-inflammatory cytokines that accompany chronic inflammatory conditions such as RA can elicit a systemic inflammatory state that could, over time, promote vascular changes which progress to increase cardiovascular risk.

Cytokines, in addition to their role in regulating immune responses, mediate a number of metabolic effects that in the short term mediate appropriate responses to injury or infection but on a chronic basis prove detrimental [15,25].

Systemic release of proinflammatory cytokines (e.g., IL-1α, IL-1β, IL-6, and TNF-α) produced in synovial tissue in individuals with RA could boost a number of pro-atherogenic functions of the liver, adipose tissue, skeletal muscle, and vascular endothelium, including insulin resistance, dyslipidemia, endothelial activation, and prothrombotic and antifibrinolytic effects[26].

The progression of atherosclerosis in rheumatoid arthritis secondary to inflammatory mediators is described in following figure 3,figure 4, figure 5,figure 6.

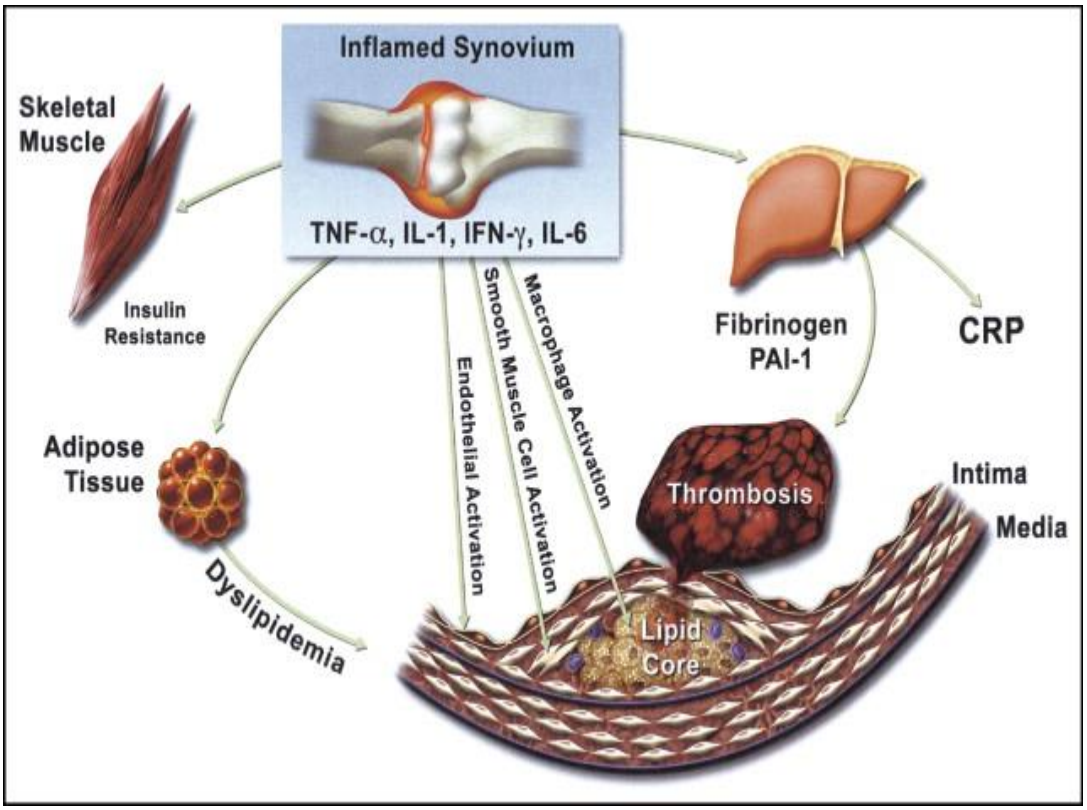


Figure 3. Inflammatory Pathway Mediating Atherosclerosis- Depicts the inflammatory pathways by which mediators of synovitis including tumor necrosis factor (TNF)–α may alter arterial biology and risk factors for atherosclerosis including insulin resistance, dyslipidemia, fibrinogen, plasminogen activator inhibitor–1 (PAI-1), and heighten the production of the biomarker of inflammation C-reactive protein (CRP), IFN = interferon; IL = interleukin[26]. The development of atherosclerosis proceeds in phases of initiation, plaque progression and formation of a complex plaque, and finally plaque rupture and thrombosis; inflammation contributes to all phases [26].Numerous mediators interacting through complex networks participate in atherogenesis, including adhesion molecules, cytokines, proteinases, and reactive oxygen species . There are various stages involved in atherosclerotic plaque development, from endothelial dysfunction to plaque rupture. Emphasis should be given for the proinflammatory cytokines and chemokines common to the pathogenesis of both RA and atherosclerosis.

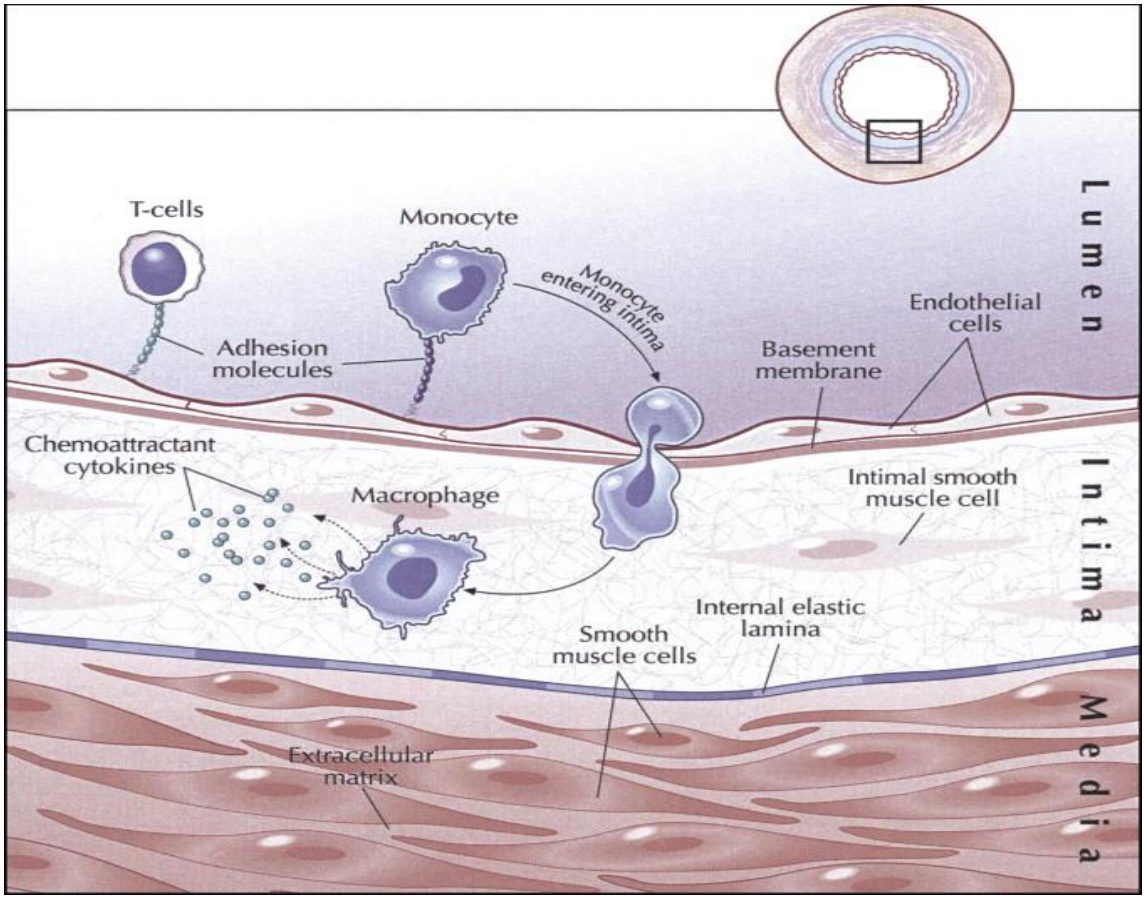


FIGURE 4: CAROTID CROSSSECTION : Transition from the normal artery wall to the growing atherosclerotic lesion. The normal muscular artery has 3 layers. A monolayer of endothelial cells lies over the intimal layer and borders a basement membrane . The intima of human arteries normally contains a few resident smooth muscle cells and a layer of extracellular matrix. The internal elastic lamina provides the boundary between the intimal layer and the tunica media, normally filled with quiescent smooth muscle cells in an elastin-rich extracellular matrix [26]. When molecules associated with risk factors provoke oxidative or inflammatory stress, they stimulate the expression of adhesion molecules for leukocytes and chemo-attractants, which bring the bound leukocytes into the intimal layer.

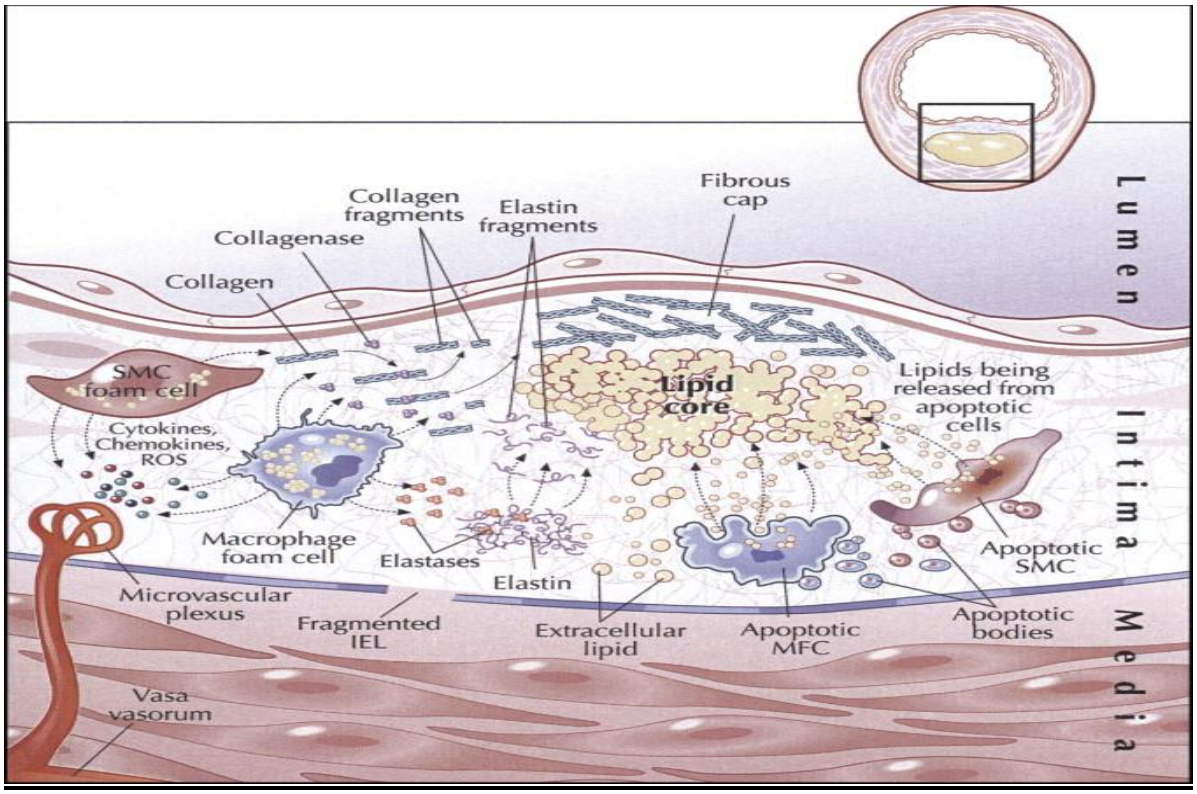


Figure 5. : FORMATION OF FIBROFATTY PLAQUE

The development from the fatty streak to the more fibrous lesion involves the passage of smooth muscle cells (SMCs) from the tunica media through the internal elastic lamina into the intima, where they release extracellular matrix molecules such as fibrillar collagen and elastin and can divide in response to mitogenic stimuli [27]. The mononuclear phagocytes absorb modified lipoproteins such as oxidized (Ox) low-density lipoprotein (LDL) through scavenger receptors to produce foam cells. The activated mononuclear phagocytes in the lesions release chemo-attractant cytokines, pro-inflammatory mediators including cytokines, and small lipid molecules such as leukotrienes and prostaglandins. When SMCs encounter fibrogenic stimuli such as transforming growth factor–β, they increase production of extracellular matrix macromolecules, including fibrillar collagen, depicted by the triple helical structures in the diagram and elastin[26,27].

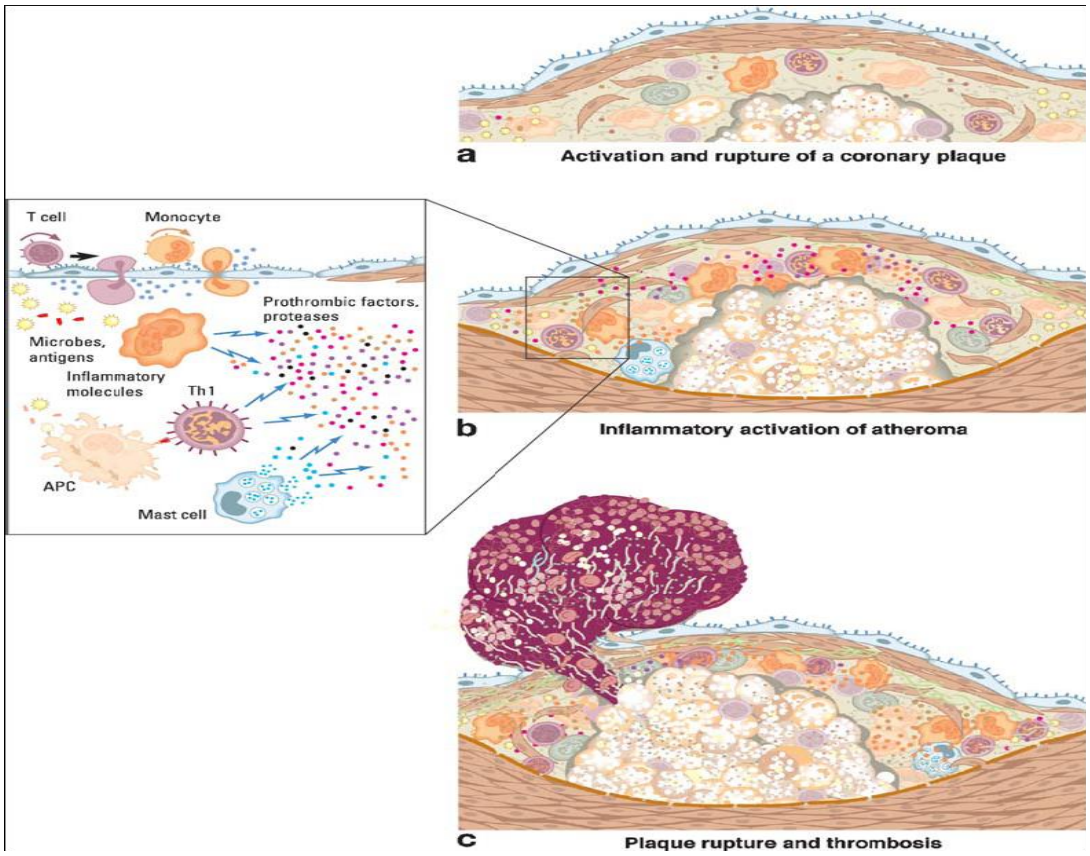


FIGURE 6 : Maturation of the atherosclerotic plaque : More mature lesions have a fibrous cap comprised of a dense extracellular matrix containing collagen and elastin . Beneath the fibrous cap, a lipid core forms containing many dying macrophages, cellular debris including apoptotic bodies, and lipids [26,27]. Pro-inflammatory mediators discharged from activated white cells and endothelial cells and smooth muscle cells (SMCs) can promote cell death by apoptosis in the advancing lesion. As SMCs die within lesions, fewer remain to replenish the extracellular matrix in the plaque's fibrous cap. The activated cells in the lesion, markedly the macrophages, secrete proteinases that can break down the macromolecules of the extracellular matrix. The interstitial collagenase can attack the triple-helical collagen fragments, weakening the fibrous cap. Elastases can degrade elastin, which is essential for migration of cells within the lesion, and arterial remodeling transpires during compensatory enlargement and aneurysm development[27]. During this phase of atherogenesis, neovessels

develop in the intima, often occurring as extensions of vasa vasorum that begin in the adventitial layer.

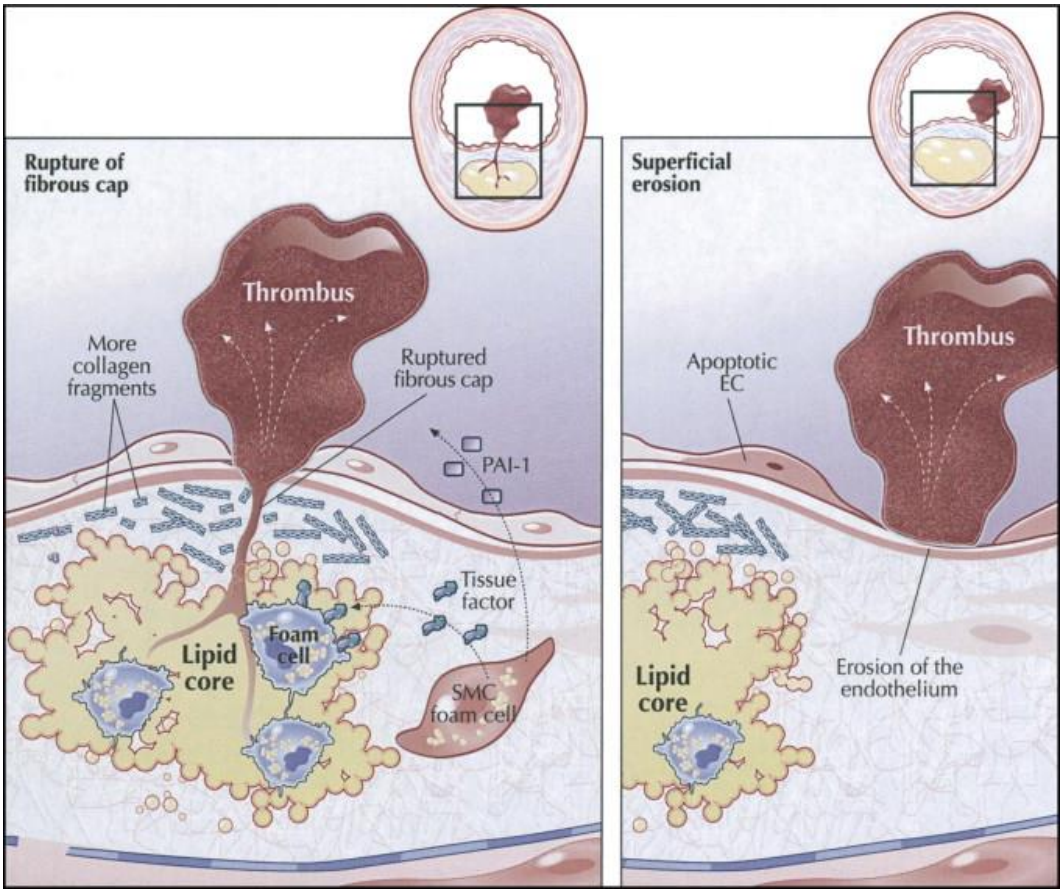


Figure 7 The thrombotic complications of atherosclerosis.

There 2 major mechanisms that produce the thrombi that complicate atheroma. The first image (Left) depicts a complete rupture of the plaque's fibrous cap. The tear in the fibrous cap allows blood and its coagulation factors to contact tissue factor expressed by macrophages and smooth muscle cells (SMCs) and on micro-particles elaborated by these cells and endothelial cells (EC). In addition, the activated cells in the local environment of the plaque, including ECs and SMCs, elaborate considerable amounts of plasminogen activator inhibitor-1 (PAI-1), a powerful inhibitor of the endogenous fibrinolytic enzymes also found in the plaque, such as urokinase and tissue-type plasminogen activator[27]. (*Right*) The second

primary mechanism of coronary thrombus formation involves a superficial erosion of the endothelial cells, possibly caused by endothelial apoptosis or desquamation.

Endothelial dysfunction: Atherosclerotic plaques contain a variety of inflammatory and immune cells (mostly T cells and macrophages), smooth muscle cells, neovascular channels, an extracellular matrix rich in collagen and elastin, and a lipid-rich core underlying a usually intact but functionally abnormal endothelial lining in contact with the blood compartment [26].Endothelial cell activation contributes early on to atherosclerosis development. Endothelial cells form the innermost surface of the artery wall and, under normal circumstances, do not bind leukocytes. Early changes that occur before plaque formation include elevated expression of leukocyte adhesion molecules and chemokines that recruit inflammatory cell migration into the arterial wall [27].

Triggers of endothelial cell dysfunction, such as high levels of low-density lipoprotein (LDL) cholesterol, smoking, hypertension, hyperglycemia, obesity, or insulin resistance, associate with increased levels of leukocyte adhesion molecules such as vascular cell adhesion molecule (VCAM)-1, which binds monocytes and T lymphocytes, the very cells found in early atherosclerotic plaques. Early VCAM-1 expression preceded intimal macrophage appearance and development of a thickened intima with foam cell lesions[28].

Proinflammatory cytokines, including interferon (IFN)-γ, TNF-α, IL-1, and IL-4 in rheumatoid arthritis mediate increased VCAM-1 expression. Incubating rabbit thoracic aortas with IFN-γ, TNF-α, IL-1β, or IL-4 stimulates endothelial VCAM-1 expression 65. Incubation of endothelial cells with IL-1 or TNF-α rapidly induces VCAM-1 expression that continues for ≥72 hours [15,26,27].

The atherogenic properties of TNF-α via augmented expression of adhesion molecules such as VCAM-1 in the vascular wall, facilitates monocyte/macrophage recruitment. IL-4 combines with TNF-α to reduce the threshold TNF-α level required to activate the VCAM-1 gene, synergistically increasing endothelial cell surface VCAM-1 levels. VCAM-1 gene expression depends in part on nuclear factor–κB; the proinflammatory cytokines IL-1β and TNF-α also use this transcription factor to induce endothelial cell VCAM-1 expression[28] .

Hemodynamic factors such as shear stresses and disturbed flows influence the distribution of adhesion molecule expression and early atheroma formation[28]. Regions of low shear stress or disturbed flow (e.g., near branch points) loose a panel of "atheroprotective" functions, thereby becoming sites of predilection for atheroma formation. Initially, fatty streaks consist of lipid-rich monocytes, macrophages (foam cells), and T lymphocytes. Following leukocyte adhesion, chemoattractants or chemokines produced by endothelial cells and smooth muscle cells, including monocyte chemoattractant protein–1 (MCP-1), macrophage colony-stimulating factor (M-CSF), and T-cell chemokines in rheumatoid arthritis induce migration and penetration of inflammatory cells into the subendothelial space [27,28]. Monocytes enter the intima of the vessel wall by diapedesis between the endothelial cells, mostly in response to a chemokine-induced chemoattractant gradient. The absence of MCP-1 or its receptor restricts monocyte and T-cell entry into the arterial intima and reduces atherogenesis.[28].

Plaque progression : Following the vascular wall infiltration of monocytes in early atherogenesis, monocytes develop into macrophages, and then into lipid-laden foam cells. Local expression of pro-inflammatory mediators such as M-CSF can amplify lesion formation and progression by promoting maturation, activation, and proliferation of mononuclear phagocytes in the intima.. These effects occur independently of plasma lipoprotein or circulating monocyte levels [28].

Macrophages also express the cytokine IL-8 and its receptor, which both contribute to atherogenesis by acting as leukocyte chemoattractants. Intimal monocyte/macrophage accumulation increases in atherosclerotic lesions. Under flow conditions, IL-8 stimulates firm adhesion of monocytes to vascular endothelium [28] . IL-8 as a factor in monocyte recruitment during atherogenesis.Activated T lymphocytes accumulate in the intima during atheroma formation.

Chemokines that contribute to T-lymphocyte recruitment and entry into the inflamed artery wall (facilitated by VCAM-1) during atherogenesis include 3 IFN-γ–inducible CXC chemokines: IFN-inducible protein-10, monokine induced by IFN-γ, and IFNγ-inducible T-cell chemoattractants bind to chemokine receptor CXCR3 expressed by lesional T cells. After entering the intima, T cells undergo antigenic activation (e.g., by oxidized LDL or heat-shock proteins) and induce expression of tissue factor, matrix metalloproteinases (MMPs), and proinflammatory cytokines by well worked-out signaling pathways[28].

Human plaque cells produce more helper T cell type 1 (T_h1) cytokines, including IFN-γ and IL-12, than helper T cell type 2 (T_h2) cytokines, such as IL-4, IL-5, and IL-10. Because T-cell cytokines such as IFN-γ promote plaque formation, these oxidized LDL-reactive T cells ($CD4^+$ T cells) likely advance atherogenesis[26,27,28]. T cells from Mediators derived from

leukocytes infiltrating the intima can recruit smooth muscle cells from the tunica media and can stimulate their proliferation.

Formation of an advanced lesion (fibrous plaque)

The evolution from fatty streak into a more complex lesion usually occurs over many years, a factor that underlies the potency of age as a risk factor for atherosclerotic events. The traditional view of this process involved evolution of fatty streaks into complicated lesions through multiplication and accumulation of smooth muscle cells in the plaque, producing an extensive extracellular matrix (Figure 5 and Figure 6). According to current thinking, many coronary arterial lesions develop discontinuously in time rather than smoothly. The arterial plaque initially grows in an outward abluminal direction that permits substantial lesion formation without luminal encroachment [28]. later in progression of plaque the lesions protrude into the lumen, producing the well-known clinical manifestations of ischemia such as angina pectoris .

Regardless of their rate of progression, complex mature plaques generally consist of foam cells and extracellular lipid droplets that form a core surrounded by a fibrous cap containing smooth muscle cells and a collagen-rich matrix (Figure 6). The macrophages, T cells, and mast cells that accumulate in the plaque produce proteases, prothrombotic molecules such as tissue factor, and vasoactive compounds that promote plaque [29].

Inflammatory signaling involves both the formation of new lesions and the evolution of existing ones. The proinflammatory cytokine CD40 ligand (CD40L) contributes to these phases of atherogenesis and figures prominently in both humoral and cell-mediated immune responses. CD40 promotes inflammation and atherogenesis by activating macrophages, T

cells, endothelial cells, smooth muscle cells, and platelets. [28,29]. These cells accumulate in plaque and localize at sites of lesion growth and complication.

The TNF-α path has particular interest in the patient with RA, as many may receive therapies that selectively target this cytokine. TNF-α may modulate the progression of atherosclerotic plaque. Lower levels of circulating endothelial progenitor cells—a possible contributor to intimal repair—correlate with higher TNF-α concentrations [26,28,29]. Patients with RA have fewer endothelial progenitor cells than healthy volunteers, but patients undergoing TNF-α antagonist therapy have levels of endothelial progenitors similar to those found in healthy volunteers. Inhibiting TNF-α (by treatment with a recombinant TNF receptor I fragment) also reduces the extent of atherosclerosis[29].

Thrombotic complications of atheroma

Inflammation promotes not only the initiation and progression of the atherosclerotic lesion, but also the development of the complicated or disrupted lesion. As previously discussed, the concept of continuous growth of the atheroma has evolved into one of apparent bursts in atheroma growth, followed by physical disruption of the plaque (weakening of the fibrous cap that renders the plaque prone to rupture), which triggers thrombosis. Healing of disrupted plaques may lead to episodes of rapid expansion (Figure 7)[26,30].

The most common form of physical disruption that occurs in the advanced or complex plaque involves rupture of the plaque's fibrous cap, releasing some of the sequestered contents of the atheroma core and allowing prothrombotic tissue factor to contact coagulation factors in the bloodstream resulting in complications [29]. Inflammatory mechanisms facilitate disruption or fracture of the fibrous cap. T lymphocytes participate in the inflammatory processes that inhibit the synthesis of and promote the degradation of the interstitial collagen matrix that

confers tensile strength upon the fibrous cap [29]. IFN-γ, produced by activated T cells in atheromata, limits collagen I and III synthesis by vascular smooth muscle cells (both basal production and transforming growth factor β-stimulated production) [30]. Proinflammatory cytokines such as CD40 ligand, IL-1, or TNF-α may also promote plaque disruption by stimulating the expression in endothelial cells, macrophages, and vascular smooth muscle cells of collagen-degrading MMPs, enzymes that catabolize collagen and other macromolecules of the arterial extracellular matrix . Postmortem evaluation of coronary arteries from RA patients with MI found large proportions of activated mast cells at the site of plaque rupture, as well as release of serine proteinases (chymase and tryptase), which may promote collagenolysis via activation of MMP proenzymes[30].

In addition to increasing expression of extracellular matrix–degrading proteinases that weaken plaques, activated T cells may promote thrombogenesis via expression of the CD40L, which stimulates macrophages to produce the potent procoagulant tissue factors. Proinflammatory cytokines such as IL-1 and TNF may also promote thrombosis by increasing tissue factor expression in endothelial cells [29,30].

A large body of evidence supports the involvement of pro-inflammatory cytokines in the development and progression of atherosclerosis, processes that overlap considerably with the pathogenic processes seen in RA [31,32]. The chronic and systemic inflammation associated with diseases such as RA and SLE may amplify atherosclerosis in multiple ways, including eliciting endothelial dysfunction and oxidative stress . Pro-inflammatory cytokines such as TNF-α and IL-1, expressed by affected joints in RA, may act on other tissues and organs at a distance, including atheromata.[29]. This systemic propagation of local synovitis can promote atherogenesis. Vasculitic complications of lupus erythematosus, RA, and allied diseases could provoke an arterial healing response that accelerates atherosclerosis [28,29]. By

involvement of mediators similar to those in the destructive proinflammatory cascade seen in RA, chronic inflammation in atherosclerosis can predispose to thrombosis, which can in turn promote more inflammation, constituting a vicious circle [32]. Appreciation of the shared inflammatory mechanisms at work in atherosclerosis and RA can lead to better recognition of cardiovascular comorbidities in patients with inflammatory conditions and to earlier intervention to reduce the concerning excess of cardiovascular-related morbidity and mortality in this patient population.

Accelerated Atherosclerosis in Rheumatoid Arthritis

Patients with rheumatoid arthritis (RA) have a reduced life expectancy, with standardized mortality ratios ranging from 0.87 to 3.0. CVDs represent the main cause of death in both clinical and community-based cohorts of RA populations[32]. In addition, there is evidence that mechanisms determining enhanced CAD mortality in RA are present very early during the natural history of the disease.[33]

Several types of cardiac involvement can occur in RA. However, ischemic heart disease secondary to atherosclerosis seems to represent the main cause of CAD deaths in RA populations [33]. RA treatment and lifestyle of RA patients may favor physical inactivity, hypertension, diabetes mellitus, and obesity, but there is no clear evidence that these factors are implicated in accelerated atherosclerosis in RA [34].

Methotrexate, widely used to treat RA, increases plasma levels of homocysteine, which is a novel, and potentially modifiable, risk factor for CVD in the general population [33]. Concomitant folate supplementation during methotrexate treatment prevented that increase of homocysteine and, more importantly, reduced CVD mortality in RA patients.

RA by itself seems to represent a significant risk factor for early atherosclerosis and CAD/CVD development [34]. In this setting, a number of epidemiological, clinical, and laboratory investigations suggested that chronic inflammation and immune dysregulation characterizing RA have a key role in accelerating atherosclerosis [26,28,29].

In RA , atherosclerotic plaques are characterized by enhanced expression of adhesion molecules and by abundance of pro inflammatory cytokine-secreting cells attracted by locally activated endothelium and chemokines. The release of a number of collagen-breaking mediators is likely to exert a fundamental role in destabilization of atherosclerotic plaques as well as erosion of cartilage and bone into the RA joint [35]. According to these observations, it is conceivable that the chronic systemic inflammation characterizing RA may trigger early events, accelerating diffuse atherosclerosis development. It has been shown that excess cardiovascular mortality occurs prevalently in RA patients with more widely diffuse disease, with lung involvement and vasculitis, who have markers of systemic inflammation[35].

Although this may support a role for rheumatoid vasculitis in promoting atherosclerosis, there are several lines of evidence suggesting that a dysfunction, rather than a full-blown "vasculitic phenotype," is the leading event to early endothelial damage in RA [35]. Functional abnormalities of the endothelium have been found in distinct cohorts of RA patients, independently of patients' age, duration of the disease, degree of disease activity, or seropositivity .Despite the fact that different factors could alter endothelium homeostasis, prevalent data support the view that abnormal endothelial function in RA is essentially linked to inflammation [35]. Persistent endothelial dysfunction predisposes to organic damage of the vascular wall that, in a preclinical stage, before overt disease, can be detectable by ultrasound measurement of carotid intimal-medial thickness (CIMT)[5,35]. Many investigations provided evidence of increased carotid IMT in RA [36]. This finding could not be explained by

corticosteroid treatment but appeared to be essentially associated with markers of systemic inflammation and disease duration, thereby emphasizing the importance of RA as a risk factor for atherosclerosis[35,36].

Clinical Features

The typical case of rheumatoid arthritis begins insidiously, with the slow development of signs and symptoms over weeks to months. Patient first notices stiffness in one or more joints, usually accompanied by pain on movement and by tenderness in the joint. The number of joints involved is highly variable, but almost always the process is eventually polyarticular, involving five or more joints [15,37]. Occasionally, patients experience an explosive polyarticular onset occurring over 24 to 48 hours. Another pattern is a palindromic presentation, in which patients describe swelling in one or two joints that may last a few days to weeks then completely go away, later to return in the same or other joints, with a pattern increasing over time [37].

The joints involved most frequently are the proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joints of the hands, the wrists, and small joints of the feet including the metatarsophalangeal (MTP) joints . The shoulders, elbows, knees, and ankles are also affected in many patients. The distal interphalangeal (DIP) joints are generally spared. With the exception of the cervical spine, the spine is unaffected [39].

Nonspecific systemic symptoms primarily fatigue, malaise, and depression, may commonly precede other symptoms of the disease by weeks to months and be indicators of ongoing disease activity. Fatigue can be an especially troubling feature of the disease for many patients. The pattern of symptoms may wax and wane over the course of a day and even from one day to the next.

Morning stiffness, persisting more than one hour but often lasting several hours, may be a feature of any inflammatory arthritis but is especially characteristic of rheumatoid arthritis [38]. Its duration is a useful gauge of the inflammatory activity of the disease. Similar stiffness can occur after long periods of sitting or inactivity .

Sometimes "flares" of RA are experienced as an increase in these systemic symptoms more than discrete joint swelling or tenderness[38]. Fever occasionally occurs and is almost always low grade (37° to 38°C; 99° to 100°F), a high grade fever suggests infectious causes, especially in patients who are taking biological therapies and immunosuppressive medications[39].

Clinical Course

The course of rheumatoid arthritis cannot be predicted in a given patient. Several patterns of activity have been described:

Patterns of progression[38]:

Monocyclic pattern : A single cycle with remission for atleast one year, seen in 20 % of patients.

Polycyclic pattern : This is seen in 70 % of patients with either intermittent or continuing subtypes.

Progressive patterns : This is seen in 10 % of patients, with progressive increasing joint Involvement.

A spontaneous remission particularly in the seronegative patient within the first 6 months of symptoms (less than 10%)[38].

Disability is higher among patients with rheumatoid arthritis with 60% being unable to work 10 years after the onset of their disease [38]. Recent studies have demonstrated an increased mortality in rheumatoid patients . Median life expectancy was shortened by an average of 7 years for men and 3 years for women compared to control populations [39]. Patients at higher risk for shortened survival are those with systemic extra-articular involvement, low functional capacity, low socioeconomic status, low education, and prednisone use [38,39].

Physical examination

Symmetrical joint swelling is characteristic of rheumatoid arthritis that has been persistent for a period of time. However when only a few joints are affected at the beginning of disease, symmetry may not be seen and should not preclude the diagnosis of RA [14,38,39]. Careful palpation of the joints can help to distinguish the swelling of joint inflammation from the bony enlargement seen in osteoarthritis, with the swelling often described as being doughy or spongy in RA in contrast to firm knobby enlargement in osteoarthritis .

Swelling of the PIP and MCP joints of the hands is a common early finding . Wrists, elbows, knees, ankles and MTP are other joints commonly affected where swelling is easily detected. Pain on passive motion is a sensitive test for joint inflammation as is squeezing across the MCPs and MTPs. Occasionally inflamed joints will feel warm to the touch [39]. Inflammation, structural deformity, or both may limit the range of motion of the joint. Over time, some patients with RA develop deformities in the hands or feet. RA spares the distal joints of the fingers (DIPs) and the spine with the exception of the cervical spine (especially the atlanto-axial joint at C1-C2), which may become involved especially with longer standing disease [39].

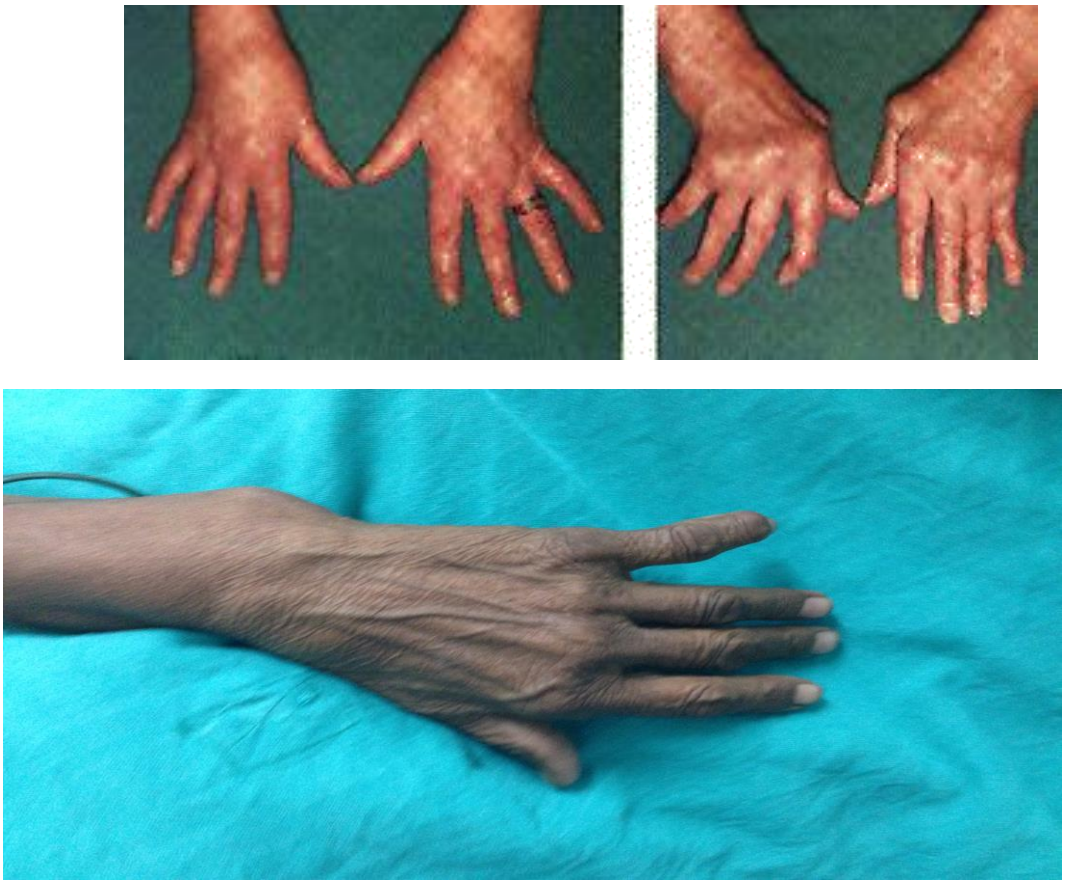


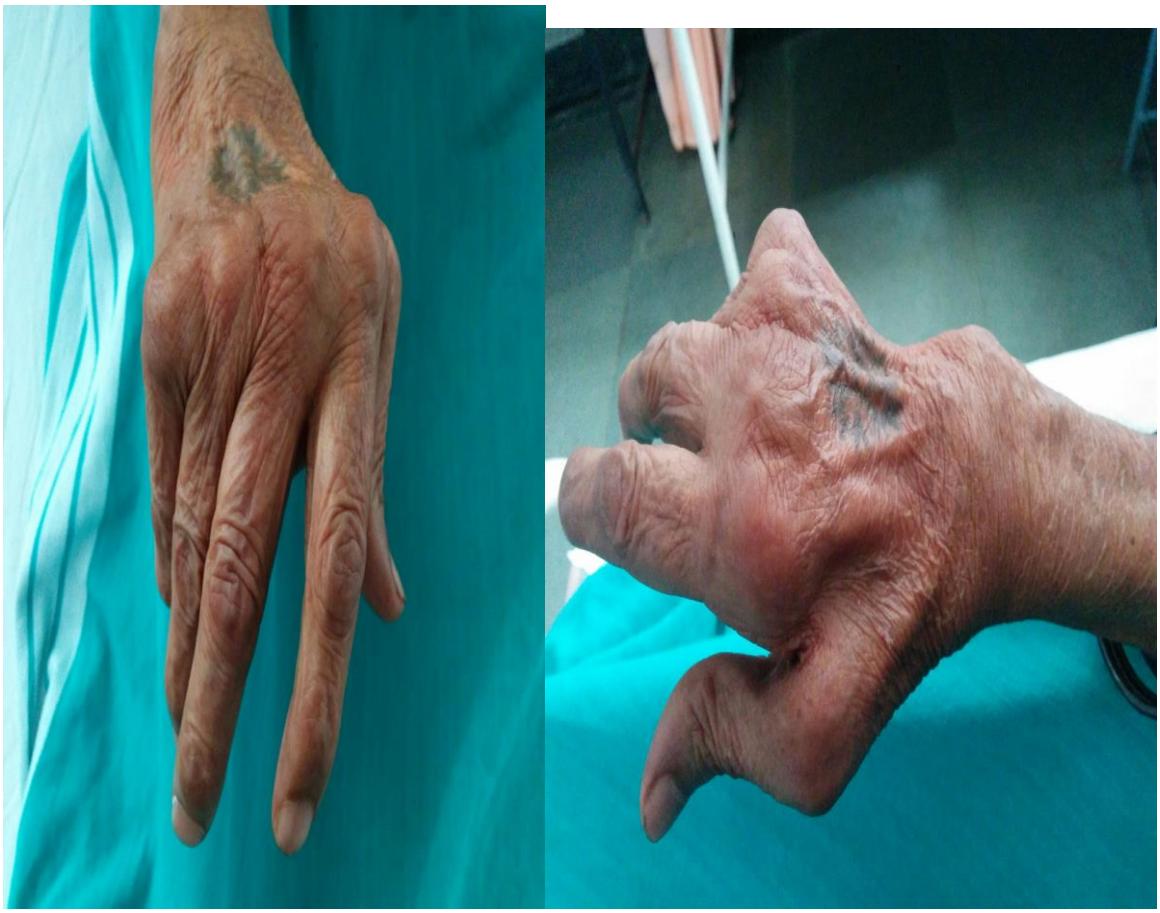
Figure 8 Effect of rheumatoid arthritis on the hand:

(left) early changes and (right)& below late deformity .

Permanent deformity is an unwanted result of the inflammatory process. Persistent tenosynovitis and synovitis leads to the formation of synovial cysts and to displaced or ruptured tendons [39]. Extensor tendon rupture at the dorsum of the hand is a common and disabling problem.

Advanced changes in RA include ulnar deviation of the fingers at the MCP joints, hyperextension or hyperflexion of the MCP and PIP joints, flexion contractures of the elbows, and subluxation of the carpal bones and toes (cocked -up) [39].

Figure 9 : ULNAR DEVIATION AND SWAN NECK DEFORMITY



Extraarticular manifestations:

Although the joints are almost always the principal focus of RA, other organ systems may also be involved. Extra-articular manifestations of RA occur most often in seropositive patients with more severe joint disease. Extra-articular manifestations can develop even in disease when there is little active joint involvement [40].

Rheumatoid Nodules. The subcutaneous nodule is the most characteristic extra-articular lesion of the disease. Nodules occur in 20 to 30% of cases, almost exclusively in seropositive patients [40]. They are located most commonly on the extensor surfaces of the arms and elbows (shown below) but are also prone to develop at pressure points on the feet and knees. Rarely, nodules may arise in visceral organs, such as the lungs, the heart, or the sclera of the eye[40].

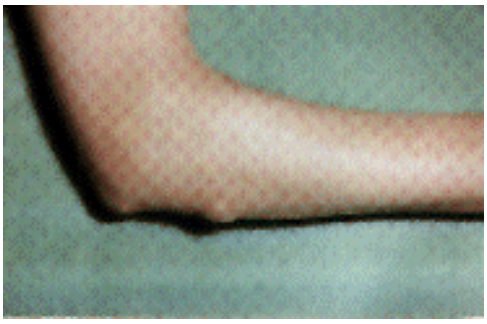


Figure 10: presence of rheumatoid nodule over the extensor aspect of forearm.

Cardiovascular disease in Rheumatoid Arthritis: Increased mortality from CAD in patients with RA has been reported [40].. The relative impact of RA on the risk of death from CAD appears to be greater in younger women, a group which in the general population has a low baseline risk. A community-based study from Finland , the largest reported increase of cardiovascular death in a group of RA patients was found among women aged 15-49 years, with a Standardized Mortality ratio (SMR) of 3.64 [41].

Several epidemiological studies have provided support for the increased incidence of cardiovascular events in RA compared with normal population [38,39,40,41]. The risk of AMI seems to be increased already within the first year after RA diagnosis as well as in patients with early inflammatory polyarthritis, especially in those who are RF positive[41].

This contrasts with the pattern for overall mortality, which has been found to be significantly increased only after more than 10 years of disease [41]. When studied, most traditional risk factors for developing cardiovascular disease appeared to be of importance also in patients with RA, but there is clearly an independent role for RA and a further increase of the risk in patients with severe disease and signs of systemic vascular inflammation [41]. RA has been suggested to be an independent cardiovascular risk factor comparable to diabetes mellitus [40,41].

Rheumatoid Arthritis and the lung :

RA is described as a systemic disease, which may involve the lungs. The nature of the relationship between inflammation in the lungs and in the joints is incompletely understood. In 1948, Ellman and Ball described three cases with classic manifestations of RA and extensive pulmonary involvement [41]. Since then a number of studies have focused on interstitial lung disease (ILD) among patients with established RA, with widely varying estimates of incidence and prevalence depending on the methods used . There is limited data on obstructive pulmonary disease in RA. Geddes et al found that 32 out of 100 patients with established RA had an obstructive lung disease, based on standard pulmonary function tests [42].

A number of pleura-pulmonary manifestations which are quite typical for RA, have been described, including íntra-pulmonary rheumatoid nodules . Pulmonary complications are common and have been reported to be directly responsible for 10 to 20% of all mortality [42].

while the prevalence of other severe ExRA seems to be declining , estimates of the incidence of RA-associated lung disease have been increasing, probably due to the improved availability of diagnostic tests [41,42]. Pulmonary infection and drug induced lung disease are common and important differential diagnosis.

Eye Disease : Keratoconjunctivitis of Sjogren's syndrome is the most common ocular manifestation of rheumatoid arthritis. Sicca (dry eyes) is a common complaint [42]. Episcleritis occurs occasionally and is manifested by mild pain and intense redness of the affected eye. Scleritis and corneal ulcerations are rare but more serious problems.

Sjogren's Syndrome. Approximately 10 to 15% of patients with rheumatoid arthritis develop Sjogren's syndrome, a chronic inflammatory disorder characterized by lymphocytic infiltration of lacrimal and salivary glands [42].

Sjogren's syndrome is an autoimmune condition that affects exocrine gland function, leading to a reduction in tear production (keratoconjunctivitis sicca), oral dryness (xerostomia) with decreased saliva of poor quality, and reduced vaginal secretions.

A polyclonal lymphoproliferative reaction characterized by lymphadenopathy is also seen, and patients have an increased risk of developing lymphoma [42].

Rheumatoid Vasculitis: The most common clinical manifestations of vasculitis are small digital infarcts along the nailbeds. The abrupt onset of an ischemic mononeuropathy (mononeuritis multiplex) or progressive scleritis is typical of rheumatoid vasculitis. The syndrome ordinarily emerges after years of seropositive, persistently active rheumatoid arthritis; however, vasculitis may occur when joints are inactive [42].

Neurologic Disease: The most common neurologic manifestation of rheumatoid arthritis is a mild, primarily sensory peripheral neuropathy, usually more marked in the lower extremities. Entrapment neuropathies (e.g., carpal tunnel syndrome and tarsal tunnel syndrome) sometimes occur in patients with rheumatoid arthritis because of compression of a peripheral nerve by inflamed edematous tissue [41]. Cervical myelopathy secondary to atlantoaxial subluxation is an uncommon but particularly worrisome complication potentially causing permanent neurologic damage.

Felty's syndrome is less commonly encountered than in the past. This is characterized by splenomegaly, and leukopenia – predominantly granulocytopenia [41,42]. Recurrent bacterial infections and chronic refractory leg ulcers are the major complications.

LABORATORY TESTS IN RHEUMATOID ARTHRITIS

No laboratory test will definitively confirm a diagnosis of rheumatoid arthritis. However, the information from the following tests contributes to diagnosis and management.

- Complete blood count (CBC)
- Comprehensive metabolic panel (CMP)
- Erythrocyte Sedimentation Rate (ESR)
- C-reactive protein (CRP)
- Rheumatoid Factor (RF)
- Antibodies to citrullinated peptides (anti-CCP)

The blood count shows a mild anemia in approximately 25 to 35% of patients with RA [45]. The white cell count is usually normal in patients with rheumatoid arthritis, but can be mildly elevated secondary to inflammation, and can also be very low in a subgroup of patients with Felty's syndrome. Similarly, the platelet count is usually normal but thrombocytosis occurs in response to inflammation [45].

Liver function tests are usually normal in rheumatoid arthritis with the exception of a slight decrease in albumin and increase in total protein reflecting the chronic inflammatory process [45]. Renal and liver function are important to check before beginning treatment and are followed over time with many medications.

Measures of inflammation are often, but not always increased in RA [46]. The erythrocyte sedimentation rate (ESR) is usually elevated in patients with RA and in some patients is a helpful adjunct in following the activity of the disease. The C-reactive protein (CRP) is another measure of inflammation that is frequently elevated, and improves with control of disease activity [45].

A positive rheumatoid factor is present in 70-80% of patients with RA and can be negative in 30 % of patients [10] . A positive Anti-CCP is a more specific marker for RA and is found in similar proportions of patients over the course of disease. High levels of Anti-CCP also appear to be linked to a greater severity of the disease [46].

Radiographic Findings In Rheumatoid Arthritis

Erosions of bone and destruction of cartilage, occur rapidly and may be seen within the first 2 years of the disease, but continue to develop over time [46]. These anatomic changes result in limitations in range of motion, flexion contractures, and subluxation (incomplete dislocation) of articulating bones.

Typical deformities include ulnar deviation of the fingers at the MCP joints, hyperextension or hyperflexion of the MCP and PIP joints (swan neck and boutonniere deformities), flexion contractures of the elbows, and subluxation of the carpal bones and toes (hammer toes and cock up deformities). Radiological findings early in the disease may show nothing other than soft tissue swelling. Thereafter, periarticular osteopenia may develop.

With progression of their disease, narrowing of the joint space is caused by loss of cartilage, and juxta-articular erosions appear, generally at the point of attachment of the synovium. In end-stage disease, large cystic erosions of bone may be seen [46].

More recently the introduction of ultrasound and MRI imaging has imporved the sensitivity of detecting joint damage earlier in disease. Ultrasound may detect synovitis, effusions, and erosions, in addition to power Doppler providing estimates of ongoing inflammation.

MRI may show inflammatory synovitis that enhances with Gadolinium and shows early erosions. The role for these modalities in following patients over time in clinical practice is still not well established, but these methods may improve the ability to detect early disease and confirm a diagnosis [45,46].

Diagnostic Considerations

DIFFERENT CRITERIA HAVE BEEN PRAPOSED FOR RHEUMATOID ARTHRITIS:

1) The American Rheumatism Association criteria of 1958.

2) 1987 revised criteria for the classification of rheumatoid arthritis

3)ACR/EULAR CRITERIA FOR RHEUMATOID ARTHRITIS.

Rheumatoid arthritis is diagnosed from a constellation of clinical and laboratory or radiographic abnormalities. Diagnosis may be obvious in some but in others it may be more difficult and require a period of clinical observation. Classification criteria for RA have been devised. The 1987 revised criteria for the classification of rheumatoid arthritis as shown in TABLE 2 ; it superseded The American Rheumatism Association criteria of 1958.

These criteria were derived from a group of typical patients who had been diagnosed with RA and had well-established disease. They have limited utility in routine practice and most clinicians diagnose RA without formal reference to such criteria, and many patients do not meet formal criteria at least early in disease as described by Harrison et al in 1998 .

Atleast 4 criteria's must be present of the following in a given patient and criteria 1-4 should be present for a period of 6 weeks to make a diagnosis of RA.

The newer criteria demonstrated 91-94% sensitivity and 89% specificity for RA when compared with non-RA rheumatic disease control subjects. Two diagnostic tests were included in the criteria: rheumatoid factor and X-ray changes.

Table 2 :1987 Criteria for the Classification of Acute Arthritis of RA[47].

S.NO	Criterion	Definition
1.	Morning stiffness	Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement
2.	Arthritis of 3 or more joint areas	At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints
3.	Arthritis of hand joints	At least 1 area swollen (as defined above) in a wrist, MCP, or PIP joint
4.	Symmetric arthritis	Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry)
5.	Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxtaarticular regions, observed by a physician
6	Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal control subjects
7.	Radiographic changes	Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)

TABLE 3 : CLASSIFICATION OF GLOBAL FUNCTIONAL STATUS IN RA

Class i	Completely able to perform usual activities of daily living (self care, vocational, and avocational)
Class ii	Able to perform usual self care and vocational activities, but limited in avocational activities.
Class iii	Able to perform usual self care activities,but limited in vocational and avocational activities
Class iv	Limited in ability to perform usual selfcare,vocational and avocational activities.

Usual self care activities include dresssing,feeding,grooming and toileting.

Avocational include recreational and for leisure.

Vocational includeswork,school,homemaking activities are patient desired and age & gender specific.

TABLE 4: RA ACR/EULAR CRITERIA 2010

S.NO	FACTORS	CLINICAL DESCRIPTION	POINTS
1)	**NUMBER OF SITES INVOLVED**	• 2 TO 10 LARGE JOINTS(SHOULDER,ELBOW,HIP,KNEE,ANKLE) • 1 TO 3 SMALL JOINTS(MCPJ,PIPJ,2TO 5TH MTPJ,THUMB IPJ,WRIST) • 4 TO 10 SMALL JOINT. • >10 JOINTS(INCLUDING ATLEAST 1 SMALL JOINT)	1 POINT 2 POINTS 3 POINTS 5 POINTS
2)	**SEROLOGICAL ABNORMALITY**	RA FACTOR OR ANTI-CITRULLINATED PEPTIDE/PROTEIN ANTIBODY POSITIVE LOW POSITIVE (ABOVE THE UPPER LIMIT OF NORMAL) HIGH POSITIVE (GREATER THAN THREE TIMES THE ULN)	 2 POINTS 3 POINTS
3)	**ELEVATED ACUTE PHASE RESPONSE**	ESR OR CRP	1 POINT
4)	**SYMPTOM DsURATION**	> 6 WEEKS	1 POINT.

score-based algorithm: add score of categories A–D; a score of ≥6/10 is needed for classifcation of a patient as having defnite RA [47].

ACR/EULAR classification criteria for RA

Joint involvement refers to any swollen or tender joint on examination, which may be confirmed by imaging evidence of synovitis. DIP joints , first carpometacarpal joints, and first MTP joint are excluded from assessment. Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement.

"Large joints" refers to shoulders, elbows, hips, knees, and ankles.

"Small joints" refers to the MCP joints, PIP joints, second through ?fth MTP joints, thumb PIP or DIP joints, and wrists.

In this category, at least 1 of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (e.g., temporomandibular, acromioclavicular, sternoclavicular, etc.).

Negative refers to IU values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are higher than the ULN .

But ≤3 times the ULN for the laboratory and assay; high-positive refers to IU values that are >3 times the ULN for the laboratory and assay. Where RF information is only available as positive or negative, a positive result should be scored as low-positive for RF.

Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (e.g., pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status.

The new ACR/EULAR classification criteria for RA identify many patients with positive test for the rheumatoid factor (RF) or antibodies to cyclic citrullinated peptides (anti-CCP) at an earlier time point, and most likely reflect current man- agement in many early arthritis clinics better than the 1987 ACR criteria. A recent study of an early arthritis cohort from Holland

reported that, compared with the 1987 criteria, the 2010 ACR/EULAR criteria classify more patients with RA and at an earlier phase of the disease. They also found that the discriminative ability of the 2010 criteria is acceptable [47].

TREATMENT OF RHEUMATOID ARTHRITIS

Rheumatoid arthritis is a chronic disorder for which there is no known cure [48]. Fortunately in the last few years, a shift in strategy toward the earlier institution of disease modifying drugs and the availability of new classes of medications have greatly improved the outcomes that can be expected by most patients. The goal of treatment now aims toward achieving the lowest possible level of arthritis disease activity and remission if possible, minimizing joint damage, and enhancing physical function and quality of life. The optimal treatment of RA requires a comprehensive program that combines medical, social, and emotional support for the patient [48]. It is essential that the patient and the patient's family be educated about the nature and course of the disease. Treatment options include medications, reduction of joint stress, physical and occupational therapy, and surgical intervention.

There are three general classes of drugs commonly used in the treatment of rheumatoid arthritis:

1) non-steroidal anti-inflammatory agents (NSAIDs)
2) corticosteroids,
3) Disease modifying anti-rheumatic drugs (DMARDs).

NSAIDs and corticosteroids have a short onset of action while DMARDs can take several weeks or months to demonstrate a clinical effect.

DMARDs include methotrexate, sulfasalazine, leflunomide, etanercept, infliximab, adalimumab, certolizumab, golimumab, abatacept,rituximab, tocilizumab, anakinra and

antimalarials. Other immunomodulators are occasionally used including azathioprine and cyclosporine. Because cartilage damage and bony erosions frequently occur within the first two years of disease, rheumatologists now move aggressively to a DMARD agent early in the course of disease, usually as soon as a diagnosis is confirmed [11].

Analgesic drugs are also sometimes helpful in decreasing pain until DMARDs take effect.

Non-steroidal Anti-inflammatory Agents (NSAIDs):

The major effect of these agents is to reduce acute inflammation thereby decreasing pain and improving function. All of these drugs also have mild to moderate analgesic properties independent of their anti-inflammatory effect [11,48,]. It is important to note however that these drugs alone do not change the course of the disease of rheumatoid arthritis or prevent joint destruction.

Aspirin is the oldest drug of the non-steroidal class, but because of its high rate of GI toxicity, a narrow window between toxic and anti-inflammatory serum levels, and the inconvenience of multiple daily doses, aspirin's use as the initial choice of drug therapy has largely been replaced by other NSAIDs. There are a large number of NSAIDs from which to choose, and at full dosages all are potentially equally effective. Likewise, the toxicities of the currently available NSAIDs are similar. However, there is a great deal of variation in tolerance and response to a particular NSAID. Many different NSAIDS are available, some over the counter including ibuprofen and naproxen and many others are available by prescription including meloxicam, nabumetone,choline magnesium salicylate ,diclofenac,diflusinal, indomethicin, ketoprofen, meloxicam, oxaprozin, and piroxicam [11,48]. Longer acting NSAIDs that allow daily or twice daily dosing may improve compliance. The NSAID class also includes drugs known as COX-2 inhibitors that are also effective in controlling inflammation. These drugs were designed to decrease the gastrointestinal risk of NSAIDS, but concerns of

possible increases in cardiovascular risk with rofecoxib & valdecoxib had led to the withdrawal these two drugs from the market [11,49].

Mechanism of action of NSAIDs:

NSAIDs inhibit the generation of prostaglandins by blocking cyclooxygenase enzymes, COX-1 and COX-2. Prostaglandins are mediators of inflammation and pain but also have important roles in maintenance of normal body functions including protection from stomach acid, maintenance of kidney blood flow, and contributing to platelet stickiness and vascular function. COX-2 selective inhibitors selectively block prostaglandins generated via COX-2 which have prominent roles in inflammation.

D**osage:** While in some cases, lower doses of NSAIDS are effective, in rheumatoid arthritis and other forms of inflammatory arthritis a higher dose is often required to decrease inflammation. A lower dosage can initially be used if inflammation is mild, if mechanical pain is the major problem, if the patient is elderly or if the patient suffers from conditions that increase the risk for toxicity . If a particular preparation is ineffective after a 4-week trial or is not tolerated, then another NSAID can be initiated. No one NSAID has been demonstrated to be better than another for the treatment of rheumatoid arthritis nor have the COX-2 agents been shown to be superior to traditional NSAIDS in terms of effectiveness.

Time to Effect: Although these agents have anti-inflammatory effect within hours, a reasonable trial period is a few weeks to 1 month.

Side Effects: The most common toxicity of NSAIDs is gastrointestinal disturbance which may clinically include burning, belching, or irritation, but which can represent irritation of the lining of the stomach, erosions, and even ulcerations that can result in bleeding. While taking the medication with food may eliminate some of these symptoms, this does not decrease a risk of bleeding. The co-administration of medications known as proton pump inhibitors such

as omeprazol,Lansoprazole,Esomeprazole,Pantoprazole and Rabeprazole and a medication that provides back protective prostaglandins called misoprostol can also decrease gastrointestinal bleeding associated with these medications. Misoprostol is combined in a single pill with the NSAID diclofenac. Selective COX-2 inhibitors exhibit safer GI profiles than conventional non-selective NSAIDs [11],[49].

Because prostaglandins play a role in the regulation of the blood flow in the kidneys and maintenance of glomerular filtration, NSAIDs can also impair renal function in certain patients leading to salt retention, edema, and increased blood pressure. The patients at highest risk are those with fluid imbalances or with compromised kidney function (e.g., heart failure, diuretic use, cirrhosis, dehydration, and renal insufficiency) [49]. NSAIDs may also increase cardiovascular risks by their effects on blood pressure and additional effects on vascular beds. Thus the use of this class of medications must into account their relative risks in an individual patient of gastrointestinal damage versus potential cardiovascular risk factors[11,49].

Corticosteroids

Corticosteroids such as prednisone; methylprenisolone, have both anti-inflammatory and immunoregulatory activity. They can be given orally, intravenously, intramuscularly or can be injected directly into the joint. Corticosteroids are useful in early disease as temporary adjunctive therapy while waiting for DMARDs to exert their antiinflammatory effects. Corticosteroids are also useful as chronic adjunctive therapy in patients with severe disease that is not well controlled on NSAIDs and DMARDs[11]. The usual dose of predinisone is 5 to 10mg daily. Although prednisone can be started at higher doses (15 to 20mg daily), attempts should be made to taper the dose over a few weeks to less than 10mg daily. Once started, corticosteroid therapy may be difficult to discontinue and even at low doses. Some patients

are very sensitive to the tapering of prednisone which may be done slowly over a few weeks [11,50].

Weight gain and a cushingoid appearance (increased fat deposition around the face, redness of the cheeks, development of a "buffalo hump" over the neck) is a frequent problem . Other side effects of prednisone include weight gain, increased blood pressure, increased blood sugar, increased risk of cataracts, and avascular necrosis of bones [11,50].

Steroid medications are also associated with accelerated osteoporosis even with relatively low dose prednisone at doses of 10 mg daily. Patients with and without osteoporosis risk factors on low dose prednisone should undergo bone densitometry to assess fracture risk. Bisphosphonates such as alendrona, risedronate , ibandronate are recommended to prevent and/or treat osteoporosis in addition to adequate calcium and vitamin D supplementation[50].

Higher doses of prednisone are rarely necessary unless there is a life-threatening complication of RA and, if used for prolonged periods, may lead to serious steroid toxicity. few patients can tolerate every other day dosing of corticosteroids which may reduce side effects, most require corticosteroids daily to avoid symptoms.

Once a day dosing of prednisone is associated with fewer side effects than the equivalent dose given twice or three times daily. Generally steroids are given in the morning upon wakening to mimic the body's own steroid surge [50]. Repetitive short courses of high-dose corticosteroids, intermittent intramuscular injections, adrenocorticotropic hormone injections, and the use of corticosteroids as the sole therapeutic agent are all to be avoided. Intra-

articular corticosteroids (e.g., triamcinolone or methylprednisolone and others) are effective for controlling a local flare in a joint without changing the overall drug regimen [50].

Disease Modifying Anti-rheumatic Drugs (DMARDS)

Although both NSAIDs and DMARD agents improve symptoms of active rheumatoid arthritis, only DMARD agents have been shown to alter the disease course and improve radiographic outcomes. DMARDs have an effect upon rheumatoid arthritis that is different and may be slower. In most cases, when the diagnosis of rheumatoid arthritis is confirmed, DMARD agents should be started [11]. The presence of erosions or joint space narrowing on x-rays of the involved joints is a clear indication for DMARD therapy, however one should not wait for x-ray changes to occur. The currently available drugs include:

•Methotrexate

•Hydroxychloroquine

•Sulfasalazine

•Leflunomide

Tumor Necrosis Factor Inhibitors— etanercept and infliximab, certolizumab pegol, golimumab.

•T-cell Costimulatory Blocking Agents—abatacept

•B cell Depleting Agents—rituximab

•Interleukin-6 (IL-6) Inhibitors– tocilizumab

•Interleukin-1 (IL-1) Receptor Antagonist Therapy—anakinra

•Intramuscular Gold

•Other Immunomodulatory and Cytotoxic agents— azathioprine and cyclosporine A

Methotrexate

Methotrexate is now considered the first-line DMARD agent for most patients with RA [11]. It has a relatively rapid onset of action at therapeutic doses (6-8 weeks), good efficacy, favorable toxicity profile, ease of administration, and relatively low cost. Majority of patients continue to take Methotrexate after 5 years, far more than other therapies reflecting both its efficacy and tolerability. Methotrexate is effective in reducing the signs and symptoms of RA, as well as slowing or halting radiographic damage. It is as effective as leflunomide and sulfasalazine in one study and its effectiveness given early and in higher doses approached the efficacy of etanercept and adalimumab as single therapies in terms of signs and symptom improvement [99]. Methotrexate is also effective in many other forms of inflammatory arthritis including psoriatic arthritis and other spondyloarthopathies, and is used in many other autoimmune diseases.

Mechanism: The anti-inflammatory effects of methotrexate in rheumatoid arthritis appear to be related at least in part to interruption of adenosine and possible effects on other inflammatory and immunoregulatory pathways. The immunosuppressive and toxic effects of methotrexate are due to the inhibition of an enzyme involved in the metabolism of folic acid, dihydrofolate reductase.

Dosage: Dosing typically begins at 12.5-15 mg once per week. A dose escalation to 20 mg within the first three months is now fairly well accepted in clinical practice. Maximal dose is usually 25 mg per week but is sometimes increased further to 30 mg. Methotrexate can be given orally or by subcutaneous injection. The latter route of administration can be advantageous for patients who have methotrexate-associated nausea. Patients starting methotrexate should be carefully evaluated for renal insufficiency, acute or chronic liver disease, significant alcohol intake or alcohol abuse, leukopenia (low white blood cell counts), thrombocytopenia (low platelet counts), or untreated folate deficiency.

Obesity, diabetes and history of hepatitis B or C are factors that have been suggested but not confirmed to increase methotrexate hepatotoxicity (liver injury). Salicylates (and other NSAIDs) and the antibiotic trimethoprim block the renal excretion of methotrexate and increase serum levels with an increased risk of toxicity. If alternatives exist, concomitant use of methotrexate and trimethoprim is to be avoided. The coadministration of NSAIDS with methotrexate is routine in patients with rheumatoid arthritis and is considered safe by rheumatologists as long as liver function tests and blood counts are closely monitored [51].

Time to Effect: The onset of action is seen in as early as 4 to 6 weeks. However the dose required to achieve a response is variable in individual patients and may require 4-6 weeks after a dose increase to determine if the drug is working. A trial of 3 to 6 months at an increased dose (e.g. 20 mg/wk) is suggested. In patients with partial responses to methotrexate, additional medications are usually added to rather than substituted for methotrexate to achieve combination therapies.

Side Effects: Fortunately the most serious complications of methotrexate therapy: hepatic cirrhosis, interstitial pneumonitis, and severe myelosuppression are quite rare, especially with proper monitoring. Stomatitis and oral ulcers, mild alopecia and hair thinning, and GI upset may occur and are related to folic acid antagonism. These side effects can be improved with folic acid supplementation. Folic acid given at a dose of 1mg daily does not diminish the efficacy of methotrexate and is routinely given with methotrexate to decrease these side effects. Some patients complain of headache, fatigue, and feeling “wiped out” (also called methotrexate “fog”) [52]. These side effects can often be overcome by increasing folic acid or using an activated form of folic acid known as folinic acid given as a 5mg dose 12 hours and sometimes 24 hours after methotrexate is given. Some patients complain of nausea or

diarrhea with oral methotrexate. This may be lessened when methotrexate is taken at night. In most cases this is completely eliminated when methotrexate is given by subcutaneous administration.

Methotrexate can be combined safely with nearly every other FDA-approved DMARDs for RA, including sulfasalazine, hydroxychloroquine, TNF inhibitors, abatacept, rituximab, tocilizumab, anakinra, and leflunomide. In all clinical trials combining methotrexate with one of these DMARDs, no unexpected toxicities or synergistic toxicities were observed with the exception of higher liver toxicity with leflunomide which is also metabolized by the liver[52].

Hepatotoxicity (liver injury) has not been significant if patients with pre-existing liver disease, alcohol abuse, or hepatic dysfunction are excluded from treatment with methotrexate. Patients are instructed to limit alcohol containing beverages to no more than one-two per week. Baseline or surveillance liver biopsies are not indicated unless pre-existing liver disease is suspected. Elevated liver enzymes do not directly correlate with toxicity but therapy should be stopped and doses of methotrexate reduced if transaminases are elevated to 2 times the upper limit of normal. Liver biopsy should be done if elevated liver enzymes persist or if methotrexate therapy is to be continued [52].

Interstitial pneumonitis is a rare complication of methotrexate (<2%), but clinicians should be alert to symptoms of cough or shortness of breath that may herald the onset of this severe complication. Methotrexate pneumonitis may occur at any time during therapy and is not dose related [53]. A baseline chest x-ray is useful for comparison. Patients with poor pulmonary reserve from other causes may be excluded from therapy over concerns of increased morbidity if methotrexate pneumonitis occurs. A more chronic form of interstitial lung

disease and fibrosis is also seen in patients with rheumatoid arthritis. This may be increased with methotrexate.

Myelosuppression (lowering of blood counts) is also rare at the low doses of methotrexate utilized for rheumatoid arthritis. Patients at particular risk include those with renal insufficiency from other causes or use of trimethoprim which increases levels of methotrexate. In the absence of leukopenia (lowered white blood cell counts), there has not been conclusive information to link methotrexate use in rheumatoid arthritis with increased risk of infection. The exception is a slight increased risk of localized herpes zoster infection (shingles)[53].

Cancer risk with methotrexate. Although there are case reports of lymphoma associated with methotrexate therapy including cases where the lymphoma resolved after cessation of therapy, increased occurrence of malignancy has not been found in large population-based studies. It is important to recognize that patient with rheumatoid arthritis have an increased risk of developing lymphoma as a consequence of their autoimmune disease, independently from any potential medication effects.

Pregnancy and Conception with methotrexate. There have not been any notable effects on sperm production or ovarian function after the prolonged administration of methotrexate. However, methotrexate is considered a teratogen; therefore, women of childbearing potential or men with partners of childbearing potential must practice effective birth control. Women should discontinue methotrexate for at least one ovulatory cycle prior to attempting conception, while men should wait 3 months [53].

Hydroxychloroquine:

Hydroxychloroquine is an antimalarial drug which is relatively safe and well-tolerated agent for the treatment of rheumatoid arthritis. Chloroquine is another antimalarial agent that is also sometimes used. Because these drugs have limited ability to prevent joint damage on their own, their use should probably be limited to patients with very mild, seronegative, and nonerosive disease. Hydroxychloroquine is sometimes combined with methotrexate for additive benefits for signs and symptoms or as part of a regimen of "triple therapy" with methotrexate and sulfasalazine[11,54].

The mechanism of action of antimalarials in the treatment of patients with rheumatoid arthritis is unknown but is thought to involve changes in antigen presentation or effects on the innate immune system.

Dosage: Hydroxychloroquine is the drug of choice among antimalarials. Chloroquine is not commonly used because of greater toxicity on the eye. The usual dose of hydroxychloroquine is 400mg/day but 600mg/day is sometimes used as part of an induction regimen [11]. It may be prescribed as a single daily dose or in divided doses twice per day.

Time to Effect: A period of 2 to 4 months is the usual time for effect of HCQ's. If a patient shows no response after 5-6 months that this should be considered a drug failure.

Side Effects: The most important toxicities are on the eyes: corneal deposits, extraocular muscular weakness, loss of accommodation and sensitivity to light, and retinopathy that may progress to irreversible visual loss. Ocular toxicity is exceedingly rare, occurring in only 1 out of 40,000 patients treated at the doses recommended. Patients with underlying retinopathies or risks may not be good candidates for antimalarial drugs. Baseline

ophthalmologic examination and a follow-up examination every 12 months are recommended during the period of treatment.

Sulfasalazine

Sulfasalazine is an effective DMARD for the treatment of RA. Its effectiveness overall is somewhat less than that of methotrexate, but it has been shown to reduce signs and symptoms and slow radiographic damage. It is given in conjunction with methotrexate and hydroxychloroquine as part of a regimen of "triple therapy" which has been shown to provide benefits to patients who have had inadequate responses to methotrexate alone. Sulfasalazine is also used in the treatment of inflammatory bowel disease and spondyloarthropathies [11]. Its mechanism of action in RA is unknown. Some of its effects may be due to folate depletion.

Dosage: The usual dose is 2-3 grams per day in a twice daily dosing regimen. The dose may be initiated at 1 gram per day and increased as tolerated.

Time to Effect: It may take 6 weeks to 3 months to see the effects of sulfasalazine [53].

Side effects: Sulfasalazine may cause hypersensitivity and allergic reactions in patients who have experienced reactions to sulfa medications. Mild gastrointestinal complaints are commonly seen and these can be decreased by using enteric coated formulations or administration of the medication with meals. Occasionally, mild cytopenias are seen. Patients should be screened before the use of sulfasalazine for a deficiency of the enzyme glucose-6-phosphate dehydrogenase (G6PD) which predispose patients to red blood cell hemolysis and anemia [53]. Blood monitoring is typically every 1-3 months depending on dose.

Though sulfasalazine may cause increases in liver function tests, it is generally considered a preferable agent to methotrexate in patients with liver disease or in patients who have hepatitis B or C.

Leflunomide

Leflunomide is also an effective DMARD. Its efficacy is similar to methotrexate in terms of signs and symptoms, and is a viable alternative to patients who have failed or are intolerant to methotrexate. Leflunomide has been demonstrated to slow radiographic progression. Studies have demonstrated that it can also be carefully combined with methotrexate in patients with no preexisting liver disease, as long as the liver function tests are carefully monitored. Leflunomide has also been studied in psoriatic arthritis with some efficacy demonstrated.

The mechanism of action of leflunomide is not fully understood but may be related to its ability to inhibit de novo pyrimidine biosynthesis through the inhibition of the enzyme dihydroorotate dehydrogenase. Laboratory studies have demonstrated that it also has effects on stimulated T cells.

Dosage: The half-life of the active metabolite of leflunomide is very long. Leflunomide and its metabolites are extensively protein bound and undergo further metabolism before excretion. When initially approved, the medication was given using a loading dose of 100mg daily for three days then followed by 20 mg daily. Due to a significant incidence of GI side effects and diarrhea, most practitioners now use a shorter loading period with lower doses or initiate treatment at 10-20 mg/day with no loading dose,. The dose may be reduced to 10mg daily if not tolerated at the 20 mg dose.

Time to Effect: The onset of action is relatively rapid within 4-8 weeks. The onset of action of Arava may be seen earlier than methotrexate when using a loading dose.

Side Effects: Leflunomide has been associated with liver transaminase elevations that reversed with cessation of the drug in clinical trials. Routine monitoring should include complete blood count and hepatic panel more frequently at the beginning of therapy then on a regular basis (at least every 2 months). Other toxicities that are common include mild diarrhea, GI upset and alopecia and hair thinning sometimes of sufficient severity to cause cessation of the drug.

Because leflunomide and its metabolites are a teratogen, extreme care must be taken for treatment of women of child bearing potential. Women must be warned about the possible risk to the fetus and cautioned to use adequate birth control. Women wishing to become pregnant must take cholestyramine 8gm 3 times daily for 11 days and then have two leflunomide metabolite levels drawn 14 days apart to document serum concentration less than 0.02mg/L. Leflunomide treatment does not appear to be associated with an increased risk for infection [54].

Tumor necrosis factor (TNF) inhibitors

Tumor necrosis factor alpha (TNF) is a pro-inflammatory cytokine produced by macrophages and lymphocytes. It is found in large quantities in the rheumatoid joint and is produced locally in the joint by synovial macrophages and lymphocytes infiltrating the joint synovium. TNF is one of the critical cytokines that mediate joint damage and destruction due to its activities on many cells in the joint as well as effects on other organs and body systems. TNF antagonists were the first of the biological DMARDS to be approved for the treatment of RA. These drugs began to enter the market for rheumatoid arthritis in 1999 and are now

considered a part the ACR recommendations for treatment of RA. There are currently five TNF inhibitors FDA approved for the treatment of RA (listed in order of their approval for RA); etanercept, infliximab , adalimumab ,certolizumab pegol , and golimumab . Etanercept if a soluble TNF receptor-Fc immunoglobulin fusion construct; infliximab, adalimumab, and golimumab are monoclonal antibodies; and certolizumab pegol is an anti-TNF antigen binding domain-polyethylene glycol construct. While differing in structure, the efficacy and safety of the drugs is similar across the class in reducing the signs and symptoms of RA, as well as in slowing or halting radiographic damage, when used either as monotherapy or in combination with methotrexate [54].

Time to Effect: TNF inhibitors have a rapid onset of action sometimes with improvements seen within 2 to 4 weeks. However, additional improvements can be seen over 3-6 months.

Side Effects: With all TNF antagonists, there is an increased risk of infection both mild and severe. The most common are upper respiratory infections, pneumonia, urinary tract infections, and skin infections. Studies are currently ongoing regarding the practice of temporarily holding the administration of any biologic DMARD in the presence of infection and use of antibiotics[11,53,54].

Disseminated tuberculosis due to reactivation of latent disease has been seen with all TNF inhibitors; therefore, screening for latent TB is prudent before treatment with any TNF inhibitor. Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis have all been seen in patients receiving TNF inhibitors. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-

fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness. Because reactivation of Hepatitis B has been seen with TNF use, patients should be screened before beginning TNF therapy [54].

In some clinical trials of TNF antagonists, lymphomas were more commonly observed in patients treated with TNF inhibitors compared to placebo controls but the incidence rates do not appear, at this time, to exceed those reported in the RA population prior to the availability of TNF inhibitors [54]. It is important to note that RA itself is a risk factor for Non-Hodgkins lymphomas. Other malignancies have been seen in patients taking TNF inhibitors. There does appear to be an increase in non melanoma skin cancer (basal and squamous cell) in patients receiving these agents. Regular dermatologic assessment is recommended with any suspicious lesions promptly evaluated. The administration of TNF inhibitors in patients with a prior malignancy should be discussed with the patient and their oncologist to assess potential risk and benefit. TNF inhibitors are not recommended in patients with demyelinating disease or with congestive heart failure [55]. Transient neutropenia (lowering of white blood cell counts) or other blood dyscrasias have been reported with TNF inhibitors. Some patients develop positive antinuclear antibodies (ANA), and cases of clinical lupus are reported but rare. The new onset of psoriasis has also been seen.

T-cell Co-stimulatory blockade

Abatacept

Abatacept is the first of a class of agents known as T-cell co-stimulatory blockers. These agent interfere with the interactions between antigen-presenting cells and T lymphocytes and affect early stages in the pathogenic cascade of events in rheumatoid arthritis. T lymphocytes become activated due to an unknown stimulus but likely involving the interaction between

antigen presented in the context of the Class II Major Histocompatability Complex molecule on the surface of antigen presenting cells. T cells recognize antigens as foreign and if they receive a second stimulus, will become active, proliferate, traffic to inflamed sites, and secrete proinflammatory cytokines including TNF. One of the important second signals for T cell activation is mediated by the molecules CD80 and CD86 found on antigen presenting cells and the CD28 molecule on the T cell surface.

Mechanism of action: Abatacept is a fusion protein that combines the extracellular domain of the molecule CTLA4 (CD154) with the Fc portion of a human immunoglobulin molecule. CTLA4 has very high affinity for CD28 [55]. When abatacept binds to CD28 on the T cell surface, it prevents the second signal from being delivered, thus turning down the T cell response. Additional effects are decreasing the production of T cell derived cytokines including TNF.

Dosing: Abatacept is administered either via IV or subcutaneously. When given by intravenous infusion it is used once per month after initial doses at baseline, 2 weeks, and 4 weeks. The IV dose is based on body weight, with patients <60 kg receiving 500 mg, 60-100 kg receiving 750 mg, and >100 kg receiving 1000 mg. The medication is administered over a period of approximately 30 minutes to one hour [53,54]. The subcutaneous version, a fixed dose of 125 mg regardless of weight, is administered once weekly with or without an intravenous loading dose based on body weight as above.

Time to Effect: Responses are typically seen within 3 months. In clinical trials, patients with initial responses continued to show improvements through the first year.

Adverse effects: As with other biological DMARDS infections are increased in patients receiving abatacept. These have ranged from mild to severe. Respiratory infections including

pneumonia were more common in clinical trials in patients with underlying COPD, thus extreme caution is suggested in this population. Opportunistic infections have been seen, though only a few cases of TB have been seen to date. TB screening is recommended. Malignancies have been seen in clinical trials but the rates appear to be similar for those expected in patients with rheumatoid arthritis. Infusion reactions have been seen in clinical trials that are typically mild.

B-Cell Depleting Agents:

Rituximab : B cells are an important inflammatory cell with multiple functions in the immune response. They serve as antigen presenting cells, directly interact with T-cells and others, can secrete cytokines, and differentiate into antibody-forming plasma cells. The depletion of B cells has been shown to be effective in reducing signs and symptoms of RA and in slowing radiographic progression. B cell depleting agent, Rituximab, is currently available for the treatment of rheumatoid arthritis [11,53,55].

Rituximab was originally developed to treat non-Hodgkin's lymphoma. Ritxuimab causes a rapid and sustained depletion of circulating B cells in the circulation with clinical improvements in many patients. Clinical trials have demonstrated that Rituximab is effective in decreasing signs and symptoms and in slowing radiographic progression in RA patients who have failed other DMARD therapies. The agent is currently approved in the US, however, only in patients who have failed TNF antagonists.

Mechanism: Rituximab is a chimeric monoclonal antibody that binds to the CD20 molecule on the B cell surface leading to the removal of B cells from the circulation. A single course of ritximab (2 infusions of 1000 mg each given 2 weeks apart) leads to a rapid and sustained depletion of B lymphocytes in the peripheral blood. This effect is sustained for 6 months to 1

year or even longer. The levels of the autoantibody rheumatoid factor decrease, but the levels of other antibodies typically remain within the normal range after the first infusion, but may drop with subsequent courses.

Time to effect : Effects from rituximab are not seen for upto 3 months after an infusion. Effects however may last 6 months and up to 2 years following a single infusion course.

Dosing: The currently approved dose is 1000 mg administered intravenously over 3-4 hours with two doses given 2 weeks apart. Patients receive intravenous corticosteroids 30 minutes prior to each infusion [55]. The optimal time for readministration is not yet clear. Some have advocated treatment every 6 months, while others wait for a return of symptoms. Doses of 500 mg have also been studied and appear to have similar clinical efficacy in patients who have failed to respond to DMARDS.

Adverse effects: Infusion reactions are seen in patients who receive Rituximab infusions. These may include itching, swelling, difficualty breathing, fever, chills, and changes in blood pressure. These are usually mild and respond to slowing the infusion rate or additional medication (such as antihistamines) but may be severe. These reactions were the most common with the first infusion.

As with other immunomodulatory therapies, infections may be increased in patients who are receiving rituximab. Rituximab may lead to the reactivation of viral infections that were dormant including hepatitis B. Cases of progressive multifocal leukoencephalopathy (PML), a severe and potentially fatal brain infection, have been seen in patients with autoimmune disease who receive rituximab though this condition has also been seen in patients with

autoimmune diseases who are not administered rituximab. Immunizations should be completed before starting therapy with rituximab and live virus vaccinations avoided. Repeat administration of rituximab has been associated with decreases in levels of IgG and IgM antibodies with subsequent courese. Whether these decreases are clinically important is under study.

Interleukin-6 (IL-6) inhibitors

Tocilizumab

Tocilizumab is the first approved drug in a class of IL-6 inhibitors. Clinical studies have shown that tocilizumab is effective in decreasing signs and symptoms and in slowing radiographic progression in RA patients who have failed other DMARD therapies [11,56]. The agent is currently approved in the US, however, only in patients who have failed TNF antagonists.

Mechanism of action: Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors and has been shown to inhibit IL-6-mediated signaling through these receptors. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, lymphocytes, monocytes and fibroblasts. IL-6 has been shown to be involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, initiation of hepatic acute phase protein synthesis, and stimulation of hematopoietic precursor cell proliferation and differentiation. IL-6 is also produced by synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes such as rheumatoid arthritis

Dosage: When used in combination with DMARDs or as monotherapy the recommended starting dose is 4 mg/kg followed by an increase to 8 mg/kg based on clinical response[11,55].

Time to effect: 4 to 8 weeks

Side effects: As with other biological DMARDs, an increase risk of infection and serious infection is present with tocilizumab. Because of a risk of GI perforation, patients with a history of diverticulitis should not receive tocilizumab. Tocilizumab has been associated with reduced platelet count, elevations in liver transaminases, increased lipid parameters (total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol) and neutropenia. Monitoring for any of these side effects should be considered every 4 to 8 weeks while on therapy.

Interleukin-1 (IL-1) Antagonist :

IL-1 is another proinflammatory cytokine implicated in the pathogenesis of RA. IL-1 receptor antagonist (IL1ra) is an endogenous blocker of the cytokine [11]. Evidence supporting an anti-inflammatory role of IL-1ra in vivo is demonstrated by the observation that IL-1ra deficient mice spontaneously develop autoimmune diseases similar to rheumatoid arthritis as well as vasculitis. IL1 has effects on cartilage degradation leading to damage as well as inhibiting repair, and is a potent stimulus to osteoclasts leading to bone erosion. One IL1 antagonist, anakinra , is currenly approved for the treatment of RA [55,56].

Anakinra, a human recombinant IL-1 receptor antagonist (hu rIL-1ra), is approved for the treatment of RA. Anakinra can be used alone or in combination with non-biologic DMARDs.

Mechanism: Anakinra is a recombinant human IL-1ra that differs from native IL-1ra by the addition of an N-terminal methionine. Anakinra blocks the biologic activity of IL-1 by binding to IL-1R type I with the same affinity as IL-1 beta.

Dosage: The recommended dose of anakinra is 100 mg/day administered daily by subcutaneous injection. The dose should be administered at approximately the same time each day. An autoinjection system is available for the medication.

Time to Effect: 2 to 4 weeks.

Side Effects : The most commonly observed side effect in all of the clinical trials with anakinra is injection site reactions, occurring in approximately two-thirds of patients. These reactions are present as erythema, itching, and discomfort and typically resolve over one to two months. In some patients these reactions can be severe leading to drug discontinuation.

Opportunistic infections including tuberculosis are less common with anakinra than with TNF antagonists. Mild to moderate decreases in absolute neutrophil counts were seen more commonly in anakinra treated patients in clinical trials, some severe. The rate of malignancies reported for anakinra was not increased

Biologic Treatment Schedule :

Etanercept : Prefilled syringe Autoinject pens 50 mg subcutaneous Once per week

Adalimumab : Prefilled syringeAutoinject pen 40 mg subcutaneous Once every 2 weeks (may ↑ to weekly)

Infliximab : IV infusion 3mg/kg -10 mg/kg Day 1, 14, 42 then every 8 wks (interim can be as short as every 4 weeks) 2-3 hours

Abatacept : IV infusion <60 kg/500 mg 60 to 100 kg/750 mg >100 kg /1 gram Day 1, 14, 28 and every 4 weeks thereafter 30 minutes Prefilled Syringe 125 mg With or without initial single IV infusion, then every month .

Rituximab : IV infusion 1000mg (500 mg also shown to be effective in DMARD inadequate responders) Day 1 and 14 4 ½ hours

Certolizumab Pegol Prefilled syringe 200mg per syringe Loading dose 400 mg at baseline, 2 weeks, 4 weeks then either 200 mg every other week or 400 mg every month

Golimumab Prefilled syringe Autoinject pen 50 mg Every 4 weeks

Tocilizumab IV infusion 4 mg/kg or 8mg/kg Every 4 weeks 1 hour[11,55,56].

Patients receiving infused biological agents including may develop a clinical syndrome of fever, chills, body aches, and headache associated with the infusion of biologics. The symptoms can often be reduced or prevented by slowing the infusion rate, administration of diphenhydramine, acetaminophen, and sometimes corticosteroids before the infusion. Injection site reactions may be seen with injectable biologics. These are typically mild and generally do not result in drug discontinuation.

Other Immunomodulatory and Cytotoxic Agents:

Some additional immunomodulatory drugs are used in RA including azathioprine, and cyclosporin A. Rarely cyclophosphamide and d-Penicillamine are used. Because the potential of high toxicity, these agents are typically utilized for life-threatening extra-articular manifestations of RA such as systemic vasculitis or with severe articular disease that is refractory to other therapy.

Azathioprine has some activity in rheumatoid arthritis but may take 8-12 weeks to see an effect[11]. It is a purine analog that can cause bone marrow suppression and lowering of blood cell counts (white blood cells, red blood cells, and platelets) particularly in patients with renal insufficiency or when used concomitantly with allopurinol or ACE inhibitors. Increased risk of secondary malignancy due to azathioprine is controversial. Screening for levels of the enzyme thiopurine methyltransferase (TPMT) is recommended before initiating therapy with azathioprine[56]. Certain individuals have deficiencies in this enzyme that metabolizes azathioprine with a concomitantly increased risk of toxicitiy for the medication. Side effects include nausea, and alopecia. Blood tests to monitor blood counts and liver function tests are necessary for patients on azathioprine.

Cyclosporine has some activity as a disease modifying therapy in rhematoid arthritis. Studies have demonstrated that cyclosporine can be combined with methotrexate in RA patients to capture clinical responses [53,56]. It is an immunosuppressive agent approved for use in preventing renal and liver transplant rejection and also has activity in psoriasis and other autoimmune diseases. Cyclosporine inhibits T cell function by inhibiting transcription of interleukin-2.

Main toxicities include infection and renal insufficiency. Increase in blood pressure is common and may require treatment. Careful monitoring of renal function and blood pressure is needed for the entire time a patient is taking cyclosporine. Numerous medication interactions may affect blood levels of cyclosporine and lead to more toxicity. The package insert contains important information concerning these medication interactions. Cyclosporine increases risks of infection and may also increase the risk of malignancies including lymphoma [57].

Cyclophosphamide is a potent immunosuppressive agent that is reserved for severe cases of refractory rheumatoid arthritis and those with manifestations such as vasculitis. It is used in the treatment of autoimmune conditions including lupus and vasculitis. Cyclophosphamide is an alkylating agent with serious toxicities including bone marrow suppression, hemorrhagic cystitis, premature ovarian failure, infection and secondary malignancy particularly an increased risk of bladder cancer [57]. Blood counts must be carefully monitored with this medication.

D-Penicillamine historically has some activity as a treatment for rheumatoid arthritis. It is prescribed primarily for patients with persistent aggressive disease who have failed other available DMARDS. Like gold it is a relatively toxic drug that has limited utility due to issues of tolerability and efficacy that is not as robust as other currently available agents. Major side effects include severe rash and effects on renal function. Careful monitoring of kidney function is required with this drug. Patients may develop a lupus like illness or other autoimmune diseases when taking d-Penicillamine [11,53,55].

Intramuscular Gold

Gold is effective in the treatment of rheumatoid arthritis when it is given intramuscularly. Intramuscular gold salts were, until the 1990's, the most often used DMARD agents but have been replaced by Methotrexate and other DMARDS as the preferred agents to treat RA [11]. Two injectable compounds are available, Myochrysine and Solganal . Gold compounds are rarely used now due to their numerous side effects and monitoring requirments, their limited efficacy, and very slow onset of action. An oral gold compound Auranofin is also available but its efficacy is even more limited than injectable compounds.

Mechanism:A number of mechanisms have been postulated, but how gold works in patients with rheumatoid arthritis remains unknown.

Dosage: Myochrysine or Solganal therapy is started at 10 mg intramuscularly, 25mg is then given the second week, then 50mg is given weekly until a response has occurred or until a total of 1 g has been given. If there is a favorable response, therapy is tapered to 50mg every 2 weeks for 3 months, then every 3 weeks for 3 months and then finally to a maintenance monthly dose. No response after a total of 1g should be considered a treatment failure. Monthly gold should be continued indefinitely [55,57].

Time to Effect: Effects are achieved within 4 to 6 months or after administration of 1g of gold.

Side Effects: Approximately 35% of patients on gold therapy experience side effects leading to discontinuation of the drug. Prior to each gold injection, patients should have a complete blood count and urine test for protein. The most common reaction is a rash, which can vary from a simple pruritic erythematous patch to a severe exfoliative dermatitis. Ulcerations and mucositis of the mouth, tongue, and pharynx can occur. If a mild mucocutaneous eruption occurs, therapy should be interrupted. If the eruption abates, therapy can be restarted at a 10-15mg weekly, titrating upwards to 50mg weekly with careful monitoring for further rash.

Up to 10% of patients have mild proteinuria due to a gold-induced membranous glomerulonephropathy that can progress to the nephrotic range. Patients with a positive urine dipstick for protein should be evaluated with a 24-hour urine collection and gold therapy stopped if proteinuria exceeds 500mg/24 hours. Mild proteinuria generally resolves with the

cessation of therapy. Occasionally patients will have isolated microscopic hematuria on gold therapy. If monitored closely gold therapy can be continued but other causes of hematuria must be excluded.

Immune thrombocytopenia, granulocytopenia, and aplastic anemia occur uncommonly but are absolute indications for cessation of gold therapy. Myochrysine, and less often Solganal, can produce a nitritoid reaction (flushing, dizziness, or fainting) occurring immediately after the gold injection. Rarely, there is a paradoxical increase in musculoskeletal pain that requires discontinuation of treatment.Long term use of gold may result in a bluish discoloration of the skin to occur that is typically irreversible.

Analgesic Drugs

Pain caused by inflammation is best treated with an anti-inflammatory drug, although occasionally the addition of acetaminophen can be helpful. Chronic narcotic therapy is not used routinely due to side effects such as diminished mental status, hypersomnolence, constipation, and dependency. Furthermore, they have no anti-inflammatory activity. They may be needed for patients with severe joint destruction who are not surgical candidates.

Treatment During Pregnancy

Rheumatoid arthritis therapy during pregnancy is complicated by the fact that none of the drugs discussed above have been shown to be safe in pregnant women with adequate, controlled studies. Although joint symptoms frequently remit during pregnancy, this effect is not universal. Treatment decisions require careful consideration of the risks and benefits to the mother and fetus.

All DMARD therapy should be stopped in women planning to conceive and in pregnant and lactating women. Evidence of the risks of these agents to the fetus either exists or cannot be ruled out. Hyrdoxychloroquine is probably the safest DMARD for use during pregnancy. Methotrexate, because of evidence of potential teratogencity should be stopped in men and women planning conception [11,58] . Leflunomide is teratogenic, and women who are considering conception should undergo a washout of this drug and have 2 separate demonstrations of blood levels of the metabolite of the drug are low. TNF antagonists are currently pregnancy category B though studies are ongoing to evaluate the outcomes of pregnancies in patients treated with these agents.

Although safety has not been proven in controlled trials, no evidence exists for risks to the fetus of low dose prednisone (less than 20mg daily) or of NSAIDs used in the first two trimesters. If necessary, joint symptoms are best managed with the lowest possible dose of prednisone. Potential prednisone complications include worsening of maternal gestational diabetes, hypertension and intrauterine growth retardation. NSAIDs should be avoided in the third trimester because of the potential for premature closure of the ductus arteriosus [11,58], prolonged labor and peripartum hemorrhage. Although both NSAIDs and prednisone are excreted in the breast milk, both are considered compatible with breast-feeding by the American Academy of Pediatrics.

Reduction of joint stress

Because obesity stresses the musculoskeletal system, ideal body weight should be achieved and maintained. Rest, in general, is an important feature of management. When the joints are actively inflamed, vigorous activity should be avoided because of the danger of intensifying joint inflammation or causing traumatic injury to structures weakened by inflammation. On

the other hand, patients should be urged to maintain a modest level of activity to prevent joint laxity and muscular atrophy. Splinting of acutely inflamed joints, particularly at night and the use of walking aids (canes, walkers) are all effective means of reducing stress on specific joints[53,58]. A consultation with a physical and an occupational therapist is recommended early in the course.

Surgical Approaches

Although rheumatoid arthritis is generally an inflammatory process of the synovium, structural or mechanical derangement is a frequent cause of pain or loss of joint function. Pain and joint mobility may be improved by a surgical approach [53,58]. The primary physician, the rheumatologist, and the orthopedist all help the patient to understand the risks and benefits of the surgical procedure. The decision to have surgery is a complex one that must take into consideration the motivation and goals of the patient, their ability to undergo rehabilitation, and their general medical status.

Synovectomy is sometimes appropriate for patients with rheumatoid arthritis, though in many patients the relief is only transient. However, an exception is synovectomy of the wrist, which is recommended if intense synovitis is persistent despite medical treatment over 6 to 12 months. Persistent synovitis involving the dorsal compartments of the wrist can lead to extensor tendon sheath rupture resulting in severe disability of hand function [59].

Total joint arthroplasties, particularly of the knee, hip, wrist, and elbow, are highly successful. Arthroplasty of the metacarpophalangeal (knuckle) joints also can reduce pain and improve function. Other operations include release of nerve entrapments (e.g., carpal tunnel

syndrome), arthroscopic procedures, and, occasionally, removal of a symptomatic rheumatoid nodule.

Outcomes

The course of RA is variable. Approximately 15 to 20 percent of patients have inter- mittent disease with periods of exacerbation and a relatively good prognosis.

The disease course may follow one of several patterns, such as a spontaneous remission, particularly in patients who are sero-negative for RF and anti-CCP, within the first 6 months of symptoms or recurrent explosive attacks followed by periods of quiescence most commonly in the early phases, though the most common pattern is of persistent and progressive disease activity that waxes and wanes in intensity[55,58]. Prognostic indicators for progressive joint destruction are the presence of RF and/or anti-CCP antibodies, high ESR (erythrocyte sedimentation rate) or CRP (C-reactive protein), early presence of radiographic erosions, and a high number of swollen joints [60]. The more numerous the unfavorable prognostic factors presented by the patient, the worse the prognosis, but the difficulty in judging prognosis in an individual patient is still considerable.

Inflammation and joint damage lead to major disability in many patients with RA, and this is associated with a reduced quality of life. RA is a systemic disease, which may also feature diffuse inflammation in many other organs and tissues such as lungs, heart and eyes, leading to extra-articular organ involvement RA [60]. Such extra-articular RA (ExRA) manifestations include interstitial lung disease, pleuritis, pericarditis, scleritis and severe vasculitis complications. The median life expectancy is lower in RA patients compared to the general population, mainly because of a higher occurrence of cardiovascular disease (CVD) among patients with RA [48,60]..

MATERIALS AND METHODS

OBJECTIVE OF THE STUDY :

1. To find association of carotid intima media thickness in rheumatoid arthritis patients.
2. To study carotid intima media thickness in healthy controls
3. To compare the carotid intima media thickness in rheumatoid arthritis patients with age and sex matched healthy controls.

SOURCE OF DATA : A total of 138 people will be selected for the present study . Subjects for our study were selected from patients at the Outpatient Clinic and inpatients of R.L.JALAPPA Hospital and Sri narsimharaja (SNR) Government Hospital, kolar. The first 69 subjects who are diagnosed as rheumatoid arthritis according to the RA ACR/EULAR 2010 criteria were taken as cases . The control group (69) were non diabetic ,non hypertensive and non smokers subjects selected from the patient bystanders attending the hospital.

METHOD OF COLLECTION OF DATA:

Study procedure: The study protocol was cleared by the Institutional Ethical Committee. A written, informed consent was obtained from all the patients and control subjects. In all of them, a detailed history was taken and a thorough physical examination and the following laboratory investigations were carried out: complete haemogram, ESR,CRP, serum lipids, Rheumatoid Factor,Anti-CCP in suspected cases, electrocardiogram and carotid intima media thickness(CIMT).

STATISTICAL METHODS

Determination Of Sample size : Sample size based on literature review which showed a mean carotid intimal thickness in Rheumatoid arthritis patients as 0.671(0.119) and the control group as 0.621(0.085)[1].which corresponds so as to detect a mean difference of 0.05mm thickness between the cases and controls with a 80% power, 95% confidence interval with α error 0.05.The sample size required for the study was determined using the following formula.

$$n = \frac{2\,S^2(Z\alpha/2 + Z\beta)^2}{(d)^2}$$

d = mean difference

Zα/2 = 1.96 (AT 95% CI)

Zβ = 0.842(AT 80 % power)

S = combined variance.

The sample size for the present study was calculated to be 138 (69 patients in each of RA and healthy normal control subjects). The study included 69 patients with RA and 69 control subjects. For deriving CIMT cut-off for the ethnic population included in the study, CIMT data obtained in 69 Rheumatoid Arthritis patients and the 69 healthy control subjects were studied.

- 138 subjects visiting R.L.Jalappa Hospital
- Normal subjects (69)
- Rheumatoid arthritis (69)

INCLUSION CRITERIA:

1. Subjects diagnosed as having rheumatoid arthritis,non diabetics,non hypertensives,non smokers fulfilling the RA ACR/EULAR CRITERIA 2010 considered as cases.
2. Non Diabetic, Non Hypertensive, non smoker subjects considered as healthy controls.

EXCLUSION CRITERIA:

Patients with history of clinically proven

. SLE, systemic sclerosis, antiphospholipid syndrome.

. Gaint cell arteritis, sjogrens syndrome,

. Gout, syphilis

. Chronic kidney disease.

. SLE, systemic sclerosis, antiphospholipid syndrome.

.Family History Of IHD, Stroke

STUDY DESIGN : CROSS SECTIONAL STUDY

All patients were evaluated with:

Detailed History : Age, sex, duration of RA, presence and duration of morning stiffness, list of painful joints, presence of other systemic disease, and history of extra-articular manifestations of RA were documented. Treatment history was also noted.

Examination

A systemic examination of all joints was done for features of activity, tender joint count and swollen joint count estimation was done.

Tender joint count and swollen joint count

A simplified 28 joint articular index as described by Fuch's et al was used to assess disease activity. Twenty-eight joints included 10 proximal interphalangeal joints of the fingers, 10 metacarpophalangeal joints, and the wrist, elbow, shoulder and the knee joints bilaterally.

Cardiovascular examination was done in detail. Abdominal, respiratory and neurological examination was also done. Extra articular manifestations were carefully looked for and documented.

The following investigations were done with special emphasis:

Erythrocyte sedimentation rate Was obtained by Westegren method. Venous blood was anti-coagulated with trisodium citrate dihydrate in the ratio of 4:1 and thoroughly mixed by gentle, repeated inversion and used to fill a Westergren-Katz tube to the zero mark. The tube was then replaced in a vertical position in a rack, which is not exposed to direct sunlight, draught or vibration and incubated at room temperature for 60 minutes. After this time, the distance (in mm) from the bottom of the surface meniscus to the top of sedimenting red cells read and reported as the ESR result. Tests were performed within 2 hours of taking the blood sample.

Figure showing testing of Rheumatoid factor and CRP, right image showng the machine used for lipid profile.

Rheumatoid factor (IgG):

A quantitative assay was performed using a latex fixation Lab kit.

C-reactive protein : A Quantitative assay was performed using latex agglutination kit.

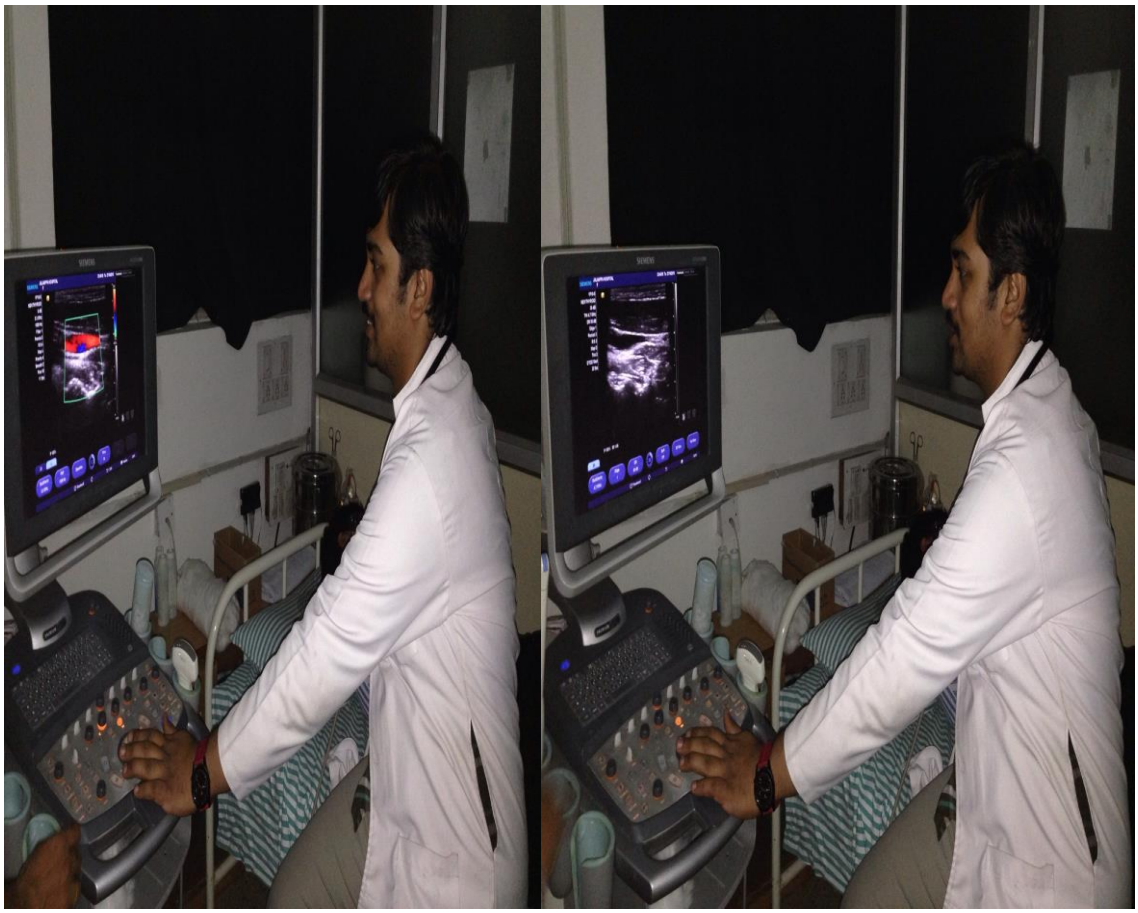
Anti-CCP assay was done using QUANTA LITE CCP IgG ELISA

Electrocardiography

A 12 lead electrocardiogram was performed on all subjects of the study.

Measurement of CIMT: Ultrasound examination of the carotids was carried out both in cases and controls using Sonoline G40 Diagnostic ultrasound system (Siemens Medical Solutions USA Inc., USA). Measurements were made bilaterally at the carotid bulb, distal 1 cm of common carotid artery far wall proximal to the bulb and in the proximal most portion of the internal carotid artery near its origin. The mean of the six readings so obtained was used to calculate the CIMT. Both right and left cimt was taken for the study . Plaque was defined as a focal protrusion of more than 50 per cent of the surrounding wall.

Figure : Measurement Of Carotid Intima Media Thickness In Subject



Two methods were used to calculate the cut-off of CIMT as a surrogate marker for atherosclerosis. The CIMT measurements in 69 patients with atherosclerosis and 69 healthy controls were used to derive the appropriate cut-off value of CIMT for defining atherosclerosis. Receiver-operator characteristic curve (ROC curve) for CIMT was plotted with (1-specificity) on the X-axis and sensitivity on the Y-axis using different cut-off levels of CIMT to arrive at the choice of the most appropriate cut-off level. The 75th percentile value of CIMT among the normal control subjects was also used as the optimal cut-off value for defining the presence of asymptomatic atherosclerosis in patients with RA . The proportion of patients with atherosclerosis among cases and controls detected using these two

cut-off values of CIMT as surrogate marker were compared using Chi-square test. The diagnostic yield of both the cut-offs in detecting subclinical atheosclerosis in patients with RA was tested using McNemar's test.

Statistical analysis: Data were recorded on a pre-designed proforma and managed using Microsoft Excel 2007 (Microsoft Corp, Redmond, WA). Descriptive statistics for the categorical variables were performed by computing the frequencies (percentages) in each category. For the quantitative variables, approximate normality of the distribution was assessed. Variables following normal distribution were summarized by mean and standard deviation. The association between two categorical variables was evaluated by Chi-square test or Fisher's exact test as appropriate. Student's 't'-test was used to compare the difference in mean values between the two groups for continuous variables that were normally distributed.

Statistical softwares PAS W Statistics 18, Release 18.0.0, (IBM SPSS Statistics, Somers NY, USA); Systat 12, Version 12.00.08 (Systat Software, Inc, Chicago IL, USA); and MedCalc Version 11.3.0 for Windows 2013/XP/Vista/7 (MedCalc Software bvba, Belgium) were used for statistical analysis.

RESULTS

During the study period, 80 patients with RA who had given consent to undergo evaluation were screened. Of these, 11 subjects were excluded and 69 patients were included in the study as 'cases'. The causes of exclusion were type 2 diabetes mellitus (n=7); Hypertension (n=5), unwillingness to undergo further diagnostic testing (n=3); and tobacco smoking (n=1).

Demographic characteristics of patients with RA , age-, gender matched normal controls; Majority of patients with RA were females in their fifth decade of life; females (n=49) outnumbered males (n=20).

Table 1: Age distribution of subjects

		Groups			
		Cases		Controls	
		Count	%	Count	%
Age	< 30 yrs	12	17.4%	12	17.4%
	31 to 40 yrs	20	29.0%	20	29.0%
	41 to 50 yrs	12	17.4%	12	17.4%
	> 50 yrs	25	36.2%	25	36.2%
Mean Age		44.70 ± 15.01		44.70 ± 15.01	

$\chi 2 = 0.000$, df = 3, p = 1.000

In the study in both groups there was no difference with respect to age group distribution. 17.4% were in the age group < 30 yrs, 29% were in the age group 31 to 40 yrs, 17.4% were in

the age group 41 to 50 yrs and majority 36.2% were in the age group > 50 yrs in both groups respectively.

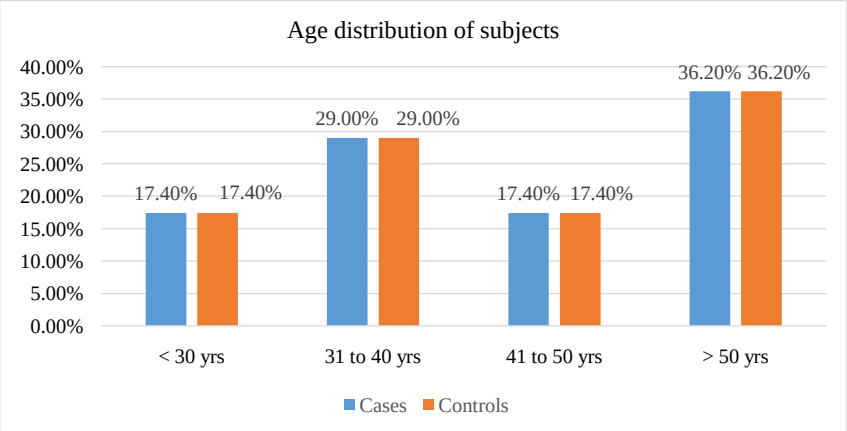


Figure 1: Bar diagram showing Age distribution of subjects

Table 2: Gender distribution of subjects

		Groups			
		Cases		Controls	
		Count	%	Count	%
Gender	Female	49	71.0%	49	71.0%
	Male	20	29.0%	20	29.0%

$\chi 2 = 0.000$, df = 1, p = 1.000

In the study majority of them were females (71%) in cases and controls respectively. 29% were males in cases and controls.

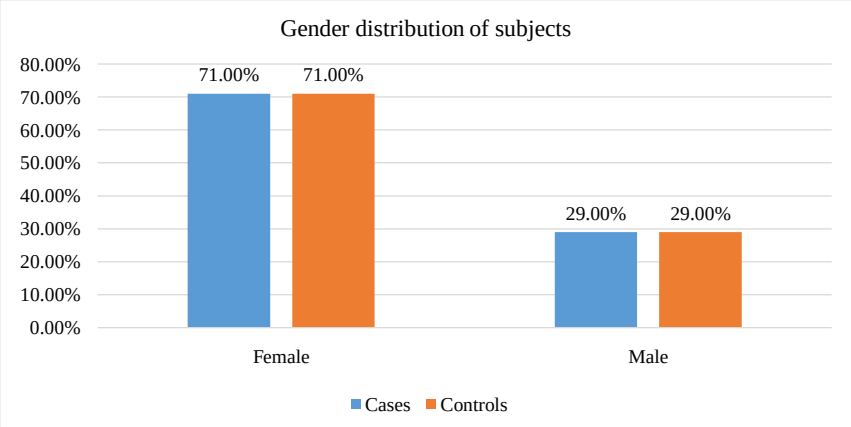


Figure 2: Bar diagram showing Gender distribution of subjects

Table 3: Complaints comparison between cases and controls

		Groups				P value
		Cases		Controls		
		Count	%	Count	%	
Painful Joints	No	0	0.0%	69	100.0%	<0.001*
	Yes	69	100.0%	0	0.0%	
Back pain	No	32	46.4%	66	95.7%	<0.001*
	Yes	37	53.6%	3	4.3%	
Joint Swelling Of > 6 Months	No	14	20.3%	69	100.0%	<0.001*
	Yes	55	79.7%	0	0.0%	

In the study all the cases had painful joints, 53.6% had back pain and 79.7% had Joint Swelling for > 6 Months in cases. Only 4.3% of controls had back pain. No history of painful joints and Joint Swelling in controls. This observation was statistically significant.

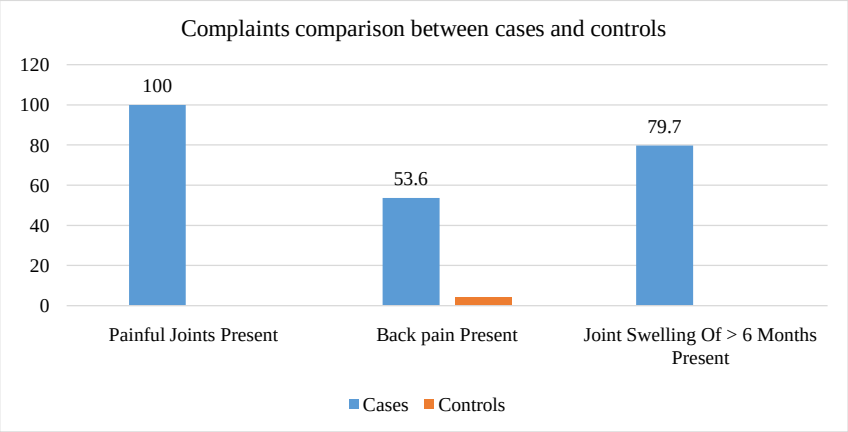


Figure 3: Bar diagram showing Complaints comparison between cases and controls

Table 4: Descriptive statistics of RA factor (IU) in Cases

RA FACTOR in IU							
Groups	N	Mean	SD	Minimum	Median	Maximum	Range
Cases	69	220.93	301.490	10	160.00	1280	1270

Mean, SD of RA factor in cases is given in the above table 4.

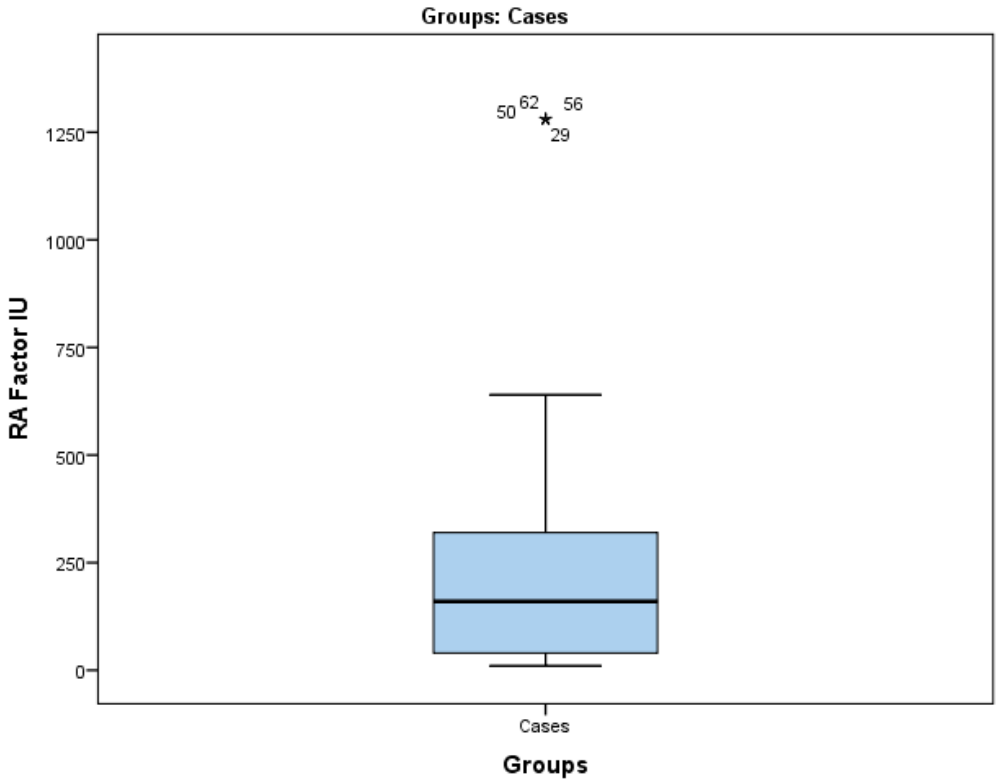


Figure 4: Box plot describing RA factor in cases

Table 5: Descriptive statistics for ESR in Cases

Groups		ESR
Cases	N	69
	Mean	41.48
	Std. Deviation	13.57
	Minimum	20
	Median	40.00
	Maximum	70
	Range	50

Mean ESR in cases was 41.48 ± 13.57.

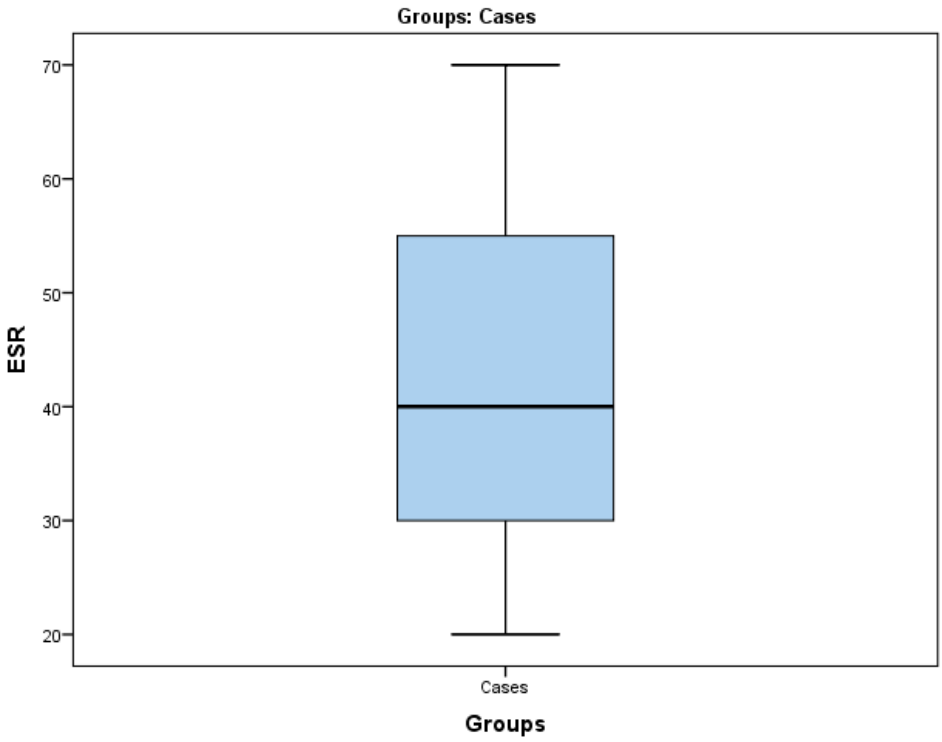


Figure 5: Box plot describing ESR in cases

Table 6: Descriptive statistics for CRP in Cases

Groups		CRP
Cases	N	69
	Mean	49.59
	Std. Deviation	32.680
	Minimum	12
	Median	48.00
	Maximum	192
	Range	180

Mean CRP in cases was 49.59 ± 32.68.

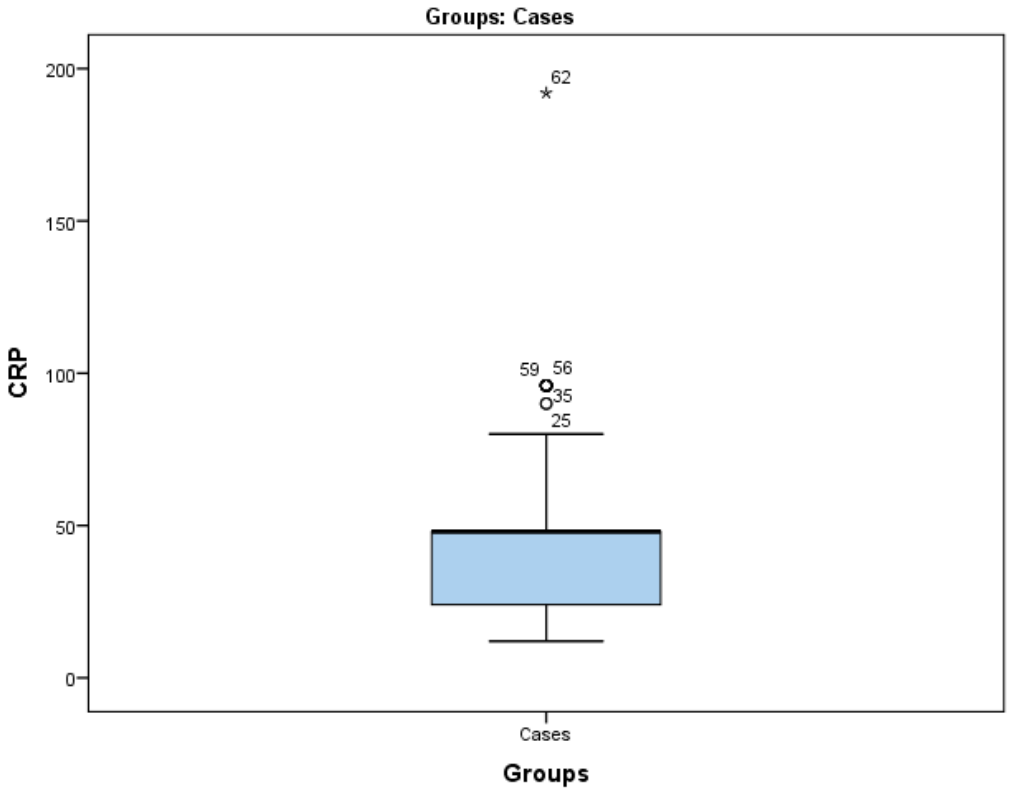


Figure 6: Box plot describing CRP in cases

A-CCP was positive in 8 cases and in remaining cases A-CCP was not done.

Table 7: Distribution of Cases according to Morning Stiffness

		Frequency	Percent
Morning stiffness	< 60 mins	7	10.1
	>60min	44	63.8
	Absent	18	26.1
	Total	69	100.0

In cases 10.1% had morning stiffness for < 60 mins, 63.8% had morning stiffness for > 60 min and in 26.1% no morning stiffness was noted.

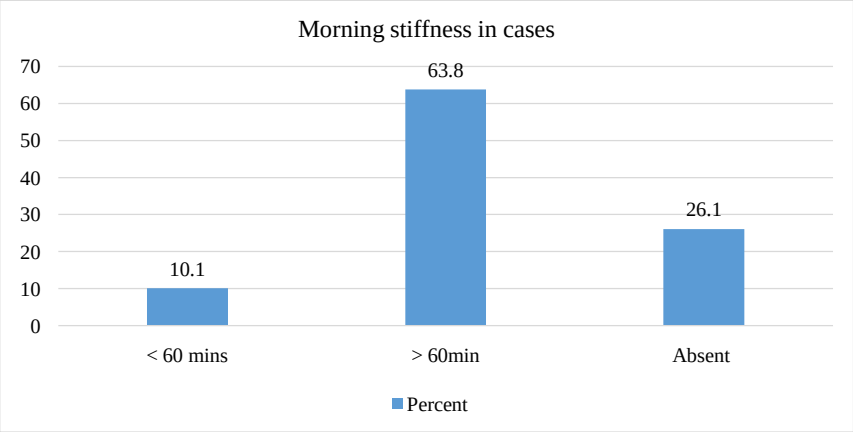


Figure 7: Bar diagram showing distribution of cases with respect to Morning stiffness

Table 8: ECG Findings and Presence of CVA in cases

		Groups	
		Count	%
ECG	Ischemic Changes	10	14.5%
	Normal Sinus Rhythm	59	85.5%
CVA	No	62	89.9%
	Yes	7	10.1%

In cases 14.5% had Ischemic changes in ECG and 10.1% had CVA.

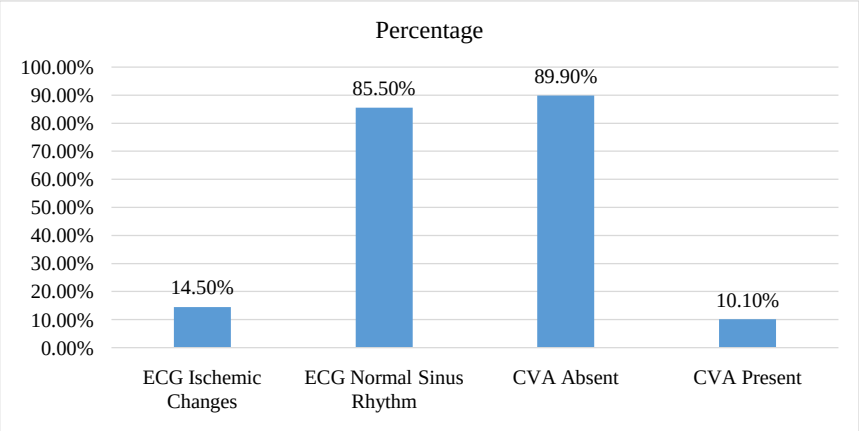


Figure 8: Bar diagram showing ECG Findings and Presence of CVA in cases

Table 9: Lipid Profile comparison between cases and controls

	Groups				P value
	Cases		Controls		
	Mean	SD	Mean	SD	
Cholesterol	159.59	15.49	156.54	14.60	0.235
Triglycerides	109.94	21.64	103.20	17.04	0.044*
HDL Cholesterol	46.87	6.27	48.45	4.50	0.091*
LDL Cholesterol	66.49	12.16	61.81	12.64	0.028*

Mean cholesterol in cases was 159.59 ± 15.49& in control was 156.54±14.60. There was no significant difference between cases and controls.

Mean Triglycerides in cases was 109.94± 21.64 & in control was 103.20± 17.04. There was significant difference between cases and controls.

Mean HDL levels in cases was 46.45± 6.27& in control was 48.87± 4.50. There was significant difference between cases and controls.

Mean LDL Cholesterol in cases was 66.49± 12.16 & in control was 61.81± 12.64. There was significant difference between cases and controls.

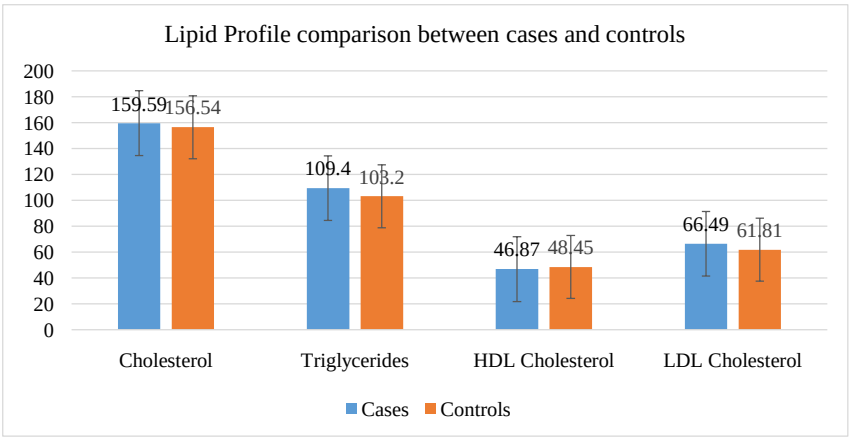


Figure 9: Bar diagram showing Lipid Profile comparison between cases and controls

Table 10: Comparison of Right and Left CIMT with Cases and Controls

	Groups				P value
	Cases		Controls		
	Mean	SD	Mean	SD	
Right CIMT	0.58	0.15	0.47	0.04	<0.001*
Left CIMT	0.60	0.15	0.46	0.04	<0.001*

Mean Right CIMT in cases was 0.58± 0.15& in control was 0.47± 0.04. There was significant difference between cases and controls.

Mean Left CIMT in cases was 0.60± 0.15& in control was 0.46± 0.04. There was significant difference between cases and controls.

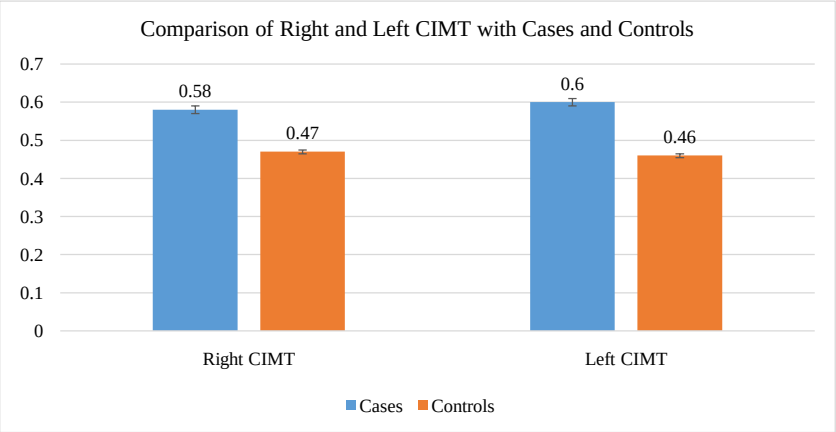


Figure 10: Bar diagram showing Comparison of Right and Left CIMT with Cases and Controls

Table 11: Correlation of Right and Left CIMT with RA Factor, ESR and CRP in cases

		RA FACTOR	ESR	CRP
Right CIMT	Pearson Correlation	0.436**	0.231	0.348**
	P value	<0.0001*	0.056	0.003*
	N	69	69	69
Left CIMT	Pearson Correlation	0.411**	0.269*	0.313**
	P value	<0.0001*	0.025*	0.009*
	N	69	69	69
**. Correlation is significant at the 0.01 level (2-tailed).				
*. Correlation is significant at the 0.05 level (2-tailed).				

In the study there was significant positive correlation between CIMT on right side with RA factor and CRP. I.e. with increase in CIMT there was increase in RA factor and CRP in cases at a significant level.

Similarly there was significant positive correlation between CIMT on left side with RA factor ESR and CRP. i.e. with increase in CIMT there was increase in RA factor, ESR and CRP in cases at a significant level.

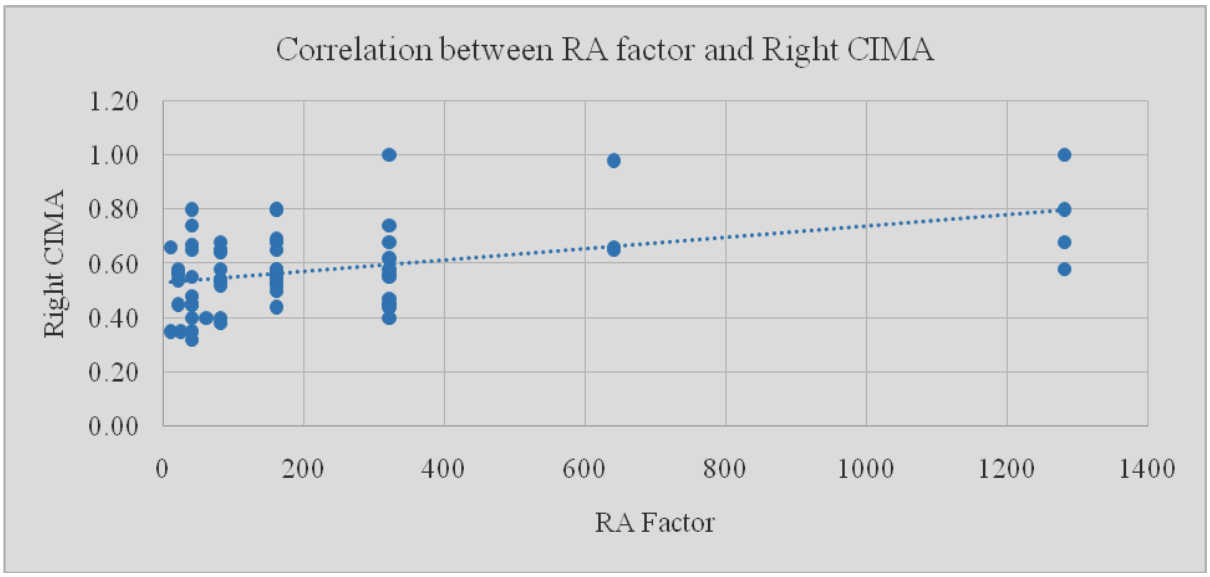


Figure 11: Scatter plot showing Positive correlation between RA factor and Right CIMT

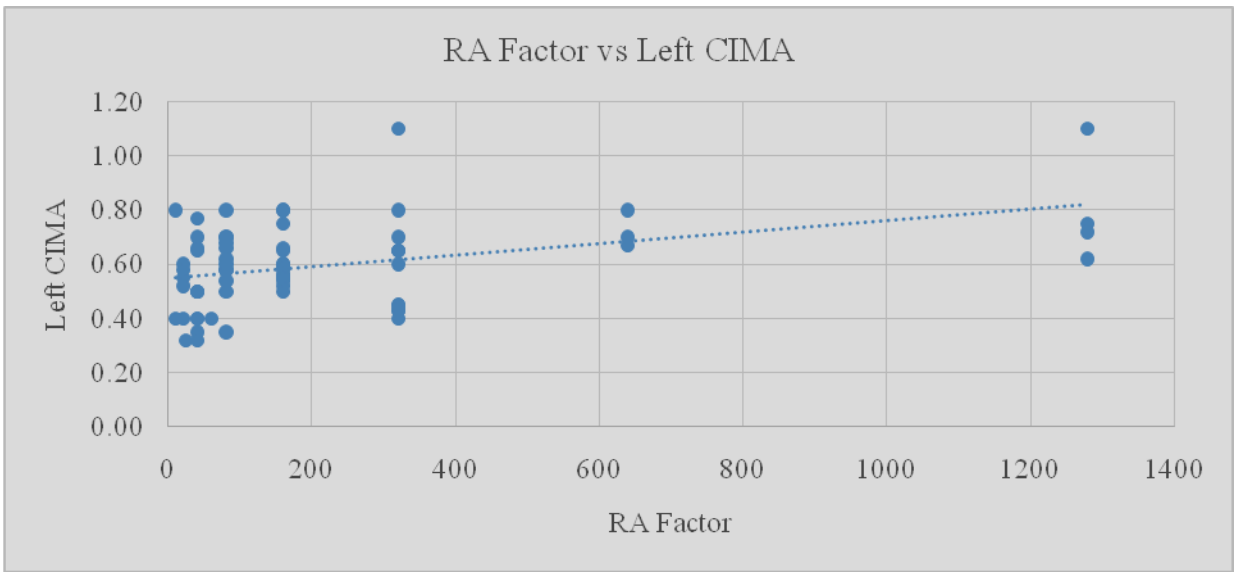


Figure 12: Scatter plot showing Positive correlation between RA factor and Left CIMT

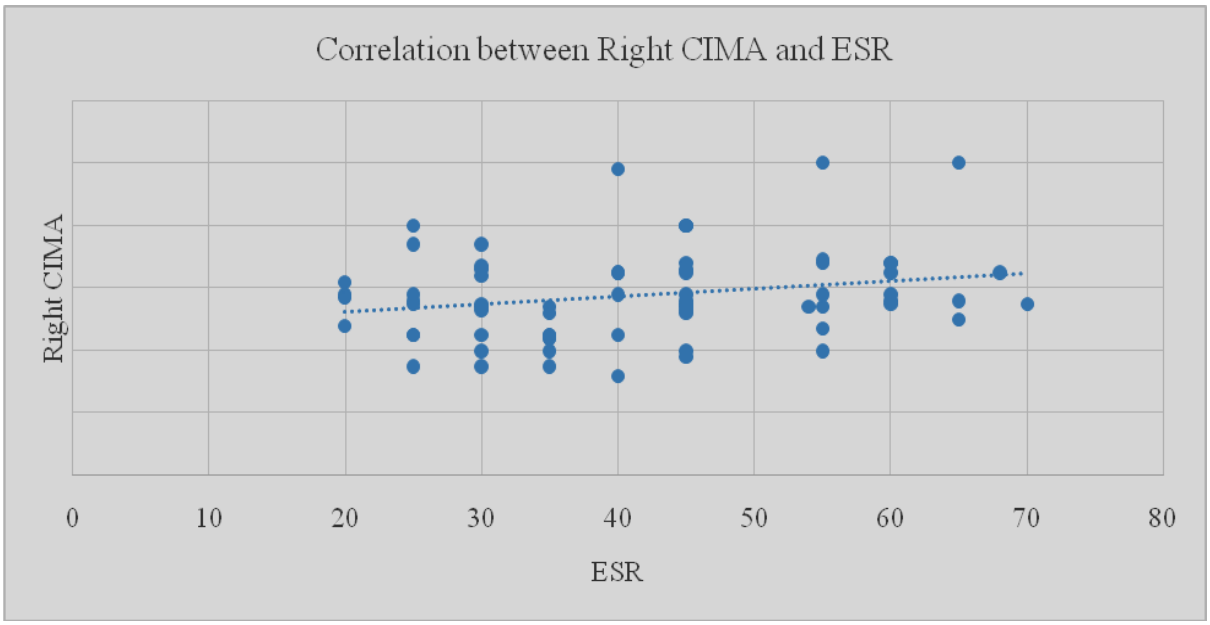


Figure 13: Scatter plot showing Positive correlation between ESR and Right CIMT

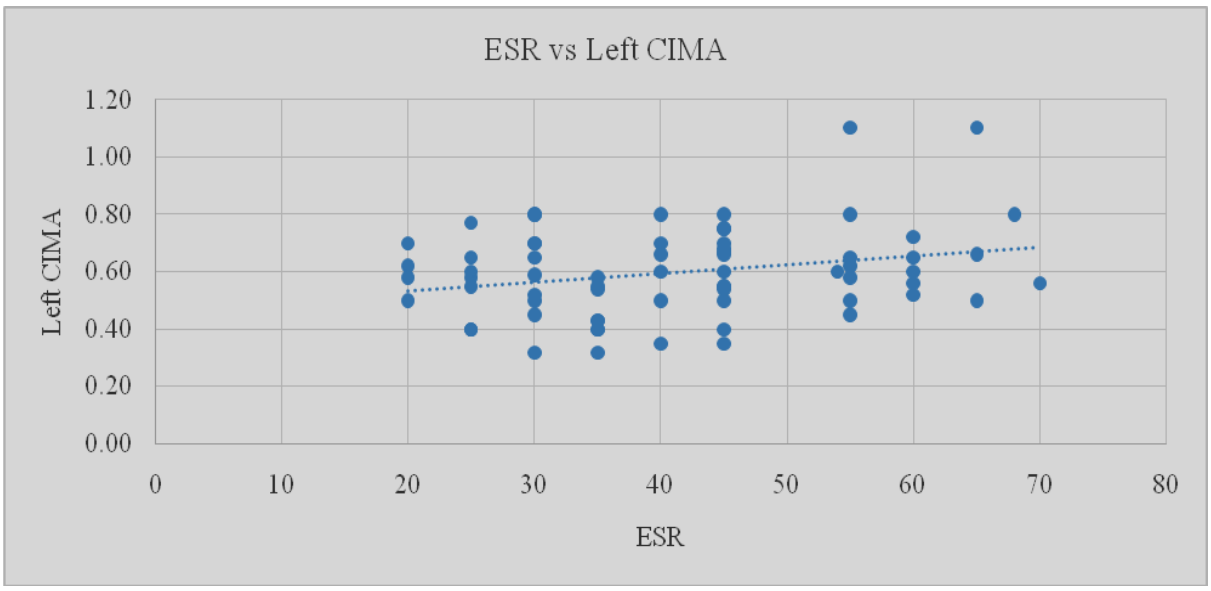


Figure 14: Scatter plot showing Positive correlation between ESR and Left CIMT

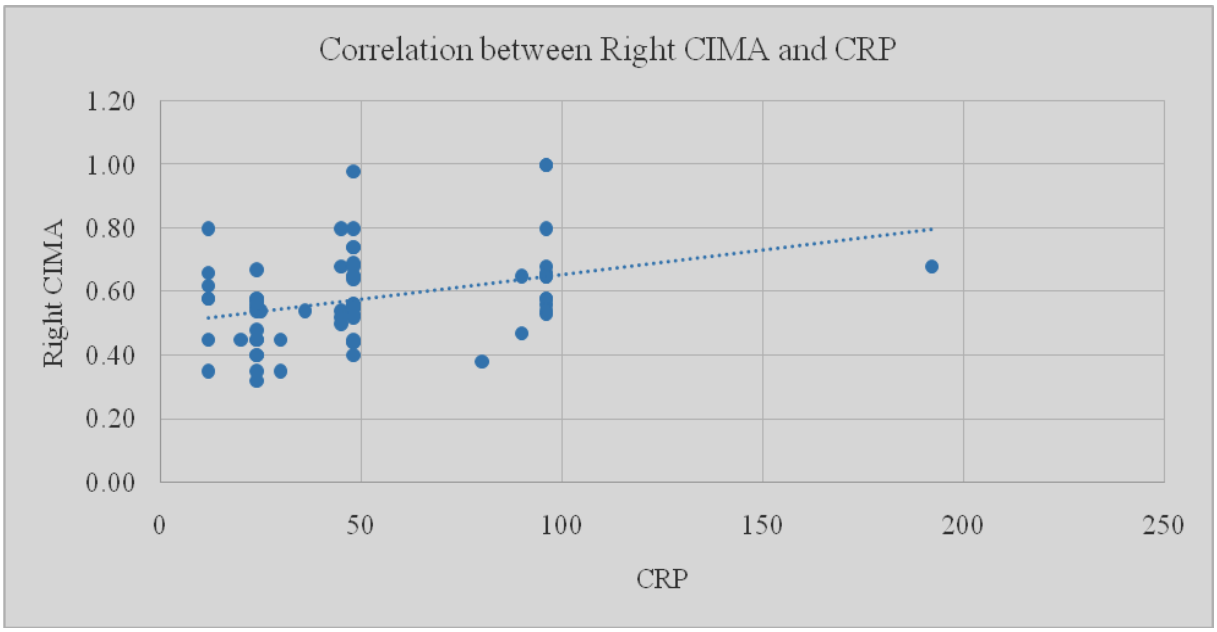


Figure 15: Scatter plot showing Positive correlation between CRP and Right CIMT

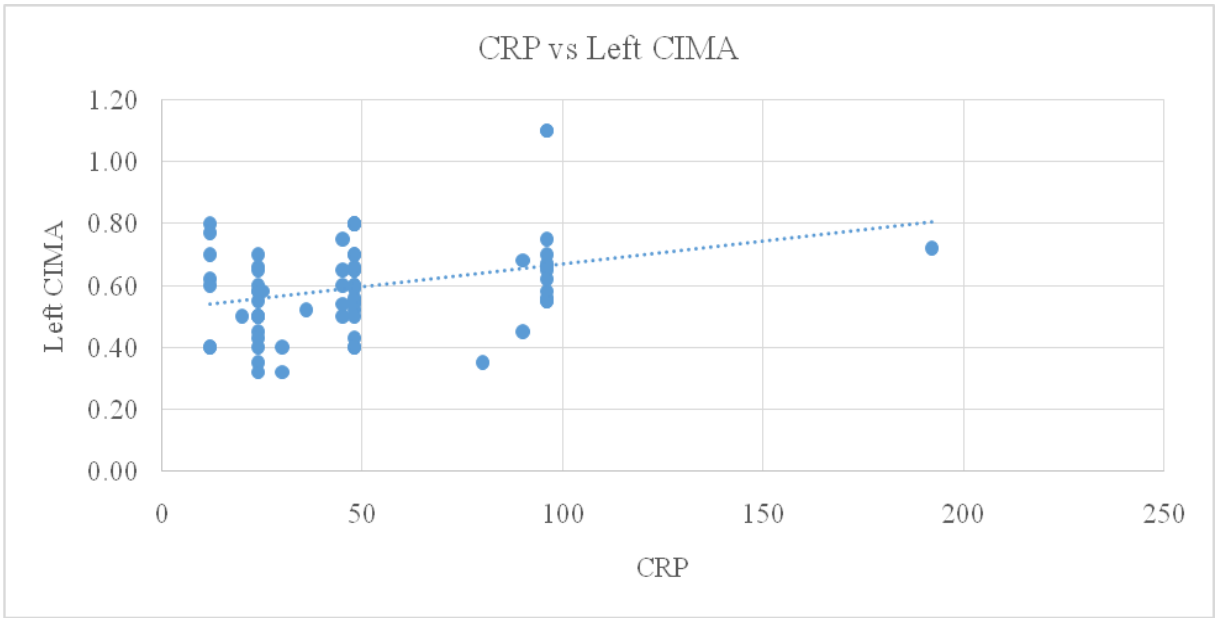


Figure 16: Scatter plot showing Positive correlation between CRP and Left CIMT

Table 12: Correlation between CIMT and Duration of Complaints in cases

		Right CIMT	Left CIMT
Duration of complaints yrs	Pearson Correlation	0.679**	0.641**
	P value	<0.0001*	<0.0001*
	N	69	69
**. Correlation is significant at the 0.01 level (2-tailed).			

In the study there was significant positive correlation between CIMT on right side and left side with duration of complaints. ie. with increase in Duration of complaints there was significant increase in CIMT on right and left side.

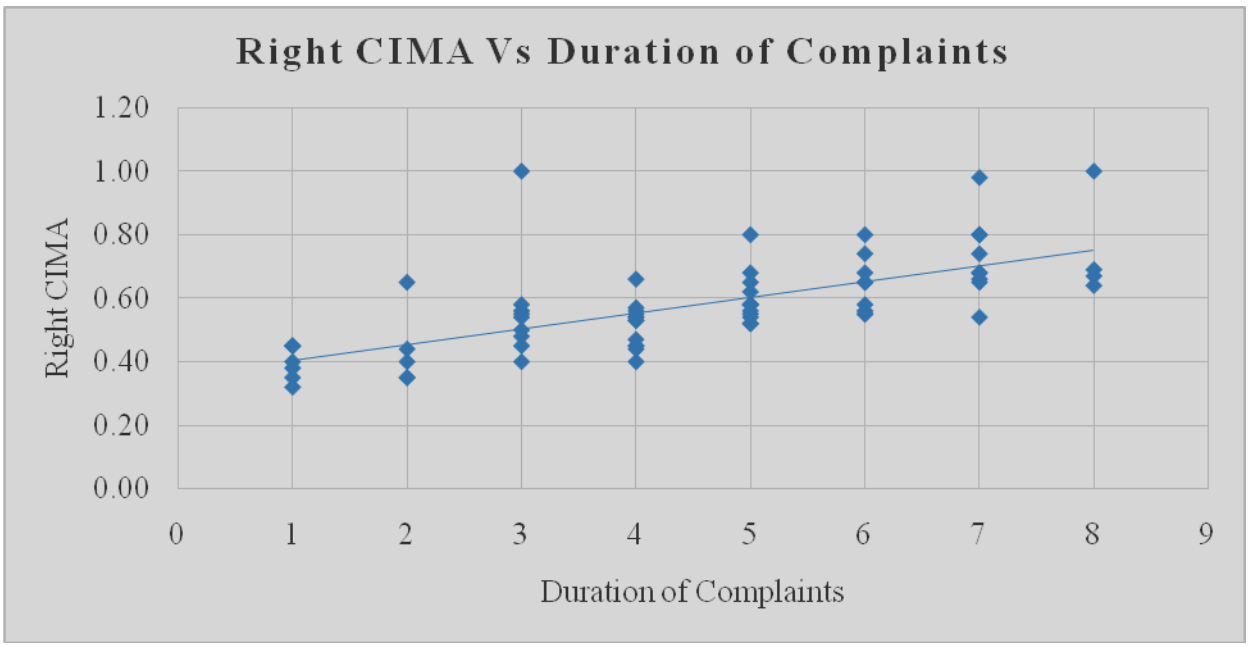


Figure 17: Scatter plot showing Positive Correlation between Right CIMT and Duration of Complaints in cases

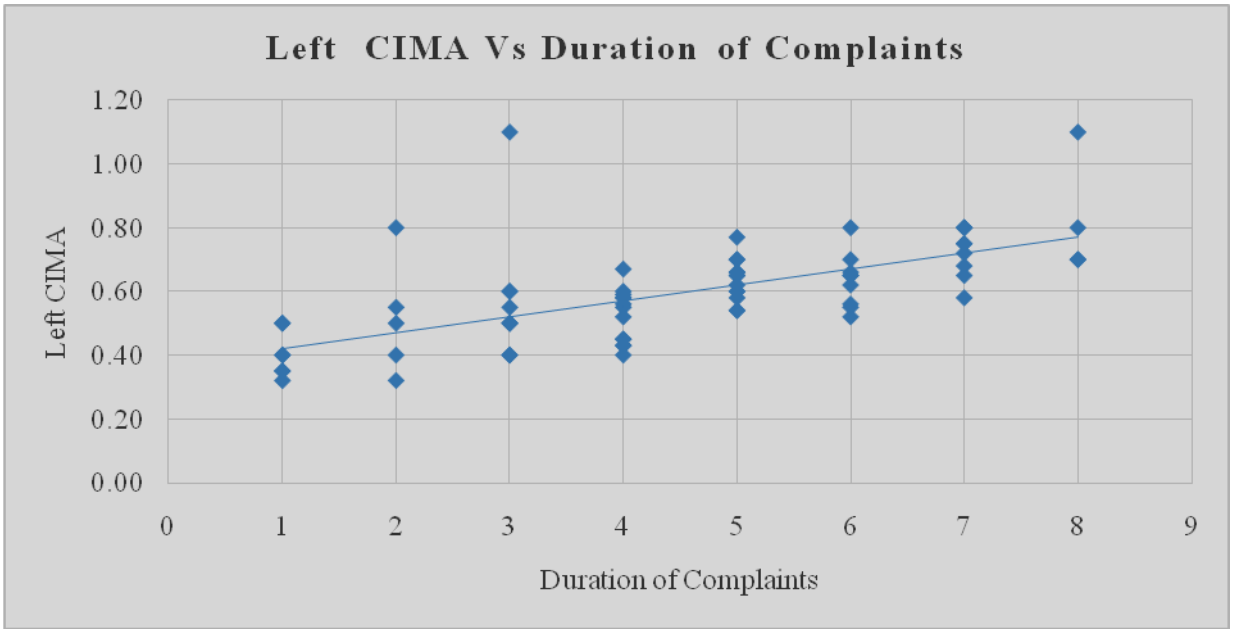


Figure 18: Scatter plot showing Positive Correlation between Left CIMT and Duration of Complaints in cases

Table 13: Area under the curve in cases for CIMT on right side

Area Under the Curve				
Test Result Variable(s): RIGHT CIMT				
Area	SE	P value	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.755	0.045	<0.0001*	0.666	0.843

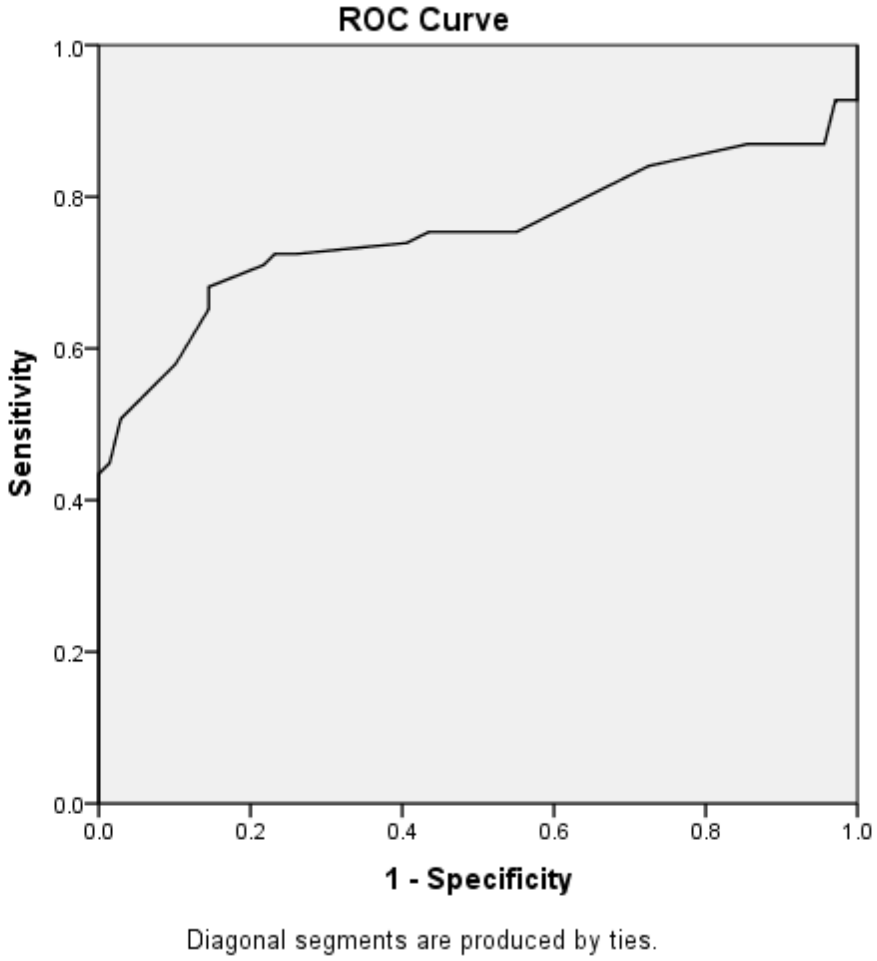


Figure 19: ROC curve showing area under the curve and for CIMT on right side in cases

Sensitivity and specificity of CIMT at different levels of values of right side in cases

Coordinates of the Curve			
Test Result Variable(s): RIGHT CIMT			
Positive if Greater Than or Equal To	Sensitivity	1 - Specificity	Specificity
0.4550	0.754	0.551	0.449
0.5600	0.725	0.232	0.739
0.5700	0.725	0.261	0.768
0.5750	0.449	0.014	0.986

From the table it is observed that at CIMT of 0.570 on right side there was highest sensitivity and specificity noted. Hence a cut off around 0.570 in Rheumatoid arthritis can predict atherosclerosis. This observation was statistically significant.

Table 14: Area under the curve in cases for CIMT on left side

Area Under the Curve				
Test Result Variable(s): LEFT CIMT				
Area	SE	P value	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.794	0.044	<0.0001*	0.708	0.881

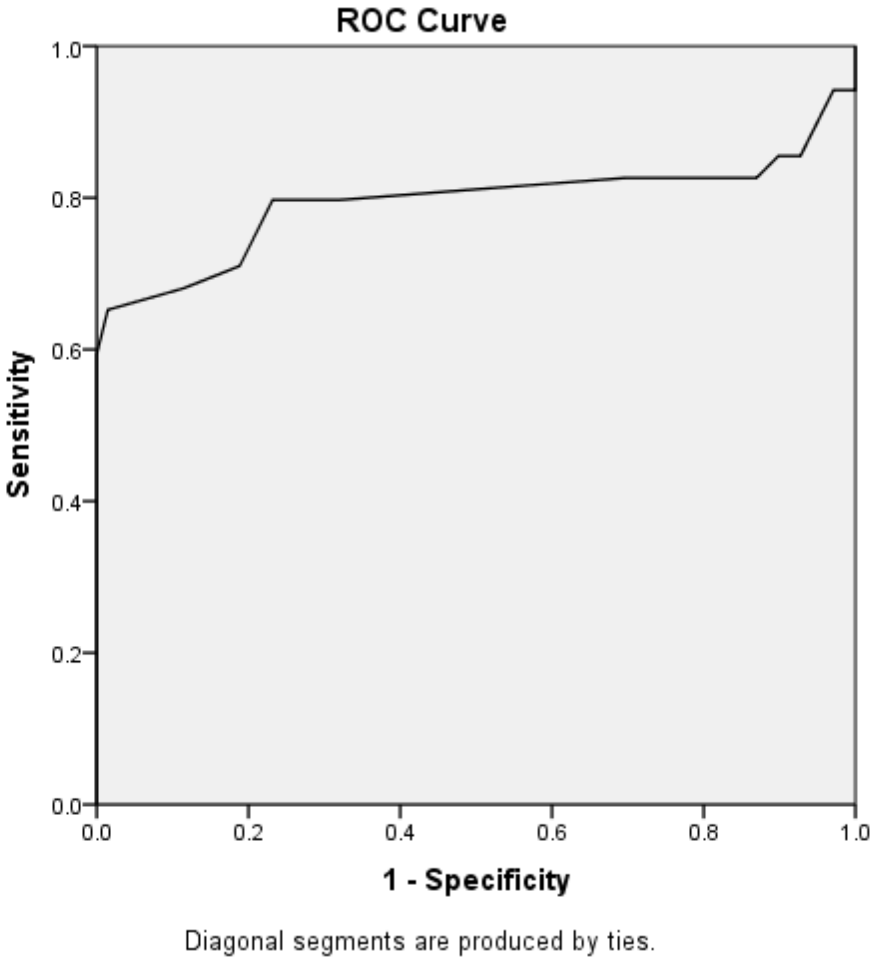


Figure 20: Bar diagram showing ROC curve showing area under the curve and for CIMT on left side in cases

Sensitivity and specificity of CIMT at different levels of values on left side in cases

Coordinates of the Curve			
Test Result Variable(s): LEFT CIMT			
Positive if Greater Than or Equal To	Sensitivity	1 - Specificity	Specificity
0.4450	0.826	0.696	0.304
0.5650	0.797	0.232	0.768
0.5700	0.710	0.188	0.812
0.5950	0.493	0.000	1.00

From the table it is observed that at CIMT of 0.565 on left side there was highest sensitivity and specificity noted. Hence a cut off around 0.565 in Rheumatoid arthritis can predict atherosclerosis. This observation was statistically significant.

Calculation of cut-off value of CIMT for the detection of atherosclerosis: The ROC-curve for calculating the optimal cut-off value of CIMT for detection of atherosclerosis is shown in Fig.20 . At a cut-off value of CIMT greater than or equal to 0.57, the sensitivity and specificity were 84.4 [95% confidence intervals (CI), 67.2 - 94.7] and 90.6 (95% CI, 75.0 - 98.0), respectively. The 75th percentile value of CIMT in normal control subjects was found to be 0.47 mm.

Presence of atherosclerosis among patients with RA and normal controls: Using the ROC-curve cut-off value (≥ 0.570 mm) as the surrogate marker, the proportion of patients with atherosclerosis was significantly higher among patients with RA compared with normal controls (59.3 vs. 12.5%; $p<0.001$). Using the 75th percentile value among normal controls (≥ 0.47 mm) as the surrogate marker, the proportion of patients with atherosclerosis was significantly higher among patients with RA compared with normal controls (62.5 vs. 25%; $p<0.001$).

DISCUSSION

Rheumatoid arthritis being a chronic systemic disease with a inflammatory background resulting in atherosclerosis [15]. The measurement of carotid intima media thickness as marker is very much essential for the detection of subclinical atherosclerosis [14]. The healthy subjects were comparable with the RA patients with regard to risk factors for atherosclerosis, including age, sex, and serum lipid levels and carotid intima media thickness .

In the present study age and gender matched 69 cases and 69 controls were included. Cases were positive for rheumatoid disease and controls did not have disease. In both groups there was no difference with respect to age group distribution. 17.4% were in the age group < 30 yrs, 29% were in the age group 31 to 40 yrs, 17.4% were in the age group 41 to 50 yrs and majority 36.2% were in the age group > 50 yrs in both groups respectively. Previous studies have shown the predominance of rheumatoid arthritis patients in the 5^{th} decade [5].

Majority of the patients with RA were females (n=49). since RA predominantly affects women, and is also an independent risk factor, a search for asymptomatic atherosclerosis especially among women with RA using CIMT appears warranted. As compared with other studies which show predominance of rheumatoid arthritis in females accounting to 70 % and male 30 % ,in the present study majority of subjects were females 71% in cases and 29% were males in cases. Observation of asymptomatic atherosclerosis among patients with RA assumes greater significance when interpreted in context of the mean age and proportion of female patients. In this study, women, a group conveniently thought to have lesser burden of atherosclerotic cardiovascular disease as compared to men, constituted 70 per cent of the patients and their mean age was only 47.4 ± 10.2 yr.

In the study all the cases had painful joints and 79.7% had Joint Swelling for > 6 Months in cases. No history of painful joints and Joint Swelling in controls. In the present study 26.1% had morning stiffness for < 60 mins, 63.8% had morning stiffness for > 60 min and in 10.1% no morning stiffness was noted.

Recent studies in the general population of the US indicated that, among various markers of inflammation, the CRP level was a particularly powerful predictor of cardiovascular disease independently of serum lipid levels . CRP is also hypothesized to be causally involved in the pathophysiology of atherosclerosis and its complications [15] . The CIMT has been associated with the inflammatory burden and the chronicity of the inflammatory response. Long-standing RA patients with mean C-reactive protein (CRP) levels greater than 15 mg/dl had higher CIMT values than those with lower CRP levels [15].The Mean CRP in cases was 49.59 ± 32.68, in the present study and there was significant positive correlation between CIMT and CRP. i.e. with increase in CIMT there was increase in CRP in cases at a significant level.

Elevated erythrocyte sedimentation rate (ESR) independently predicts radiographic progression of joint disease, increased disability, and poorer outcomes in RA[8] .ESR also increases linearly with increased carotid artery intimal-medial thickness in both patients with RA and healthy controls [26]. Patients with RA with elevated ESR have a higher rate of cardiovascular death than do those without elevated ESR[8].Similarly there was significant positive correlation between CIMT with RA factor ,ESR i.e. with increase in CIMT there was increase in RA factor, ESR in cases at a significant level.In the present study the mean ESR in cases was 41.48 ± 13.57.

There are several possible explanations for the observed association between arterial wall thickness and RA. The first is a possible relationship between atherosclerosis and chronic inflammation due to RA. It has recently been hypothesized that inflammation plays a major

role in the process of atherosclerosis [24]. Previous studies have demonstrated that atherosclerosis shares many similarities with other inflammatory diseases [24,32]. Although many other factors besides inflammation cause atherosclerosis, inflammation at the site of vascular injury probably mediates atherogenesis. It is therefore not surprising that the arterial wall was found to be thicker in patients with RA characterized by chronic inflammation. Since it has been suggested that vasculitis, whether overt or subclinical, has a major effect on the increase in cardiovascular disease in RA patients [32,37], a low-grade inflammatory response might have enhanced the arterial wall changes in these patients. In the present study there was significant positive correlation between CIMT with RA factor Mean of RA factor in cases was 220.93 . The values of RA FACTOR had a positive co relation with the increased CIMT in our study i.e. with increase in CIMT there was increase in RA factor in cases at a significant level.

Data on dyslipidemia in RA are conflicting, and the more convincing findings, a decrease of high-density lipoprotein (HDL) cholesterol and an increase in small LDL levels, appear to be secondary to chronic inflammation rather than to primary metabolic alteration in RA [15].
In the present study Mean cholesterol in cases was 159.59 ± 15.49& in control was 156.54±14.60. There was no significant difference between cases and controls. Mean Triglycerides in cases was 109.94± 21.64 & in control was 103.20± 17.40 . Mean HDL levels in cases was 46.45± 6.27& in control was 48.87± 4.50. There was significant difference between cases and controls. Mean LDL Cholesterol in cases was 66.49± 12.16 & in control was 61.81± 12.64. There was significant difference between cases and controls.

A question that needs to be answered is whether carotid ultrasonography should routinely be performed in all patients with RA to improve CV risk management. With respect to this

question, carotid IMT was found to be an independent predictor of vascular events in high-risk individuals without RA in whom risk factors were managed clinically. Since the risk of CV disease is increased in patients with RA, carotid ultrasound might be a potential additional tool for stratifying CV risk in patients with RA [5,14].

Multiple regression analysis revealed a significant association between RA and the common carotid artery IMT [14]. Moreover, the common carotid artery IMT in RA patients was positively associated with disease duration . No significant association was found between corticosteroid treatment and common carotid artery IMT. In the present study there was significant positive correlation between CIMT on right side and left side with duration of complaints. ie. with increase in Duration of complaints there was significant increase in CIMT on right and left side.

Multiple regression analysis also revealed that the presence of RA was an independent risk factor associated with arterial wall thickness [14]. Previous cohort studies found that RA patients exhibited a significant increase in either overall mortality or mortality due to cardiovascular diseases [8, 9].

CIMT has been recommended to screen for heart disease in apparently healthy individuals and has been endorsed as a surrogate end-point for evaluating the regression and/or progression of atherosclerotic cardiovascular disease and as a predictor of the presence of coronary atherosclerosis and its clinical sequel [5,8]. Other surrogate markers of cardiovascular disease such as flow-mediated dilatation have been also been found to be abnormal in RA . However, CIMT seems to be the more appropriate tool for establishing structural atherosclerotic disease. CIMT also offers the advantage of low cost, wide availability in developing countries like India, relative comfort and convenience for the patient as it is a non-invasive investigation.

The mean CIMT value among patients with RA was significantly higher than that observed among normal control subjects in the present study. Similar observations were reported in other studies from India [23-25] and from other parts of the world[26,27]. Patients with other factors that influence atherosclerosis such as hypertension, diabetes mellitus, family history of hyperlipidaemia, among others were not excluded in some studies[24,28]. care was taken in the present study to exclude patients with other conditions that may contribute to atherosclerosis.

In the present study the Mean Right CIMT in cases was 0.58± 0.15 & in control was 0.47± 0.04. There was significant difference between cases and controls. The Mean Left CIMT in cases was 0.60± 0.15& in control was 0.46± 0.04. There was significant difference between cases and controls. The study shows a significant increase in CIMT in patients with healthy controls which is a surrogate marker of atherosclerosis and thus advocates screening of rheumatoid arthritis patients for atherosclerosis and helps in predicting the risk of CAD.

However, a major limitation of CIMT as a marker for atherosclerosis is that there is no clear "threshold" for demarcating 'normal' and 'abnormal' values[30]. The consensus statement from the American Society of Echocardiography[9] suggested that a value greater than 75th percentile for the patient's age, sex and race/ethnicity should be considered high and indicative of increased vascular risk. Normative values of CIMT for adult South Indian patients are not available in the published literature. In the present study an attempt was made to define the appropriate "cut-off" value for defining atherosclerosis. For this two methods, namely, construction of ROC-curve; and defining the 75th percentile value from normal control subject data were used.

From the ROC table it is observed that at CIMT of 0.570 on right side there was highest sensitivity and specificity noted. Hence a cut off around 0.570 in Rheumatoid arthritis can predict atherosclerosis. This observation was statistically significant.

From the table it is observed that at CIMT of 0.565 on left side there was highest sensitivity and specificity noted. Hence a cut off around 0.565 in Rheumatoid arthritis can predict atherosclerosis. This observation was statistically significant.

Using this cut-off value derived by the receiver operator characteristic curve method (≥ 0.57 mm; sensitivity 84.4; specificity 90.6%) and the 75th percentile value among normal controls (≥ 0.54 mm) as surrogate markers, the presence of subclinical atherosclerosis was significantly more among asymptomatic patients with RA compared with normal controls .

Our findings strongly suggest that RA itself is an independent risk factor for arterial wall thickening and that the chronicity and severity of the RA, are associated with the arterial wall changes we identified.

The present study revealed that subclinical atherosclerosis, detected by CIMT as a surrogate marker in patients with RA . CIMT measurement was found to be a safe, inexpensive, reproducible, and repeatable strategy for detecting subclinical atherosclerosis. The cost- effectiveness of screening strategies for atherosclerosis like carotid ultrasound and the effect of interventional therapeutic strategies in risk reduction needs to be further evaluated in longitudinal studies with a larger sample size.

The present study was a cross-sectional study. Further longitudinal follow up these patients over a period of time to look for clinical events that reflect the consequences of atherosclerosis would provide valuable corroboration of the observations from the present study. The number of male participants was small in our study, so the upper limit as defined would perhaps be largely applicable to women.

CONCLUSION

The present study revealed that subclinical atherosclerosis, detected by CIMT as surrogate marker in patients with RA . A positive co-relation was established between duration of disease, ESR,CRP,RA factor and increasing CIMT . CIMT measurement was found to be a safe, inexpensive, reproducible, and repeatable strategy for detecting subclinical atherosclerosis and helps in determining the patients at risk of CAD and enables optimized care and treatment in the prevention of CAD/CVD in rheumatoid arthritis patients.

SUMMARY

Rheumatoid arthritis being a chronic systemic disease with a inflammatory background resulting in atherosclerosis . The measurement of carotid intima media thickness as marker is very much essential for the detection of subclinical atherosclerosis.

The study was aimed at proving rheumatoid arthritis as an independent risk factor for atherosclerosis and studied the carotid intima media thickness in patients with rheumatoid arthritis and compared the CIMT with age and gender matched healthy controls. A positive correlation between rheumatoid arthritis and increase in carotid intima media thickness (CIMT) was shown in the present study . Similarly ESR,CRP and RA factor showed a positive correlation with CIMT.

Our findings strongly suggest that RA itself is an independent risk factor for arterial wall thickening and that the chronicity and severity of the RA, are associated with the arterial wall changes we identified.

The present study revealed that subclinical atherosclerosis, can detected by CIMT as a surrogate marker in patients with RA. Carotid intima media thickness can be used as marker of atherosclerosis in these patients which determines rheumatoid arthritis patients who are at potential risk for a cardiovascular & cerebrovascular event. CIMT measurement was found to be a safe, inexpensive, reproducible, and repeatable strategy for detecting subclinical atherosclerosis.

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Informed Consent Form for Clinical Studies

Informed Consent form for Study of carotid intimal thickness in rheumatoid arthritis as marker of atherosclerosis**.** This Informed Consent Form is for men and women who attend the outpatient and inpatient at R.L.Jalappa Hospital and who we are inviting to participate in research on **Rheumatoid Arthritis.**

The title of our research project is "study on carotid intimal thickness in rheumatoid arthritis patients as marker of atherosclerosis in a rural population of kolar district".

The study will be conducted by Dr. Sridhar Sreenivasan Gandhi G under the guidance of Dr.Prabhakar K, from the Department of medicine,SDUMC.

This Informed Consent Form has two parts:

- **Information Sheet (to share information about the research with you)**
- **Certificate of Consent (for signatures if you agree to take part)**

You will be given a copy of the full Informed Consent Form

PART I: Information Sheet

Introduction

I am Dr.Sridhar Sreenivasan G, working under the guidance of Dr.Prabhakar K from R.L.JALAPPA Research Institute. We are doing research on Rheumatoid Arthritis, which is very common in this country. I am going to give you information and invite you to be part of this research. You do not have to decide today whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research. There may be some words that you do not understand. Please ask me to stop as we go through the information and I will take time to explain. If you have questions later, you can ask them of me, the study doctor or the staff.

Purpose of the research

Rheumatoid Arthritis is one of the most common systemic diseases in this region. The increase incidence of cardiovascular events in rheumatoid arthritis has prompted the us to study carotid intimal thickness for early detection of atherosclerosis . The reason we are doing this research is to find out if the increased carotid intimal thickness can be assessed as early marker of atherosclerosis and cardiovascular risk.

Type of Research Intervention

This research will involve collection of clinical history and necessary blood investigations such as complete haemogram, ESR, CRP, RA factor ,ACPA ,ECG, Ultrasonography for carotid intimal thickness.

Participant selection

We are inviting all individuals who attend outpatients and inpatients to participate in the research on carotid intimal thickness in rheumatoid arthritis as early marker of atherosclerosis and cardiovascular risk. We have chosen you as case/control.

Voluntary Participation

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive at this clinic will continue and nothing will change. If you choose not to participate in this research project, you will offered the treatment that is routinely offered in this clinic/hospital for rheumatoid arthritis, and we will tell you more about it later. You may change your mind later and stop participating even if you agreed earlier.

Procedures and Protocol

We will take blood from your arm using a syringe and needle. we will take about 3 vials blood. The provided blood samples will be used for routine investigations like complete haemogram, esr/crp,ra factor. At the end of the research, any leftover blood sample will be destroyed. For study purpose we will be performing ultrasonography for determining the carotid intimal thickness. The values of which will be statistically analyzed and matched with controls.

B. Description of the Process

During the research you make two visits to the clinic.

- In the first visit, a small amount of blood, equal to about a teaspoon, will be taken from your arm with a syringe. This blood will be tested for complete heamogram, esr/crp ,RA factor,ACPA levels. We will also ask you a few questions about your general health and measure how tall you are and how much you weigh.
- At the next visit, you will be asked to undergo an ultrasonography for carotid artery thickness.

Duration

The research takes place over 365 days/ or 12 months in total. During that time, it will be necessary for you to come to the clinic/hospital/health facility 2 days for 2 hours each day. You will be followed up till the end of the study.

Side Effects .

No side effects in participating in the study.

Risks:

No significant risk involved for participating in the study.

Benefits

If you participate in this research, you will have the following benefits: any interim illnesses will be treated at no charge to you. There may not be any benefit for you but your participation is likely to help us find the answer to the research question. There may not be any benefit to the society at this stage of the research, but future generations are likely to benefit.

Reimbursements

You will not be given any money or gifts to take part in this research.

Confidentiality.

With this research, something out of the ordinary is being done in your community. It is possible that if others in the community are aware that you are participating, they may ask you questions. We will not be sharing the identity of those participating in the research.The

information that we collect from this research project will be kept confidential. Information about you that will be collected during the research will be put away and no-one but the researchers will be able to see it. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is.It will not be shared with or given to anyone except Dr.Prabhakar,

Sharing the Results

The knowledge that we get from doing this research will be shared with you through community meetings before it is made widely available to the public. Confidential information will not be shared. After these meetings, we will publish the results in order that other interested people may learn from our research.

Right to Refuse or Withdraw

You do not have to take part in this research if you do not wish to do so and refusing to participate will not affect your treatment at this clinic in any way. You will still have all the benefits that you would otherwise have at this clinic. You may stop participating in the research at any time that you wish without losing any of your rights as a patient here. Your treatment at this clinic will not be affected in any way.

Alternatives to Participating

If you do not wish to take part in the research, you will be provided with the established standard treatment available at the center/institute/hospital.

Who to Contact

If you wish to ask questions later, you may contact :

Dr.Sridhar sreenivasan G
Postgraduate in general medicine
Sri devaraj urs medical college.
Tamaka kolar,Karnataka , Pin:563101
Ph no-9972233242,Email.id- lgsridhar@gmail.com

This proposal has been reviewed and approved by [name of the local IRB], which is a committee whose task it is to make sure that research participants are protected from harm. If you wish to find about more about the IRB,. It has also been reviewed by the Ethics Review Committee of Sri Devaraj Urs Medical College, which is supporting the study.

PART II: Certificate of Consent

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

Print Name of Participant_____

Signature of Participant _____

Date _____

Day/month/year

If illiterate,

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness_____ AND Thumb print of participant

Signature of witness _____

Date _____

Day/month/year

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:

1.

2.

3.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Print Name of Researcher/person taking the consent_____

Signature of Researcher /person taking the consent_____

Date _____(Day/month/year)

CASE DATA COLLECTION PROFORMA:

S.NO	PARTICULARS	PATIENT DETILS
1	NAME	
2	AGE	
3	GENDER	
4	OCCUPATION	
5	ADDRESS	
6	CONSENT	
7	DURATION OF COMPLAINTS	
8	JOINT PAINS EARLY MORNING JOINT STIFFNESS- (TIME TO SPECIFY) <60 MINS >60 MINS BACK PAIN SWOLLEN JOINTS ACR/EULAR 2010 CRITERIA	YES/NO
9	ESR CRP RA FACTOR Anti CCP(IF RA FACTOR IS NEGATIVE /SUSPECTED CASES)	
10	LIPID PROFILE	
11	ECG	
12	RIGHT CIMT	
13	LEFT CIMT	
14	CVA/MI IN THE PAST	

CIMACODI	PITAL NUM	NAME	AGE	SEX	ation of compla	CUPATION	PAINFUL JOIN	BACKPAIN	JOINT SWELLING OF > 6 MONTHS	RA FACTOR IU	ACAP	ESR	CRP	>60 MINS	<60 mins morning stiffness	CHOLESTEROL	TGL	HDL CHOL	LDL CHOL	RIGHT CIMA	LEFT CIMA	ECG		CVA
1	186411	HAGYAMM	18	female	4 YEARS	housewife	YES	yes	YES	320	NOT DONE	35	48	YES	NO	175	98	44	68	0.45	0.43	SINUS RHYTHM-NSR		NO
2	186438	krishna	18	male	1 YEAR	student	YES	NO	YES	80	NOT DONE	45	80	NO	YES	148	87	51	56	0.38	0.35	NSR		NO
3	180360	vijayamma	18	female	6 YEARS	housewife	YES	NO	YES	20	POSITIVE	25	24	NO	NO	165	105	39	67	0.56	0.55	NSR		NO
4	124959	sujatha	20	female	3 YEARS	BUSSINESS	YES	NO	YES	40	NOT DONE	20	24	NO	NO	134	129	46	56	0.48	0.5	NSR		NO
5	187035	sukanya	23	female	2 YEARS	student	YES	NO	NO	10	NOT DONE	25	12	NO	YES	140	86	48	54	0.35	0.4	NSR		NO
6	177657	hankarapp	26	male	6 YEARS	farmer	YES	NO	YES	160	NOT DONE	60	48	YES	NO	148	97	46	65	0.55	0.52	NSR		NO
7	195831	asha	28	female	3 YEARS	student	YES	N0	YES	60	NOT DONE	45	48	NO	NO	155	98	44	68	0.4	0.4	NSR		YES
8	175075	padmamma	30	female	5 YEARS	housewife	YES	NO	YES	160	NOT DONE	40	24	NO	NO	148	87	51	56	0.58	0.6	NSR		YES
9	11096	KSHMAMN	30	FEMALE	7 YEARS	FARMER	YES	YES	YES	10	NOT DONE	30	12	YES	NO	168	79	63	76	0.66	0.8	EMIC CHANGES		NO
10	17954	HAGYAMM	30	female	3years	HOUSEWIFE	YES	NO	YES	80	NOT DONE	54	45	NO	NO	157	88	58	75	0.54	0.6	NSR		NO
11	19189	ANU	30	female	2Years	TEACHER	YES	NO	NO	160	NOT DONE	35	48	YES	YES	158	96	38	75	0.44	0.55	NSR		NO
12	19646	KACHAR	30	MALE	5 YEARS	LABOURER	YES	NO	YES	80	NOT DONE	45	24	NO	NO	186	70	56	69	0.54	0.66	NSR		NO
13	20275	UBIN AHM	32	MALE	5 YEARS	HOP OWNER	YES	NO	NO	160	NOT DONE	65	96	YES	NO	176	117	55	94	0.56	0.66	NSR		YES
14	1918	MUNIRAJU	32	male	1YEAR	LABOURER	YES	NO	YES	40	NOT DONE	40	20	NO	YES	178	129	49	58	0.45	0.5	EMIC CHANGES		NO
15	993627	MANJULLA	32	female	4 YEARS	housewife	YES	NO	YES	640	NOT DONE	45	96	YES	NO	150	117	45	47	0.66	0.67	NSR		NO
16	998510	GIRIYAMMA	32	female	3 YEARS	housewife	YES	YES	YES	160	NOT DONE	60	48	YES	NO	183	120	53	59	0.56	0.6	NSR		NO
17	998059	AJIDUNNIS	32	female	7 YEARS	housewife	YES	YES	YES	160	NOT DONE	45	45	yes	NO	165	105	39	67	0.8	0.75	NSR		NO
18	99917	ARALAKSHM	33	FEMALE	1 YEAR	HOUSEWIFE	YES	YES	NO	40	NOT DONE	30	24	NO	YES	157	88	58	75	0.45	0.5	NSR		YES
19	1008037	ARAYANAPI	34	MALE	5 YEARS	FARMER	YES	NO	YES	40	NOT DONE	25	12	NO	NO	145	105	59	86	0.8	0.77	EMIC CHANGES		YES
20		MUNISWAMA	34	MALE	7 YEARS	lice conistable	YES	NO	YES	640	NOT DONE	40	48	YES	NO	175	98	44	68	0.98	0.8	EMIC CHANGES		NO
21	9154769	KALPANA	34	female	5 YEARS	HOP OWNER	YES	NO	NO	80	NOT DONE	45	45	YES	NO	166	103	47	56	0.52	0.54	NSR		NO
22	942641	ADERAMM	35	FEMALE	1YEAR	student	YES	NO	YES	40	NOT DONE	25	30	NO	YES	165	105	39	67	0.45	0.4	NSR		YES
23	148093	name gowd	35	male	6 YEARS	farmer	YES	yes	YES	320	NOT DONE	30	48	NO	NO	148	87	51	56	0.55	0.65	EMIC CHANGES		NO
24	1213650	MUTHAMM	35	FEMALE	6 YEARS	housewife	YES	YES	YES	160	NOT DONE	60	96	YES	NO	168	79	63	76	0.65	0.56	EMIC CHANGES		NO
25	87652	BYRAMMA	35	FEMALE	7 YEARS	housewife	YES	YES	YES	80	NOT DONE	45	90	YES	NO	157	88	58	75	0.65	0.68	NSR		NO
26	182077	naveen	35	male	1 YEAR	student	YES	no	yes	40		40	24	YES	yes	168	96	38	75	0.32	0.35	NSR		NO
27	186871	nasreen taj	35	female	3years	housewife	YES	yes	yes	40	POSITIVE	45	48	yes	NO	186	70	56	69	0.55	0.5	NSR		NO
28	80673	shmidevam	36	female	4 YEARS	housewife	YES	no	yes	80		35	25	YES	NO	176	117	55	94	0.54	0.58	NSR		NO
29	189210	nirathnam	36	female	8 YEARS	housewife	yes	yes	yes	1280	POSITIVE	65	96	yes	NO	178	129	49	58	1	1.1	NSR		YES
30	189076	tatarathnar	38	female	5 YEARS	housewife	YES	YES	NO	320	NOT DONE	60	24	YES	NO	148	117	45	47	0.58	0.65	NSR		NO
31	189587	ijayalakshn	40	female	7 YEARS	housewife	YES	YES	YES	160	NOT DONE	60	96	YES	NO	183	120	53	59	0.68	0.65	NSR		NO
32	173918	manjula	40	female	4 YEARS	teacher	YES	YES	YES	20	POSITIVE	30	36	NO	NO	165	120	39	67	0.54	0.52	NSR		NO
33	189678	ARAYANAPI	43	male	6 YEARS	farmer	YES	NO	YES	40	NOT DONE	25	48	NO	NO	134	129	46	56	0.74	0.65	EMIC CHANGES		NO
34	170450	shoba bai	43	female	3 YEARS	housewife	YES	NO	YES	20	NOT DONE	25	12	NO	NO	164	86	48	54	0.45	0.4	NSR		NO
35	173561	venkatesh	45	male	4 YEARS	salesman	YES	NO	NO	320		55	90	YES	NO	148	97	46	65	0.47	0.45	NSR		NO
36	175127	kamala	45	female	1 YEAR	HOP KEEPER	YES	NO	YES	40		35	24	NO	YES	139	124	49	87	0.35	0.32	NSR		NO
37	173135	shyamala	45	female	2 YEARS	TEACHER	YES	NO	YES	24	POSITIVE	30	30	NO	YES	134	129	46	56	0.35	0.32	NSR		NO
38	177657	hankarapp	45	male	5 YEARS	LABOURER	YES	NO	YES	160	NOT DONE	35	48	YES	NO	164	86	48	54	0.52	0.54	NSR		NO
39	180747	ATHNAMM	45	female	8 YEARS	housewife	YES	NO	YES	40	NOT DONE	30	24	NO	NO	178	129	49	58	0.67	0.7	EMIC CHANGES		NO
40	185369	shameen	45	female	5 YEARS	housewife	YES	NO	NO	320	NOT DONE	55	45	YES	NO	145	105	59	86	0.68	0.65	NSR		NO
41	87964	anjinappa	45	male	2Years	farmer	yes	NO	yes	80	NOT DONE	68	48	yes	YES	134	129	46	56	0.65	0.8	NSR		NO
42	87953	muniyappa	50	male	4 YEARS	lice conistable	yes	NO	yes	160	NOT DONE	70	48	yes	NO	164	86	48	54	0.55	0.56	NSR		NO
43	132745	ATHNAMM	50	female	3 YEARS	housewife	yes	yes	yes	160	NOT DONE	45	96	YES	NO	148	97	46	65	0.58	0.55	NSR		NO
44	87934	inivas gowd	50	male	1YEAR	LABOURER	YES	NO	NO	40	NOT DONE	35	24	YES	YES	139	124	49	87	0.4	0.4	NSR		NO
45	63876	SHA SULTH	52	FEMALE	2YEARS	HOUSEWIFE	YES	NO	YES	80	NOT DONE	55	24	YES	YES	175	98	44	68	0.4	0.5	NSR		NO
46	88978	IADAS SWA	52	MALE	3years	SWAMIJI	YES	YES	YES	320	NOT DONE	55	96	YES	NO	166	103	47	56	1	1.1	NSR		NO
47	78563	JYA LAKSHI	52	female	3YEARS	HOUSEWIFE	YES	NO	YES	160	NOT DONE	65	45	YES	NO	165	105	39	67	0.5	0.5	NSR		NO
48	89754	ARATHNAN	52	FEMALE	6YEARS	HOUSEWIFE	YES	YES	YES	160	NOT DONE	45	48	YES	NO	148	87	51	56	0.8	0.8	NSR		NO
49	182891	kkaiahamm	55	female	6 YEARS	housewife	YES	YES	YES	80	NOT DONE	45	48	NO	NO	168	96	38	75	0.68	0.7	NSR		NO
50	127572	akkayanna	55	female	7YEARS	housewife	YES	YES	NO	1280	NOT DONE	45	96	YES	NO	134	129	46	56	0.8	0.75	NSR		NO
51	76016	kamar taj	55	female	4 YEARS	student	YES	YES	YES	320	NOT DONE	30	24	YES	NO	164	86	48	54	0.4	0.45	NSR		NO
52	17768	haritha	55	female	4 YEARS	TEACHER	YES	YES	YES	320	NOT DONE	35	48	YES	NO	170	97	46	65	0.44	0.4	NSR		NO
53	64371	nagyalaksh	56	female	5 YEARS	LABOURER	YES	YES	YES	160	NOT DONE	25	24	YES	NO	175	98	44	68	0.55	0.58	NSR		NO
54	65634	nangamma	58	female	5 YEARS	housewife	YES	YES	YES	640	NOT DONE	40	96	yes	NO	148	87	51	56	0.65	0.7	NSR		NO
55	65838	umadevi	60	female	4 YEARS	housewife	YES	YES	NO	160	NOT DONE	45	96	YES	NO	168	96	38	75	0.53	0.55	NSR		NO
56	63396	anjinappa	60	male	5 YEARS	NO WORK	YES	YES	YES	1280	NOT DONE	55	96	YES	NO	134	129	46	56	0.58	0.62	NSR		NO
57	96520	shmidevam	60	female	4 YEARS	housewife	YES	YES	YES	320	NOT DONE	45	48	YES	NO	139	124	49	87	0.56	0.6	NSR		NO
58	37976	ajid unniss	65	female	6 YEARS	housewife	YES	YES	YES	80	NOT DONE	20	12	NO	NO	166	103	47	56	0.58	0.62	NSR		NO
59	69219	gulaz begu	65	female	7 YEARS	housewife	YES	YES	YES	80	NOT DONE	55	96	YES	NO	186	70	56	69	0.54	0.58	NSR		NO
60	199855	akshmamm	65	female	8 YEARS	housewife	YES	YES	NO	80	POSITIVE	30	48	YES	NO	176	117	55	94	0.64	0.7	NSR		NO
61	155029	farzeena	65	female	4YEARS	housewife	YES	YES	YES	320	NOT DONE	35	24	YES	NO	178	129	49	58	0.45	0.43	NSR		NO
62	154689	pushparaj	66	male	7 YEARS	NO WORK	YES	YES	YES	1280	NOT DONE	60	192	YES	NO	145	105	59	86	0.68	0.72	NSR		NO
63	148093	name gowd	68	male	7 YEARS	NO WORK	YES	YES	YES	320	NOT DONE	30	48	YES	NO	175	98	44	68	0.74	0.8	EMIC CHANGES		NO
64	1631511	akeba begu	68	female	8 YEARS	housewife	YES	YES	NO	160	NOT DONE	55	48	YES	NO	148	87	51	56	0.69	0.8	EMIC CHANGES		NO
65	162199	pillamma	68	female	6 YEARS	housewife	YES	YES	NO	40	NOT DONE	40	48	NO	NO	168	96	38	75	0.65	0.66	NSR		NO
66	161084	ATHNAMM	70	female	5 YEARS	LABOURER	YES	YES	YES	20	POSITIVE	25	12	NO	NO	134	129	46	56	0.58	0.6	NSR		NO
67	160638	ayaramapp	70	male	4 YEARS	NO WORK	YES	YES	YES	20	POSITIVE	20	24	NO	NO	148	97	46	65	0.57	0.58	NSR		NO
68	157272	gowramma	70	female	4 YEARS	housewife	YES	YES	YES	160	NOT DONE	30	48	NO	NO	176	117	55	94	0.53	0.59	NSR		NO
69	159329	arvathamm	75	female	5 YEARS	housewife	YES	YES	YES	320	NOT DONE	20	12	YES	NO	148	87	51	56	0.62	0.7	NSR		NO